Psychological Review
1991, Vol. 98, No. 4, 488-505

0033-295X/91/$3.00

The Eating Paradox: How We Tolerate Food

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It is hypothesized that food, which is certainly a necessary commodity with powerful positive reinforcing qualities, also provides a potential threat to organisms, including humans. The act of eating, although necessary for the provision of energy, is a particularly disruptive event in a homeostatic sense. Just as humans learn responses to help them tolerate the administration of dangerous drugs, so do they learn to make anticipatory responses that help minimize the impact of meals on the body, to limit the amount of food consumed within any individual meal, to recruit several parts of the protective stress–response system while meals are being processed, and to limit postprandial behaviors so as to minimize the possibility of disrupting homeostatic systems even more. It is further hypothesized that defenses against eating too much may become activated inappropriately and contribute to clinical problems such as reactive hypoglycemia.

I find myself in the hapless position of having to speak out against the virtues of eating. For a person who not only loves to eat but was trained in experimental psychology, this is nothing less than heresy. It might well be construed as a frontal attack on the very cornerstone of this science. After all, where would psychology be if not for the positive reinforcing qualities of food? Think of C. L. Hull, of B. F. Skinner, of almost any reinforcement or motivational theorist. In light of this honored tradition, I shall attempt to be as gentle and understanding as possible in this exposé. Indeed, have I not already scoured the literature in an attempt to prove my suspicions groundless? Failing that, however, I find that I must fall back on the famous dictum of Sherlock Holmes on analyzing a problem: When you can eliminate all other alternatives as feasible, whatever remains, no matter how unlikely, must be the case.

Perhaps it would be wise to ponder a bit on the intake of food and what it means to animals. An easy analogy might be made with that necessity of modern American life, the automobile. Cars, when they are running, use energy in proportion to the work that they do. At such times, they expend available energy somewhat continuously, albeit at different rates under different conditions. Energy intake, on the other hand, is intermittent. There are periodic stops at refueling centers so that the car's storage organ, the gasoline tank, can be refilled. With ample fuel, the automobile can go on its merry way with few cares related to energy. All that is required is a conscientious driver who, with the aid of feedback from the car itself through the gasoline gauge, can anticipate potential needs and deficits and behave accordingly in terms of trips to the refueling station. Other than the fact that living animals expend some energy all the time and not only when they are actively moving, there is a clear parallel between cars and animals.

It is true that the analogy is oversimplified, but I delve into it slightly deeper for the sake of the arguments that I ultimately want to make. For a car to continue functioning, gasoline or some acceptable alternative fuel is an absolute necessity. Gasoline therefore acquires very positively reinforcing properties for drivers of cars. Consider the operants that are strengthened as a driver attempts to secure gasoline. Some of the best examples developed several years ago when there was a severe gas shortage. Drivers spent enormous periods of time in long, unpleasant lines in order to receive their meager ration of fuel; they had to tolerate arbitrary rules (such as alternate-day availability), ever-increasing prices, less overall service at so-called service stations, and often surly attendants. In short, drivers put up with numerous unpleasantries and expended considerable energy so that they would be able to secure an adequate supply of this desirable commodity.

The point in all this, of course, is that there is nothing inherently pleasant about the act of taking in fuel per se. As mentioned earlier, it is costly; attendants and coconsumers may be abusive; the driver is exposed to noxious odors, dirty surroundings, and so on; and there is genuine danger in transferring the flammable fuel from the pump into the gasoline tank. Receiving gasoline has become so routine that drivers often forget the necessities of turning off the engine, not smoking in the vicinity, and similar behaviors. Even though the energy-providing effects of the fuel are rewarding, the act of acquiring the fuel is not necessarily so. I suggest that this is also true of fuel taking (i.e., the act of eating) by animals, including humans.

Digression Into Drugs

To illustrate my point more thoroughly, I make one further digression, this time into the recent literature on the taking of certain drugs. Many scientists have been indoctrinated in the homeostatic theory of organisms. Often attributed to such luminaries as Claude Bernard and Walter Cannon, the tenet of

Preparation of this article was supported in part by National Institutes of Health Grant DK 17844 to Stephen C. Woods.

The ideas expressed in this article resulted from discussions of the author with numerous people over a period of several years. Noteworthy among them are Daniel Porte, Jr.; Bernard Jeanrenaud; Terry Powley; Robert Bolles; Ilene Bernstein; Alan Marlatt; George Collier; Art Campfield; Douglas Ramsay; Anton Steffens; John Pinel; Ed Stricker; James Smith; and many students and fellows in the author's laboratory.

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homeostasis is that organisms have a somewhat delicate (and fragile) internal milieu and possess numerous reflexes at many levels that function to maintain this environment as near to optimal values as possible. The acceptable range varies considerably among regulated parameters, so that for some (e.g., osmotic pressure) the range is relatively narrow and the feedback controls are relatively stringent, whereas for others (body adiposity among humans, as a possibility; see Keesey & Corbett, 1984) the acceptable range appears much wider in terms of a proportion of the average.

The traditionally cited example of temperature regulation, especially by warm-blooded animals, provides an illustration of the homeostatic process. Their biochemical processes function best in a narrow range of internal temperature. When conditions are such that this function is challenged (e.g., in a particularly cold or warm setting), their homeostatic controls become more obvious. A number of adaptive physiologic responses (reflexes, actually) enable them to generate additional heat in a cold environment and to give off excess heat in a warm one. Warm-blooded organisms, including humans, can also contribute to this act of homeostasis behaviorally. When they begin to feel cold, they can turn up the thermostat, or put on more and more protective clothing, or move to a warmer location, and so forth. The point is that many processes contribute to this marvelous phenomenon of homeostasis. The particularly well-adapted organism can learn to anticipate potential threats to its ideal temperature and put on a sweater before it goes outdoors or crawl under a rock before the sun gets too high.

What does all this have to do with drug taking, or with eating? Consider an organism living in homeostatic bliss so that all of its physiologic processes are functioning in the best possible internal universe. The vital fluids of the body contain appropriate levels of nutrients, minerals, vitamins, oxygen, and so forth, so that the organs and tissues are best served. Toxins, wastes, and any other compounds undesirable from the body's point of view are efficiently eliminated. Contentment reigns. Now, consider what happens when a drug is administered to this organism. The internal Eden is suddenly and devastatingly altered because of the precipitous presence of a novel and disruptive chemical compound. To make the discussion more manageable, I limit this discussion to a few drugs that are commonly taken by humans in an act of personal or social abuse and that are often also inflicted on laboratory animals in an attempt to learn how and why these drugs cause such abuse.

Physiological Tolerance

Compounds such as alcohol, nicotine, the opiates (heroin, morphine, etc), amphetamine, cocaine, and caffeine are called *drugs* because they have a biological effect on the body. At the very least, their presence in the body adds an alien factor to the fluids and cells and thereby necessarily upsets the delicate, homeostatically controlled milieu. All of these drugs in addition cause specific disruptions as they interact with particular classes of cells or receptors to cause specific reactions (which are often desirable; this is presumably one reason why humans take them). In a biochemical sense, the insult to the body must be tremendous the first time such a drug is experienced. For example, alcohol creates physiologic changes ranging from hypothermia (a lowering of temperature) to excess water loss as urine to dysfunction of the nervous system. The dysfunction affects behaviors ranging from the disruption of motor coordination to a difficulty in performing certain cognitive tasks, such as learning, to complex changes of social behavior, including perhaps alcoholic disinhibition (see Woods & Mansfield, 1983). Although the relative contribution of homeostatic processes to each of these behaviors varies, it should be clear that many homeostatically controlled systems are affected.

The important point here is not so much what the drug does to the body as what the body does in response. It is already known that to the extent that a finely controlled variable such as body temperature is changed, the body invokes automatic responses to reverse the change. Therefore, as body temperature begins to decline as a result of alcohol administration, homeostatic reflexes are recruited to counter the drug's effect and to curb the decline. These reflexes continue until temperature returns to its normal range or level. If one's thermic reflexes were somehow incapacitated, the hypothermic effect of alcohol would be greatly enhanced. Presumably, analogous responses are enacted to counter each of the other disruptive effects of the drug. Simultaneously, the body acts at another front to destroy, eliminate, or otherwise inactivate the drug, and so organs such as the liver and the kidneys work overtime to minimize the absolute time that the drug is active and hence hasten the restorative process.

This scenario is intended to depict, in somewhat simplified terms, what happens when a drug is thrust upon an organism. The next important point to consider is what happens when this process is repeated in some sort of regular pattern. At the molar level, the process of drug tolerance develops. *Drug tolerance* is a term that refers to the diminishing of an effect of a drug when it is given repeatedly (Jaffe, 1985; Kalant, Leblanc, & Gibbins, 1971; Tabakoff & Rothstein, 1983). For example, the hypothermia caused by a particular dose of ethanol is considerably less after the tenth administration than after the first, and the ability of heroin to reduce pain or to elicit a psychological high is also diminished over repeated drug administrations. Tolerance can also be described in terms of the amount of drug required to create a particular magnitude of effect. If motor performance in animals is to be disrupted by a particular, constant amount, the dose of ethanol necessary to achieve this disruption will increase over trials. The important point is that a drug becomes less efficacious over trials.

Drug tolerance has been described and studied for years, but only recently have experiments begun to reveal its complexity. In secondary texts, until the past few years, tolerance has been partitioned into dispositional and pharmacodynamic subgroups (e.g., Jaffe, 1985; see Overstreet & Yamamura, 1979). *Dispositional* tolerance exists when the body's ability to dispose of the drug becomes enhanced over repeated trials. This may mean that the liver more easily degrades the drug or that the kidney more readily excretes it into the urine. Ultimately it means that less of a given dose of a drug ever reaches critical sites within the body, and the drug effect is therefore smaller. *Pharmacodynamic* (sometimes called *functional*) tolerance exists if a constant amount of a drug reaches some critical organ or tissue but the response of that organ or tissue is reduced. Such tolerance is often described in terms of altered receptor

numbers or affinity, changes of available neurotransmitters, and the like (Overstreet & Yamamura, 1979). The bottom line is that drug tolerance has been logically and conveniently considered to represent a reduction in the amount of the drug that reaches critical target organs, or a dulling of the responsivity of those same target organs, or both. Although these possibilities are not mutually exclusive, they were taken to be exhaustive. A smaller net drug effect could be a result of a lower amount of the drug or to decreased sensitivity to the drug.

Behavioral Tolerance

Considerable recent research suggests yet another, quite orthogonal mechanism for tolerance. The concept is simple: When an animal has become accustomed to receiving a drug in a certain situation and is again presented with that same situation, it anticipates the drug administration and makes compensatory responses that serve to reduce the impact of the impending presence of the drug. Given this mobilization of the body's homeostatic processes before the actual drug presentation, the drug is effectively compromised, and the result is less total drug effect or increased drug tolerance. The existence of such tolerance neither excludes the possibility of dispositional or functional tolerance nor requires their existence. Many reviews of this concept have been written (e.g., Eikelboom & Stewart, 1982; Goudie & Demellweek, 1987; O'Brien, 1976; Siegel, 1985, 1989; Siegel, Krank, & Hinson, 1987; Stewart & Eikelboom, 1987).

This conceptually new type of tolerance has come to be called *behavioral tolerance* (Corfield-Sumner & Stolerman, 1978) because its properties easily fit a conditioning paradigm. For example, if the normal biochemistry of the mouth is disrupted by infusion of a mild acidic solution into it, the response is a reflexive increase in the flow rate of saliva to dilute and rinse away the acid. If such an event is repeated and if the organism so insulted can predict when the event will occur, it learns to anticipate it. Hence Pavlov (1927) was able to show that dogs, in the presence of stimuli predicting that acid would soon be put on their tongues, would drool in anticipation. The cues repeatedly associated with the presentation of a drug develop the capacity to elicit compensatory homeostatic responses.

Now, consider the case of drugs of abuse such as heroin or alcohol. When alcohol is given and causes hypothermia, homeostatic hyperthermia-producing reflexes are elicited. If the alcohol administration is repeated and if there is some stimulus or cue that is reliably predictive of this event, the animal ought to be able to anticipate receiving the drug, make the appropriate hyperthermic response, and thus circumvent the otherwise inevitable onset of hypothermia. If this indeed happened, it would be an example of behavioral tolerance.

My intent in this article is not to convince the reader that conditioning may be the predominant cause of drug tolerance. That can be done in another forum, and indeed the point has been adequately made elsewhere (Siegel, 1983, 1989; Wenger, Tiffany, Bombadier, Nicholls, & Woods, 1981; Wenger & Woods, 1984). Rather, my intent is merely to convince the reader that behavioral tolerance does exist and can become an important part of an animal's behavioral repertoire. This persuasion can perhaps most easily be accomplished by the example just developed: the thermic changes associated with alcohol administration. Mansfield and Cunningham (1980) gave rats ethanol in a unique environment and a control injection of saline in a different unique environment. Over several trials, tolerance to the hypothermic effect of the alcohol developed. Those authors then administered the same dose of ethanol to their rats but in the presence of the stimuli that had always previously been associated with saline administration. The rats did not demonstrate that they were tolerant and became hypothermic as if they were receiving ethanol for the first time. The manifestation of tolerance was, therefore, specific to the stimulus situation; that is, the same rats were tolerant in the presence of one set of stimuli and not tolerant in the presence of another. There is now considerable support for the notion of situational specificity of drug tolerance (Siegel & MacRae, 1984).

Mansfield and Cunningham (1980) gave a perhaps more convincing demonstration that the animals had learned a compensatory response to prevent ethanol-induced hypothermia from occurring. They found that once tolerance was established and the rats were given a placebo injection of saline in the presence of the stimuli previously associated with ethanol administration, their body temperatures increased in response to the placebo injection. Rats given comparable saline administration under other conditions had no change of temperature. Mansfield and Cunningham were therefore able to demonstrate that the animals, faced with the certainty of alcohol (as indicated by the stimulus situation), would actually elevate their body temperatures in anticipation, and the response was specific to the stimulus situation. Analogous results were reported by Le, Poulos, and Cappell (1979).

My colleagues and I recently provided evidence that behavioral tolerance to alcohol is also response specific (Hjeresen, Reed, & Woods, 1986; Mansfield, Benedict, & Woods, 1983). Depending on the precise conditions of repeated drug administration, some rats were rendered tolerant to the hypothermic effect of ethanol as well as to its motor disruption, whereas other rats were tolerant to one or the other effect, but not to both effects, of the drug. Various control groups were tolerant to neither effect of alcohol. Tolerance to alcohol, it seems, is a rather complex response that depends at least as much on behavioral experience as on drug history.

Similarly persuasive demonstrations have been made with morphine. Siegel (1975), in an impressive series of experiments, found that when rats were repeatedly administered morphine in the presence of unique cues, they rapidly developed tolerance to its analgesic effect. When administered morphine in the absence of these cues, they did not demonstrate tolerance; when given a placebo injection in the presence of cues indicating that morphine was about to be given, the rats became more sensitive to pain. Siegel completed numerous experiments along this theme that show that tolerance to morphine shares many properties with conditioning (Siegel, 1976, 1977, 1989; Siegel, Hinson, & Krank, 1981). Many other drugs and many other responses have been studied in a similar manner, always with the same conclusion (see Goudie & Demellweek, 1987; Siegel et al., 1987). Animals faced with the prospect of receiving a drug make anticipatory responses that create an effect opposite in nature to that created by the drug itself. The net effect of

the combination of the drug with the anticipatory responses is little overall change of critical physiologic parameters, and this in turn is called *drug tolerance.* If only the drug is given, the drug effect is manifest; if only the anticipatory response occurs, an opposite effect is manifest.

Perhaps one final argument might convince even the most skeptical reader of the importance of learning in the development of tolerance and maintenance of homeostasis. A former student of mine, John Wenger, investigated behavioral tolerance to alcohol and other depressant drugs as part of his doctoral dissertation (Wenger, 1980). He reasoned that if tolerance is actually nothing more than the reflection of a learned response elicited by specific environmental cues, the animal ought to be able to learn that same response without necessarily taking the drug in the first place. To test this hypothesis, Wenger built the rat equivalent of the schoolyard merry-go-round, one of those devilishly enticing rotating platforms that a child would run around and push to maximal velocity before attempting to jump on and grasp for dear life. Who can forget stepping off the slowing platform, losing their equilibrium, and being unable to walk normally (if at all) for a brief period? Wenger's rats were placed into a large coffee can mounted on a rotating motor and spun until they were dizzy. Immediately afterwards, they were unceremoniously dumped onto a moving treadmill, on which any false step produced a mild footshock. Needless to say, their overall treadmill performance over the subsequent minute was greatly impaired, which is somewhat reminiscent of the impairment caused by an initial injection of alcohol or any other depressant drug.

To make a long story short, the rats, when subjected to this particular form of barbarism every day, became "tolerant" in the sense that comparable centrifugation had much less disruptive effect on treadmill performance on the 10th than on the 1st day. This tolerance to what was termed *rotation-induced dizziness* developed gradually over trials (Wenger, Tiffany, & Woods, 1980). A control group received comparable spinning experience and comparable time on the treadmill every day, but not in the same temporal contiguity. After tolerance had developed in the experimental rats, both groups of rats were given either diazepam or alcohol, were placed in the spinning apparatus without being spun, and then were put onto the treadmill. Rats that had previously become "tolerant" to being spun performed significantly better than rats that had not; even though the experimental rats had never previously received the drug (or any other drug, for that matter), they behaved as if they were tolerant to the alcohol. They had learned a response that enabled them to walk on the treadmill while they were equilibrially disrupted, and they transferred this learning to the drug situation.

Using changes of temperature as the response, Hjeresen, Loebel, and Woods (1982) generated analogous findings. One group of rats was put into individual cages in a freezer every day until their temperature dropped by an amount equivalent to that caused initially by alcohol. Control rats were put in similar cages but on a shelf alongside the freezer. After several trials, both groups were given alcohol for the first time, put into the small cages, and put on the shelf alongside the freezer. Rats accustomed simply to being on the shelf became hypothermic in response to the alcohol; rats accustomed to going into the freezer did not. To demonstrate that the rats had learned an anticipatory hyperthermic response, comparably trained groups of rats were given a saline injection and put in their cages on the shelf. Shelf-trained rats had no change of temperature, whereas freezer-trained rats became significantly hyperthermic. The point is that tolerance can be instilled in rats by giving them an experience somewhat comparable to that caused by a drug. Drugs need not be given to render animals tolerant to them; rather, the drugs merely create a perturbation of homeostatically controlled variables so that the animal can make and learn to make specific compensatory responses.

Cephalic Insulin

It is curious that what seems to me to be an analogous response, the secretion of cephalic insulin, has never previously been described as being comparable with drug tolerance. When one eats, the digestive system processes food into a form amenable for entry into the body (from the gut into the blood) and ultimately for immediate use by the cells as fuel or energy or for storage. During and after a meal, digested fuels (the smallest functional units of carbohydrates, fats, and proteins) are absorbed into the blood and hence change the existing biochemistry of the body. The body responds, not surprisingly, by making responses to cope with this surge of fuels as they enter the blood: It facilitates the uptake of ingested fuels by most of the tissues of the body and hastens their cellular consumption and storage.

One of the most important characters in this alimentary drama is the hormone insulin. Insulin is a peptide hormone (smaller than but biochemically similar to a protein) secreted by the B cells of the islets of Langerhans of the pancreas. These B cells respond directly to a local increase of fuels (whether carbohydrate, mainly in the form of glucose; fat, in the form of free fatty acids; or proteins, in the form of amino acids) by increasing the amount of insulin released into the blood. The insulin in turn is dispersed throughout the body to most tissues and increases the rate at which these tissues remove the ingested fuels from the blood. The more insulin there is, the faster the fuels are removed from the blood; the higher the amount of fuels rises in the blood after a meal, the greater is the elicited increase of insulin secretion (Cook & Taborsky, 1990; Porte & Halter, 1981). The point is that the body, in its wisdom, does what it can to expedite the removal of elevated fuels from the blood during and after a meal, thus helping homeostatically to preserve the normally low blood fuel levels. When a meal consists mainly (or only) of carbohydrates, the term used to describe the efficient removal of ingested glucose from the blood is *glucose tolerance.* As shown later, this is a particularly apt play on words.

To stretch the analogy, consider the act of food taking to be similar the act of drug taking. Granted, there are fundamental and important differences. Food is a requirement for life and drugs are not, and the reasons for instigation of their use are therefore quite different, but both food taking and drug taking appear to activate analogous physiologic responses. In both instances the body is actively maintaining its internal environment as near to optimal parameters as possible when exogenous materials are introduced. The influx of exogenous compounds perturbs the internal milieu, and the organism reflexively responds by reestablishing the status quo. It therefore follows that,

as in the instance of drug taking, the clever organism ought to be able to predict when such disturbances will occur and make appropriate anticipatory responses to hasten the proper disposal of the fuels from the blood and thus minimize this impact of the meal. In fact, this is exactly what happens. It is well established that animals, including people, begin secreting insulin as soon as they start eating, before any increase of ingested fuels into the blood. Such insulin is called *cephalic insulin* because its secretion is triggered more by food-related stimuli such as tastes or smells, which presumably act through the brain to increase insulin secretion, than by actual ingested fuels that reach the pancreas through blood circulation (e.g., Steffens, 1976; Strubbe & Steffens, 1975). It is completely analogous to the increase of salivation by Pavlov's (1927) dogs when they were presented with stimuli indicating that they would soon receive food. In fact, many if not all of the well-studied digestive processes have been shown to have a cephalic phase (Powley, 1977).

What is particularly pertinent about cephalic insulin is that its secretion often begins before food is actually eaten. When placed in eating-related situations, in which there are abundant cues normally associated with food, animals and people secrete insulin. This can be shown by an experiment in which animals sham eat (i.e., they see, smell, chew, or swallow food, but it exits the body before being digested or absorbed; Hommel, Fischer, Retzlaff, & Knofler, 1972); by giving them nonnutritive foods to eat, such as saccharin or paraffin or even plain water (Louis-Sylvestre, 1976, 1978a; Steffens, 1976); or, in the case of humans, by simply showing them food and letting them see and smell but not consume it (Johnson & Wildman, 1983; Parra-Covarrubias, Rivera-Rodriguez, & Almarez-Ugalde, 1971; Simon, Schlienger, Sapin, & Imler, 1986; Sjöström, Garellick, Krotkiewski, & Luyckx, 1980). There is even one experiment in which people were hypnotized and were told that they were eating; some of them made responses indicative of increased insulin secretion (Goldfine, Abraira, Gruenwald, & Goldstein, 1970).

This cephalic insulin secretion is easily modifiable and brought under arbitrary stimulus control (Woods, 1983; Woods & Kulkosky, 1976). After first demonstrating that animals can be trained to secrete insulin (Woods, Alexander, & Porte, 1972; Woods, Hutton, & Makous, 1970), my colleagues and I found that arbitrary stimuli associated with food presentation can develop the ability to elicit insulin secretion (Woods, 1976; Woods et al., 1977). These stimuli included specific sounds, odors, and even the time of day (Woods et al., 1977). Anything that informed the animals that food was imminent seemed capable of acquiring this ability. Furthermore, the same specific neural mechanisms used in cephalic insulin secretion were used in this conditioned insulin secretion (Porte & Woods, 1990; Powley, 1977; Woods, 1972, 1983; Woods & Porte, 1974), and we concluded that cephalic insulin secretion could readily be brought under the control of any stimulus predictive of food (Woods, 1983; Woods & Burchfield, 1980; Woods & Kulkosky, 1976). We have since found that the process of cephalic insulin secretion develops at an early age (Bernstein & Woods, 1980), which suggests its lifelong importance.

The inference from all this, of course, is that by successfully anticipating the ingestion of food, animals can make appropriate compensatory responses and hence lessen the impact of eating upon the body; that is, the secretion of cephalic insulin enables the organism to tolerate food to a greater extent. The proof of this is easily demonstrable. When an animal is prevented from secreting insulin cephalically (typically accomplished by the cutting of the neural link between the brain and the pancreas, the vagus nerve) and then the animal is given the same caloric load as that given to a control animal, the animal is glucose intolerant (Berthoud, Bereiter, Trimble, Siegel, & Jeanrenaud, 1981; Louis-Sylvestre, 1978b). This means that the amount of glucose detectable in the blood after a test meal attains significantly higher levels when there is no cephalic insulin. Another way of saying this is that without cephalic insulin, animals secrete insufficient insulin during a meal to eliminate the ingested glucose from the blood in the normal time, and they therefore appear diabetic after meals (see Berthoud et al., 1981; Nicolaidis, 1977). Comparable results in terms of abnormally elevated blood glucose levels occur if food is simply put into the stomach so that the mouth-to-brain-to-pancreas reflex is circumvented (Proietto, Rohner-Jeanrenaud, Ionescu, & Jeanrenaud, 1987; Steffens, 1976).

To restrict the inevitable rise of postprandial glucose levels to what would occur in normal rats, rats incapable of secreting insulin cephalically would have to eat much smaller meals, and this behavior is well-documented (Snowden, 1970; Snowden & Epstein, 1970). One function of cephalic insulin can therefore be construed as enabling animals to take in greater amounts of food at one time (i.e., to eat larger meals) and still be able to cope relatively well with the nutrient load.

An underweight organism, which would benefit from consuming larger-than-normal meals, might therefore be expected to have a relatively large cephalic insulin response. It has been reported that restrained eaters (who by definition are below their ideal weights) have relatively large cephalic insulin responses to foods (Simon et al., 1986). Furthermore, Broberg and Bernstein (1989a) recently reported that women with anorexia nervosa, who are underweight and restrained eaters, have an abnormally large cephalic insulin response. This is in contrast to women of normal weight with a different eating disorder, bulimia; they have a normal cephalic insulin response (Broberg & Bernstein, 1989b).

The Problem With Eating

An underlying theme throughout the preceding paragraphs suggests that food, in addition to being the prototypical positive reinforcer as everyone has been led to believe, also poses a sufficient threat or problem to animals that they learn responses to cope with and minimize the impact of food intake. After all, the ingestion of food seems to be a behavior that is sufficiently necessary to warrant a wider acceptable range of postprandial fuel levels in the blood. Why the tight homeostatic controls to keep them in check? Here, one can only speculate. It may be instructive to consider that elevated fuels in the blood (at least on a chronic basis) are associated with and indeed are risk factors for many metabolic abnormalities. Elevated blood glucose levels and glucose intolerance when food is ingested are the defining symptoms of diabetes mellitus (see Rifkin & Porte, 1990). Elevated levels of fats of one type or another in the blood

are characteristic of obesity, of several cardiovascular disorders, and of many more unusual metabolic disorders (Bray, 1976; Brunzell & Schrott, 1973). Chronic nutritional excesses have also been linked with hypertension (Klaff & Palmer, 1986; Landsberg & Young, 1981; McCarron, Morris, Henry, & Stanton, 1984; J. B. Young & Landsberg, 1981), and oral intake of carbohydrates reportedly exacerbates a tendency to develop hypertension in susceptible persons (J. B. Young & Landsberg, 1981). Elevated dietary levels of carbohydrates, cholesterol, and other kinds of fat are thought to predispose a person to cardiovascular disease and several types of cancer (Armstrong & Doll, 1975; Caroll, 1980; Correa, 1981; Ginsberg, 1988; Goldberg, 1988; Hems, 1970; Keys et al., 1986; Seely, 1983; Turpeinen et al., 1979), and development of numerous metabolic abnormalities is associated with chronic consumption of calorically dense meals (Coulston, Hollenbeck, Swislocki, Chen & Reaven, 1987; Service et al., 1983). Because all these risk factors are modifiable through altered nutrition, strong dietary recommendations to reduce meal size have recently been made by the National Cancer Institute (Greenwald & Sondik, 1986) and the National Institutes of Health (1987).

It is noteworthy that a major current thrust of the American Diabetes Association is achievement of tighter lifetime control over blood glucose levels as a means of reducing many of the physical complications of diabetes mellitus. This approach is based on the finding that the integral of individual (typically meal-related) instances of hyperglycemia over a prolonged interval is associated with many of the complications of diabetes mellitus. (See review and update of this project by the DCCT Research Group, 1986, 1990.) Long-term control of glycemia within strict normal levels reportedly decreases the severity and incidence of many chronic complications of diabetes mellitus (Borch-Johnsen et al., 1987; Chazan, Balodimos, Ryan, & Marble, 1970; Orchard et al., 1990; Service, Rizza, Daube, O'Brien, & Dyck, 1985).

The case can be (and has been) made that a major factor related to stress is a tendency to mobilize fuels from storage depots, followed by failure to burn these excess fuels immediately, which thus allows them to accumulate in the blood (e.g., Selye, 1956). The fuel mobilization capacity was presumably fine tuned (in an evolutionary sense) when stressors posed a real physical danger to animals. Failing to get out a manuscript on time or losing a business deal are probably equally as effective at raising glucose and fat levels in the blood as is being chased by a lion, but no related concomitant increase of exercise is performed by the skeletal muscles in the former cases to provide a sink for the elevated fuels. Elevated levels of fuels may therefore also be a contributing factor to the illness-associated aspects of chronic stress.

Chronically elevated levels of glucose have been associated with a higher reported incidence of perceived stress and anxiety in humans (Dejours, Assan, & Tassin, 1983; Jacobson, Rand, & Hauser, 1985; Linn, Linn, Skyler, & Jensen, 1983), as well as with impaired performance on neuropsychological tests (e.g., Holmes, Hayford, Gonzalez, & Weydert, 1983; Holmes, Koepke, & Thompson, 1986; see reviews by Leedom & Meehan, 1989, and Rowland & Bellush, 1989). Sexual performance is also impaired in both genders as a result of chronic hyperglycemia (see review by Leedom & Meehan, 1989). Finally, chronic hyperglycemia is also associated with a greater sensitivity and greater magnitude of response to acute stressors (Leedom & Meehan, 1989; Meehan, Leedom, Nagayama, & Zeidler, 1987), and with altered brain anatomy (Jakobsen, Sidenius, Gundersen, & Osterby, 1987).

On an acute basis, elevations of fuels, and especially glucose, cause alterations of many central nervous system neurotransmitter systems (Fernstrom, 1983; Fernstrom & Faller, 1978; Fernstrom & Wurtman, 1971; Leedom & Meehan, 1989; Rowland & Bellush, 1989; Saller & Chiodo, 1980). This in turn is thought to have an impact on myriad behavioral systems (Leedom, Meehan, & Zeidler, 1987). In a review of this area of literature, Rowland and Bellush (1989) recently concluded, "It is apparent that a widespread alteration in the functional dynamics of several transmitters/neuromodulators occurs during chronic hyperglycemia." (p. 202)

It is noteworthy that acute elevations of glucose levels in the blood are sufficient to cause the formation of conditioned taste aversions (R. Deutsch, 1974), and the effect is greatest in diabetics with already elevated levels of blood glucose (Tordoff, Tepper, & Friedman, 1987). Finally, there is considerable evidence that animals that eat less food per day live longer (and therefore that eating relatively more food is associated with a shorter life span; Brody, 1945; Masoro, Yu, & Bertrand, 1982; Nelson, 1988; Sacher, 1977), and fasting has become a healthful practice and has been compared with drug withdrawal (see Garfield, 1981a, 1981b).

Therefore, there is no simple, intuitive reason why elevated fuels in the blood should pose a problem to animals. What can be concluded is that such elevations, when prolonged, create risk to health and longevity. Furthermore, the very existence of such an efficient mechanism for keeping fuels low when organisms eat is evidence of its utility. The unwillingness of animals to tolerate severe elevations of fuel levels when they eat may also help explain another behavior that has often puzzled me: satiety.

The Problem of Satiety

Satiety is usually defined as the state of being full or sated. When an animal or a person is given sufficient food that it can eat for a while and then stop while excess food remains, it is operationally stated to be sated. But why does satiety exist at all, at least as it normally occurs? Sociobiologists are wont to develop elaborate models explaining the foraging behavior of animals. They talk about such factors as search time, search images, the nutrient value of different food stuffs, the threat of predators, and so on, while trying to explain the apparent foraging strategies of one creature or another (e.g., Kamil & Sargent, 1981; Shettleworth, 1985). I have yet to see such a model include the ubiquitous behavior of satiety. It is true that some models do account for the potential incapacitation of a particularly large meal, but one gets the impression that the concern is with a physical incapacitation rather than a metabolic rush. After all, if one is weighted down with excessive food in the gut, one cannot elude predators as easily.

Consider the phenomenon of satiety. Some researchers have theorized that satiety is caused by a stretching of the stomach wall, as if some sort of physical limit is normally placed on meal

size (Cannon & Washburn, 1912; Gonzales & Deutsch, 1981). However, studies in which food has been calorically diluted (i.e., by the addition of nonnutritive bulk so that more volume must be eaten to achieve the same caloric load) have shown that animals easily adapt to this manipulation by increasing their meal size (Adolph, 1947; Janowitz & Grossman, 1949). They readily consume a larger volume to get their calories, which suggests that gastric capacity is rarely a factor in normal consumption. This should not be taken to imply that stimuli related to stomach or gut volume are not important determinants of satiety; rather, I suspect that such cues are associative, given a familiar environment and a constant diet, and therefore become convenient indicators as to the progress of a meal (e.g., Booth, 1985).

Why, then, when animals must search for food and often expend considerable energy to get it and when there are no apparent predators around, do they stop eating even if excess food is available? I suggest that there is a maximal caloric load that they can safely (or at least comfortably) consume and handle in a metabolic homeostatic sense. Several reports over the years have shown that even animals that are severely food deprived cannot eat particularly large meals; this phenomenon is called *postingestive inhibition* (Mook, Brane, & Whitt, 1983). As the degree of food deprivation increases, the size of the first meal consumed when food is available increases over a small temporal range and then increases only very slightly and appears to approach an asymptote (Horenstein, 1951; Lawrence & Mason, 1955; Levitsky, 1970). In fact, animals that have been specifically deprived of either protein (Andik, Donhoffer, Farkas, & Schmidt, 1963) or water (Bruce & Kennedy, 1951) will not consume excess calories in a meal in order to get their requisite commodity. Finally, as animals become more sated, they develop decreased preference for sweet-tasting foods (Cabanac, 1971; Cabanac & Duclaux, 1970) which, if consumed, would elevate blood glucose levels even further (but see Jacobs & Sharma, 1969).

I do not mean to imply that animals cannot vary their meal size and routinely eat large meals under some circumstances. The ubiquitous diurnal variation of meal size by humans (e.g., in our culture, suppers tend to be much larger than breakfasts) proves this point, and many species (e.g., hibernators and migrators) necessarily increase meal size during appropriate times of the year. However, I suspect that associative strategies underlie most diurnal variations of meal size, and I further suspect that some species adopt different eating strategies and control systems (in a physiologic sense) when gaining weight rapidly in anticipation of a period of fasting. My colleagues and I recently found support for this view in studies of a hibernator, the yellow-bellied marmot. Whereas the food intake of marmots at a time of the year when they are eating relatively normal amounts appears to be influenced by the same homeostatic and hormonal controls common to most mammals (Florant, Singer, et al., 1991), different control systems function around the time of hibernation (Florant, Richardson, Mahan, Singer, & Woods, 1991).

When a meal is eaten, among the body's other means of reducing the levels of fuels in the blood is activation of reflexes to burn excess ingested energy rapidly. Some of what is ingested is therefore converted to heat and lost to the body, but fuels can be rapidly taken out of the blood by this mechanism. Such excessive wastage is usually attributed to the brown adipose tissue in rodents; this phenomenon is called *dietary-* or *meal-induced thermogenesis* (Rothwell & Stock, 1979). In humans, the causal mechanism for the phenomenon is not as well understood, although changes in the efficiency of thyroid hormone may play a role (Hesse, Spahn, & Pienert, 1981).

Satiety is a state that has received much attention lately because of the advent of compounds that cause animals or people to eat smaller meals or to become sated sooner during a meal (e.g., see reviews by Gibbs & Smith, 1986; Morley, Bartness, Gosnell, & Levine, 1985; Smith, 1984; Smith & Gibbs, 1985; Woods et al., 1981). It turns out that these satiety factors are, for the most part, peptide hormones secreted by the gut in response to the specific composition of the food being eaten. It is as if the gut, with its myriad chemoreceptors, conducts an ongoing analysis and keeps a record of what is being consumed and secretes a specific cocktail of hormones into the blood in response. These hormones then customize the digestive process (the secretion of the proper digestive hormones and juices, and in the right concentrations and points in the process, and so on) to the meal being eaten, as well as inform the brain as to the total nutrient load consumed. At some point, the cumulative impact of these various factors stops the eating process. The animal or person is thereby sated. This process seems an excessive control system for species or individuals living from day to day in terms of having enough nutrients to survive. It would seem more teleological for a hungry or starving animal to continue eating and thus consume all that it could (up to the actual physical limits of its stomach) when faced with ample food and no predators. The existence of satiety, like that of cephalic insulin, implies a fundamental danger or risk associated with overeating.

Sympathetic Nervous System

Another line of evidence can be engendered to make the point that eating can create genuine problems. As a student, I was taught (and believed) that the body was normally controlled by the branch of the autonomic nervous system called the parasympathetic division. This neural control supposedly ran the body during "vegetative" times: that is, when there was no extra demand or special need such as during stress or exercise. The parasympathetic system was said to control normal bodily functioning, and included in its umbrella was the control of digestion. The sympathetic nervous system, on the other hand, could be activated and therefore superimposed upon the parasympathetic system in times of emergency. It prepared the body for the proverbial fight-or-flight response and included such responses as elevated blood pressure, elevated heart rate, and elevated levels of fuels in the blood (e.g., Cannon, 1932).

It was generally thought that eating and its associated digestive processes were under parasympathetic control and that fasting (or starvation in the extreme) were times of sympathetic arousal so as to keep sufficient fuel in the blood for the body to function. However, it was not until recently that levels of the prototypical sympathetic hormones, epinephrine and norepinephrine, could be accurately measured in the blood (e.g., Evans, Halter, & Porte, 1978). With this technical advance came the realization that the sympathetic nervous system is in fact

relatively suppressed during fasting and becomes activated during eating (Landsberg & Young, 1984; J. B. Young & Landsberg, 1977a, 1977b). Eating causes an increase of epinephrine and norepinephrine in the blood (e.g., de Boer, de Beun, Slangen, & van der Gugten, 1990; O'Dea, Esler, Leonard, Stockigt, & Nestel, 1982; J. H. Schwartz, Young, & Landsberg, 1983; Steffens, van der Gugten, Godeke, Luiten, & Strubbe, 1986; Welle & Feldman, 1986; Welle, Lilavivathana, & Campbell, 1980) and an increased rate of turnover of these compounds in most tissues (e.g., O'Dea et al., 1982; J. B. Young & Landsberg, 1977a; J. B. Young, Saville, Rothwell, Stock, & Landsberg, 1982). Intrahypothalamic administration of glucose has a comparable effect (Sakaguchi & Bray, 1987), and intravenous glucose increases plasma levels of catecholamines in humans (Rowe et al., 1981).

In close, detailed analyses of plasma epinephrine and norepinephrine levels over a 24-hour period, it has been found that each individual meal in rats is associated with a small but reliable increase of both of these hormones in the blood (de Boer & van der Gugten, 1987). All meal-related excursions of catecholamines into the blood during meals might be considered relatively minor; however, these excursions over a prolonged basis have been implicated in the development of obesity, atherosclerosis, and hypertension (R. S. Schwartz, Jaeger, Veith, & Lakshminarayan, 1989), and they can be rapidly normalized in the acute hypocaloric state (Sakaguchi, Arase, Fisler, & Bray, 1988; J. B. Young & Landsberg, 1977b).

In accordance with these findings, levels of other "stress" hormones, including adrenocorticotropic hormone (ACTH), glucocorticoids, and beta-endorphin, also become elevated at the time of meals (e.g., Al-Damluji et al., 1987; de Boer & van der Gugten, 1987; Ishizuka, Quigley, & Yen, 1983; Moberg, Bellinger, & Mendel, 1975; Slag, Ahmed, Gannon, & Nuttall, 1981; Wilkinson, Shinsako, & Dallman, 1979). In an endocrine sense, therefore, the act of eating resembles certain aspects of a real or potential stress situation for the body. The point can be made that all behaviors are at least minor stressors of a sort and that a meal-related increase of stress hormones is no different than the increase of these same hormones that occurs in association with other behaviors. However, the demonstration that stimuli that signal meals or food availability also elicit increased stress hormone secretion (Follenius, Brandenberger, & Hetter, 1982; Quigley & Yen, 1979) suggests that physical activity per se cannot be the only important variable.

Additional Problems Associated With Meals

As just summarized, several lines of evidence can be mustered to support the postulate that eating is not just a life-sustaining activity, as traditionally thought. The body's emergency nervous system is activated, hormones are secreted in anticipation to minimize the impact of the meal, and the meal is terminated before physical capacities are realized. People respond to food in the same way that they respond to exogenous drugs. They tolerate drugs and their passage into the body in order to derive certain benefits from them. The benefits (indeed, necessities) of food are obvious. It is the adverse effects that have been less obvious.

I do not wish to imply that elevated blood levels of fuels are the only potential problem associated with food intake. Probably many additional vital systems are affected by eating. One obvious possibility relates to the tendency of animals to consume water at and around the time of meals. In the well-studied laboratory rat (Fitzsimons & LeMagnen, 1969; Kissileff, 1969), as well as in humans (de Castro, 1988; Engell, 1988; Phillips, Rolls, Ledingham, & Morton, 1984), prandial water consumption accounts for up to 90% of total water intake (see review by Kraly, 1990). I have yet to read a thoroughly satisfying explanation for this phenomenon. One thing is clear: When food is eaten, its processing requires considerable water in the gut. There is therefore an obligatory shift of water from elsewhere in the body into the gut during the digestive process (Almli & Gardina, 1974; Deaux, Sato, & Kakolewski, 1970). This is of course only a short-term state, in that the sequestered water is reabsorbed into the blood as digestion comes to an end, but there must be some penalty nevertheless in terms of reduced blood or cell volume. Prandial water consumption seems to be an ideal means of reducing the need to borrow body water during and after meals. To the extent that the animal or the person can supply exogenous water, the ongoing water/osmotic balance need be only minimally disturbed during meals. Of importance is that unlike the case with food, excess water consumed for this temporary process can be rapidly excreted from the body as it is absorbed into the blood from the gut.

In a preliminary test of the concept that one important function of prandial water intake is to lessen the osmotic shift (or other unpleasantries) associated with eating large meals, my colleagues and I divided rats into two groups and gave each group access to food for only 2 hr per day. Each group also had access to water for 12 hr per day. For one group, the 2-hr access to food occurred in the middle of the 12-hr period of access to water; for the other group, the food was available in the middle of the dry 12 hr. Two hours is insufficient time for adult rats to derive enough energy each day to maintain their weight, and so all rats lost some weight. However, those animals that were allowed to drink prandially ate more food and lost weight at a significantly slower rate. Rats without access to water during meals ate less and subsequently lost weight significantly faster (L. J. Stein, S. Roddy, R. C. Bolles, and S. C. Woods, April, 1983, unpublished observations). When animals are forced to consume all of their daily food in a restricted interval, the ability to maximize meal size is an obvious asset. Prandial water, like cephalic insulin, may facilitate this process. It is noteworthy that treatments that reduce prandial drinking, such as vagotomy (Kraly, Jerome, & Smith, 1986), are also associated with a reduction of meal size (Snowden, 1970; Snowden & Epstein, 1970).

Implications of a Model Suggesting That Eating Can Be Dangerous

Numerous predictions follow from the thesis that I have advanced in this article. I explore a number of the more obvious of these in this section.

Meal Size Should Normally Be Small

Given that eating poses a problem that is reflected in elevated levels of fuels in the blood, animals should, in an ideal environ-

ment, routinely eat very small meals so as to lessen the impact of any individual meal. This is exactly what happens. Collier and his colleagues showed that when there is essentially no cost to acquiring food, animals of a variety of species opt to eat a large number of small meals each day (Collier, 1982, 1989). They can be considered nibblers in that the individual episodes of eating are short. However, when costs are added to the system, these same animals eat fewer and larger meals. They presumably reach a compromise between what is optimal physiologically (small meals) and the cost of obtaining each individual meal. The change does not happen instantly, however (Collier, 1982, 1989), and I suspect that the animal, as it adapts to consuming larger and larger meals, also learns to anticipate such meals by secreting more and more cephalic insulin and developing other adaptive responses. As long as the environment is perfectly predictable, large meals can be consumed and well tolerated. Cephalic insulin and other processes enable such consumption.

There is also evidence that eating a larger number of small meals is relatively beneficial to humans in terms of lowering glucose and lipid levels in the blood on both an acute and a chronic basis (Fábry, Hejl, Fodor, Braun, & Zvolankova, 1964; Gwinup, Byron, Roush, Kruger, & Hamwi, 1963; Irwin & Feeley, 1967; Jenkins et al., 1989) as well as causing other beneficial metabolic changes (Bray, 1972; Bray, Zachary, Dahms, Atkinson, & Oddie, 1980; Cohn, Joseph, Bell, & Oler, 1963; Metzner, Lamphiear, Wheeler, & Larkin, 1977; C. M. Young et al., 1972). The farther apart individual meals are spaced, the better are the metabolic consequences (Beebe et al., 1990). Conversely, eating fewer and larger meals is associated with increased risk of cardiovascular disease (Bray, 1972; Fábry & Tepperman, 1970).

Organisms Must Adapt to Large Meals

If the capability to secrete cephalic insulin is compromised, animals should be expected to reduce their meal size. One way in which this could be accomplished would be to disallow adequate anticipation of what is to come. When animals are put into a novel situation, they eat smaller meals (Barnett, 1956; Bolles, 1962). Of more importance, when they are given novel foods to eat, they also eat very small quantities (Barnett, 1956; Richter, 1953; Rzoska, 1953). Rozin and colleagues (Kalat & Rozin, 1973; Rozin, 1976; Rozin & Kalat, 1971) investigated this neophobic behavior extensively and concluded that animals must learn that food is safe. Reducing this complex behavior to a binary system of interpretation such as "safe" or "unsafe" may overly simplify the situation. I believe that animals also learn the specific metabolic consequences of eating their food and therefore how much they can comfortably ingest at one time. As a specific food stuff, or a specific eating environment, becomes more familiar, increasingly larger individual meals can be consumed and tolerated.

This relates to what I call the "rich food" phenomenon. When one visits another country for the first time, a country with a different and quite distinct cuisine, there is an initial tendency not to eat large meals. Of course palatability and social factors can override the normal checks on meal size, and so mistakes are made. I remember well my first visit to France and Parisian restaurants. The sauces and the desserts were incredibly delicious and rich. I overate several times and suffered severe stomach upset and heartburn for my efforts. However, a steady diet of such exquisite food conditions one's constitution in the true sense of the word. When one knows what to expect from food, one knows how to prepare for it. When one does not, one either demonstrates (sometimes incredible) restraint when one eats or risks the consequences.

Investigators who research food intake by animals often put them onto particular feeding schedules so as to optimize conditions for their particular investigations. For example, when one is studying potential satiety factors and their properties, it is routine to adapt or habituate the animals to a particular feeding regimen. This usually consists of a period of food deprivation each day followed by the availability of the animal's food for a test interval. In my laboratory, rats typically are deprived for 4 to 7 hr and then are given a palatable liquid diet for 30 min. Rat chow is then available until the next day's deprivation (e.g., Kulkosky, Breckenridge, Krinsky, & Woods, 1976; Stein & Woods, 1981). Such a schedule ensures that the animals will eat at a particular time of day (conveniently chosen to suit the experimenter) and will likely eat a large meal. After the period of habituation, the animals also typically eat a meal of relatively constant and therefore predictable size so that even if meal size between animals is quite variable, within-animal comparisons can be meaningfully made across days.

I have noticed that only very rarely are data from the habituation period published. (See an example by Mook, Kushner, & Kushner, 1981, and an excellent analysis of the phenomenon by Williams, 1968.) After all, the usual point of those reports is to extol the virtues of yet another satiety factor, not to take a stand on the philosophy of eating meals. The increase of meal size that occurs over days is more obvious and well documented for animals that are sham feeding, however (e.g., Davis & Campbell, 1973; Van Vort & Smith, 1987).

In our laboratory, what occurs during the habituation period for normally feeding rats is almost stereotyped. Relatively little is consumed when the palatable diet is presented on the 1st day. Over days, the amount eaten in 30 min gradually increases, and it begins to approach asymptotic consumption after 10 to 14 days. I suspect that animals simply learn what to anticipate each day and that the cephalic insulin response (to a small test dose of the diet) increases in parallel with the increase in meal size. I have commented on this phenomenon previously (Woods & Kenney, 1979).

Preventing Cephalic Insulin Should Reduce Meal Size

An alternative way to compromise cephalic insulin would be to cut the vagus nerve, the neural link between the brain and the endocrine pancreas (Woods & Porte, 1974), or else to administer drugs that block neurally elicited insulin secretion. The former is the preferred strategy because the latter typically interferes with salivation and swallowing as well. Vagotomized animals and vagotomized people eat smaller meals (e.g., Snowden, 1970; Snowden & Epstein, 1970).

The argument can be made that this phenomenon is caused by the myriad digestive problems associated with vagotomy and not with compromised cephalic insulin per se. However, several years ago the clever ploy of denervating only the insulin-secret-

ing B cells was developed. A drug that selectively destroys the rats' own B cells is initially given to them. Once it is established that the animals cannot secrete insulin (i.e., that they are completely diabetic), they are given a transplant of new B cells from histocompatible donors. These new cells respond well to changes of blood sugar, but they are not innervated; that is, there is no neural pathway by which the brain can directly stimulate them. Such animals have no cephalic insulin secretion (Louis-Sylvestre, 1978b; Trimble, Siegel, Berthoud, & Renold, 1980). Even though their digestive system functions normally, these animals eat meals that are smaller than normal (Inoue, Bray, & Mullen, 1978). Animals that cannot secrete cephalic insulin compensate behaviorally and keep the excursions of postprandial fuels into the blood as small as possible.

Fuel Mobilization Should Be Inhibited Postprandially

To the extent there is a real or potential danger to having elevated fuels in the blood, the postprandial period is one of especial risk. Because of this, any behaviors likely to cause the mobilization of endogenous fuels into the blood should be reduced or inhibited at this time. Exercise is associated with sympathetic arousal (Christensen & Galbo, 1983; Galbo, 1983; Scheurink et al., 1989a) and with fuel mobilization (e.g., Ahlborg, Felig, Hagenfeldt, Hendler, & Wahren, 1974; Galbo, 1983; Scheurink & Steffens, 1990; Scheurink et al., 1989b), and everyone is aware of the taboo against exercising soon after eating. (Those who have actually tried it, especially vigorous exercise, are aware of the feeling of discomfort that occurs.) There certainly appears to be some merit to this advice. Danguir and Nicolaidis (1980) amassed considerable evidence that there is an almost absolute reciprocity between eating (or receiving nutrients) and sleeping in rats. After they eat, they sleep. This postprandial depression of behavior is, of course, well known and well studied (e.g., Bernstein, 1975). A sleeping or resting animal that has recently eaten is mobilizing little if any fuel from its storage depots, and endogenous fuels are therefore not adding to the burden of the meal.

As an interesting parallel, researchers who study satiety describe it as being a coordinated, almost stereotyped sequence of related behaviors (Smith, 1984). After a rat stops eating a meal, it goes through a brief interval of grooming behavior and mild activity and soon goes to sleep or at least rests very quietly (Antin, Gibbs, Holt, Young, & Smith, 1975). This pattern, termed the *complete behavioral sequence of satiety,* has become a criterion of sorts to differentiate true satiety from other factors that might cause an animal to stop eating prematurely (Smith, 1984; Smith & Gibbs, 1985; Woods et al., 1981). One function of this behavioral pattern may be to reduce the risk of engaging in behaviors that would mobilize fuels during the postprandial period.

A link can also be made to the literature relating meal size with the postmeal interval. The majority of experiments on this topic have yielded a positive correlation between these two variables: When an animal eats more food, it waits longer until it eats again (LeMagnen & Tallon, 1966). Such behavior is obviously consistent with the hypothesis that each meal poses a risk factor to an animal's system and that restraint from eating during the postprandial period has real benefits.

Fuel Mobilization Should Inhibit Eating

The converse of the preceding argument is that if endogenous fuels have been mobilized because of acute metabolic needs, feeding should be simultaneously inhibited so that fuels in the blood do not attain even higher levels. In fact, eating is inhibited immediately after exercise (Epstein, Masek, & Marshall, 1978; Holm, Bjorntorp, & Jagenburg, 1978; Oscai & Williams, 1968; and see review by Brownell & Stunkard, 1980), as well as during certain stress situations (Schachter, Goldman, & Gordon, 1968; and see Morley et al., 1985); both situations involve the mobilization of stored fuels into the blood. Certain stressors are associated with increases of food intake (Morley, Levine, & Rowland, 1983), but the stressors (as well as administration of the individual stress hormones) that activate the hypothalamic-pituitary-adrenal axis (and presumably increase blood glucose as a consequence) cause decreases of food intake (see Morley et al., 1985).

Small increases of glucose directly into the hypothalamus also decrease food intake (Panksepp & Meeker, 1976). In regard to this, the administration of a small amount of glucose when animals are exercising causes an excessive increase of plasma glucose as well as elevated levels of stress hormones in the blood (Winder et al., 1988). The point is that eating is more likely to occur during metabolically "safe" intervals when the impact of the meal is likely to be minimal.

Meal Anticipatory Responses May Become Maladaptive

The tendency to anticipate meals and make appropriate (learned) homeostatic adjustments, although adaptive in a relatively constant and predictable environment, may become maladaptive in certain situations. Before addressing this issue directly, I return to the drug-taking analogy developed earlier in this article. Recall that when the administration of a drug becomes predictable, animals make anticipatory responses that serve to lessen the drug's impact, hence contributing to drug tolerance. Recall also that if only the stimuli predictive of a drug are presented and not the drug itself, the anticipatory response creates an effect opposite to what the drug would have caused. An animal anticipating alcohol (and not getting it) becomes hyperthermic, an animal anticipating morphine becomes hyperalgesic, and so on.

It is easy to extrapolate this phenomenon to account for drug withdrawal. Consider the heroin addict who, several times a day, takes a fix in customary surroundings. One day, either because of a lack of funds to purchase more or because the supply has dried up, the addict is faced with the situation of still habitating the normal haunts but having no drug to take. The cues in this environment, as they do on the drug-taking days, elicit the learned compensatory responses, and the addict becomes hyperalgesic—that is, supersensitive to pain. The addict hurts. The pain is real and at least partly caused by the self-generated conditioned response.

Symptoms of withdrawal from drugs are universally opposite in nature to symptoms created by the drugs (for reviews of this concept, see Hinson & Siegel, 1980; Jaffe, 1985; Siegel, 1983). Alcohol is a depressant; alcoholic withdrawal is characterized by hyperactivity, tremors, and nervousness. Withdrawal from

stimulants is characterized by extreme depression. Withdrawal from analgesics such as heroin is characterized by hyperalgesia. Siegel (1984) pointed out that when the drug addict is removed from customary surroundings, withdrawal is far less severe. Similar conclusions were reached by Maddux and Desmond (1982). The point of all of this is that the learned compensatory response becomes maladaptive when elicited inappropriately; it can in fact cause disruptions of the body's homeostatic balance as severe as the drug itself but in the opposite direction. The spiraling problem of addiction hence becomes predictable. Dangerous drugs perturb the body in such a way that it reflexively defends itself. As the process becomes routine, the body anticipates the threat and does what it can to circumvent it; when the drug is no longer available but drug-taking cues are still present, these same life-saving compensatory responses disrupt the body in a manner that can best be alleviated by taking the drug again. It is the discomfort of withdrawal that maintains drug-taking behavior, not the reasons for which the drug was originally taken; in extreme circumstances, the conditioned withdrawal responses can lead to death (Siegel, Hinson, Krank, & McCulley, 1982).

What about the anticipatory responses related to eating? Do people go through an analogous phase of food withdrawal? Powley (1977) suggested that the cephalic secretion of insulin as animals begin to eat creates a degree of biochemical imbalance (specifically, hypoglycemia) and that this in turn stimulates greater appetite. In his schema, cephalic insulin provides a feedforward stimulus that causes animals to eat more. Hypothalamically obese animals have a larger cephalic insulin response than do lean controls (Berthoud et al., 1981; Louis-Sylvestre, 1976), and they eat larger meals (Brobeck, Tepperman, & Long, 1943; Hoebel, 1965; Kennedy, 1950). Powley (1977) suggested that this exaggerated cephalic response may contribute to the obesity of these animals. Herman and Polivy (1980), in an innovative series of experiments, expanded on this theme and found that when humans are below their ideal weight (i.e., when they are "restrained" eaters; see Herman & Mack, 1975), whether obese or lean, their cephalic responses (salivation, in their experiments) are exaggerated. This would presumably enable the consumption of larger meals when animals or people should be (at least in a biological sense) eating more food and increasing their adipose stores.

A debilitating clinical phenomenon, reactive hypoglycemia, may be related to the tendency to secrete unneeded excess insulin in anticipation of or in response to meals. This syndrome is characterized by the oversecretion of insulin during eating. So much insulin is secreted that sufferers of this disorder become severely hypoglycemic; that is, whereas in normal persons the level of glucose rises in the blood after eating, persons with reactive hypoglycemia may experience a drastic lowering of glucose levels when they eat, and this is associated with feelings of discomfort and can lead to fainting or coma (Bennion, 1985; Permutt, 1976; Rotwein, Giddings, & Permutt, 1982). Such people experience extreme sensations of hunger during these episodes. The analogy to drug withdrawal is obvious.

Reactive hypoglycemia is alleviated by drugs that block the neural link between the brain and the insulin-secreting B cells (Veverbrants, Olsen, & Arky, 1969), which suggests that the problem may be a supersensitive or overlearned cephalic insulin response. In accordance with this, there is at least one report that vagotomy cures reactive hypoglycemia in humans (Boulet, Vidal, Joyeux, & Mirouze, 1954). It is reasonable to speculate that former dietary habits enabled the secretion of insulin to become conditioned to a number of food cues (perhaps tastes) and that as the available food stuffs or eating habits changed, the learned response persisted and became maladaptive and perhaps clinically dangerous.

When I was actively researching conditioned insulin secretion and its consequent conditioned hypoglycemia, one group of rats was inadvertantly overlooked at feeding time in one experiment. When the conditioned stimulus was subsequently applied, the rats, without their usual reserve of quick endogenous energy, secreted insulin, became severely hypoglycemic, and died (S. C. Woods, R. A. Hutton, and W. Makous, 1969, unpublished observations). The ability of such learned responses to alter normal physiologic controls is obviously very powerful. Analogous results were obtained by Valenstein and Weber (1965). They found that rats deprived of all food and given a sweet saccharine solution to consume died significantly sooner than rats similarly deprived and given unflavored water to drink. R. Deutsch (1974) subsequently replicated this study and found that such rats had a conditioned hypoglycemic response to the sweet taste of the saccharin.

Reactive hypoglycemia has only recently received official recognition as being a bona fide clinical disorder. It has been highly touted in the popular literature as the underlying cause or explanation for numerous physical and psychological symptoms (e.g., Abrahamson & Pezet, 1951; Bennion, 1983; Fredericks & Goodman, 1969). However, until recently, many physicians ignored it as a genuine physical syndrome, pointing to the normal variability of postprandial blood glucose levels in asymptomatic people and to the presence of similar psychological symptoms in the absence of hypoglycemia (Bennion, 1985; Permutt, 1976; Rotwein et al., 1982). Symptoms of reactive hypoglycemia were therefore attributed to psychosomatic causes of unknown origin. A revealing disclosure was made by the editor of the journal *Clinical Diabetes* in an editorial on reactive hypoglycemia. Even though "countless" patients had been referred to him for diagnosis or treatment or both of reactive hypoglycemia, he could find nothing wrong with them and insisted that "I have *never* seen a patient with reactive hypoglycemia" (Raskin, 1985, p. 74)

The American Diabetes Association (1982) only recently acknowledged the syndrome's existence. I believe that the nature of the syndrome may partially account for its questionable status. I recall one session several years ago at the annual meetings of the American Diabetes Association. Reactive hypoglycemia had come up as a topic after an oral presentation, and a lively discussion ensued as to whether it was a legitimate clinical syndrome. A practicing physician gave a thumbnail sketch of a patient who, in his clinic, when given an oral glucose tolerance test, developed severe hypoglycemia and almost passed out. He admitted the patient to a hospital and, once the patient was safely in bed, administered a second oral glucose tolerance test; the patient was totally asymptomatic. After the session, I ascertained from the physician that in his clinic, the patient had sat at a table and consumed a cola-flavored glucose solution, whereas in the hospital, the patient had consumed an unflavored glu-

cose solution while sitting in bed. It was obvious to me that the clinic test provided far more cues likely to be associated with normal eating than did the hospital test. To the extent that learned responses were a factor, the data are consistent.

It is noteworthy that although the range of glucose values and related symptoms of sufferers of reactive hypoglycemia vary greatly, within any individual patient the responses are "repetitive and stereotyped" (Bennion, 1985, p. 85). The reported greater incidence of symptoms in patients when at home than in the office or clinic and the resultant variability of observed symptoms in the clinic (Bennion, 1985; Palardy et al., 1989; Permutt, 1976; Rotwein et al., 1982; Service, 1989) may well have helped endow this syndrome with its former questionable status.

I have often been amused by the fact that the most universally accepted treatment strategy for reactive hypoglycemia is the consumption of a large number of small meals each day, preferably meals containing few carbohydrates (American Diabetes Association, 1982; Permutt, 1976; Rotwein et al., 1982). The amusement derives not so much from the fact that this is exactly what should be done (even though no clear rationale other than outcome has ever been given) as from the fact that the same dietary regimen is recommended for people with diabetes mellitus (Vinik & Wing, 1990), a syndrome with exactly the opposite glycemic symptoms after meals. One effect of this regimen, in both syndromes, is to disrupt the habitual pattern of the intake of foods while simultaneously lessening the metabolic impact of meals and hence reducing the incidence of potentially harmful situations.

I think that to the extent that learning or conditioning plays a role in the development of symptoms of reactive hypoglycemia, established behavioral techniques might be applied therapeutically. The obvious choice to eliminate a learned response is extinction (in this case, presenting the food-related stimuli and never allowing actual food ingestion), but this is not feasible because people have to eat. Another choice might be counterconditioning, but I know of no scientific studies in which it has been applied to this syndrome.

Aversions Should Develop to Large Meals

If food (or at least the act of taking in food) is indeed associated with such dire consequences, why do conditioned aversions to eating fail to develop? After all, for the past 20 years psychologists have been inundated with information on the ease of developing conditioned aversions to stimuli associated with food and with subsequent negative effects (e.g., see Braveman & Bronstein, 1985). Should not similar aversions arise whenever one overindulges? In practice, this may actually happen. The problem is terribly confounded with the necessity and the strong reward value of food itself. There is also the complexity based on amount eaten: When relatively small amounts of food are eaten, there is presumably a relative dominance of positive aftereffects; as the amount of the same food eaten is increased, the negative aspects assume more importance (see Booth, 1985), and it is not clear how the positive attributes change. The net outcome of a particular meal is therefore generally unknown, and the integrated outcomes of thousands of individual meals over a lifetime are almost impossible, to predict.

The complexity of the situation may be reflected in the present controversy concerning the determination of true satiety. As discussed, a plethora of new compounds (mainly peptide hormones) has recently become available to behaviorists interested in the causes and the prevention of overeating (Gibbs & Smith, 1986; Morley et al., 1985; Smith & Gibbs, 1985; Woods & Gibbs, 1989; Woods, Porte, Strubbe, & Steffens, 1986). In the typical experiment, a "satiety factor" is given to an animal just before it gets food, and the amount eaten is determined. Satiety factors are so-named because they reduce the size of a meal in relation to the effect of a control compound. However, many factors can and do reduce the amount eaten independently of creating a normal sensation of satiety. Sickness, or general malaise, is often associated with reduced food intake (J. A. Deutsch & Gonzalez, 1978; Kulkosky, 1985). Stressors often reduce meal size (Morley et al., 1985; Schachter et al., 1968), and any treatment causing general incapacitation (e.g., soporific doses of depressant drugs; muscle relaxants) reduces eating behavior. In order to determine whether animals eat less because they feel full or because there is some other mitigating condition, elaborate behavioral paradigms have been developed.

To be complete these days, a study must show that a putative satiety agent does not cause the development of conditioned taste averions (the lack-of-illness argument), that it does not reduce other behaviors (the specificity argument), and that it elicits the complete behavioral sequence of satiety (the normality argument). In spite of such controls, skeptics still maintain that there is an element of aversion to such drugs (J. A. Deutsch & Gonzalez, 1978; J. A. Deutsch & Hardy, 1977). Both parties in such debates may well be correct. Eating to the point of fullness or beyond should have both positive and negative aftereffects, and endogenous hormones normally secreted at that time might therefore become associated with mixed results. My colleagues and I have recently found evidence for this. Neuropeptide Y is a peptide that causes rats to eat very large meals (Clark, Kalra, Crowley, & Kalra, 1984; Levine & Morley, 1984; Stanley & Leibowitz, 1984). We have verified this but found that the same amount of this peptide also causes the formation of conditioned taste aversions (Sipols, Brief, Ginter, Saghafi, & Woods, 1987).

It is tempting to try to stretch the hypothesis presented in this article to account for eating disorders such as bulimia or anorexia nervosa. (In fact, Polivy & Herman, 1985, made a somewhat comparable argument in a compelling review of the effects of dieting and especially refeeding.) Instead, I simply point out that a common symptom of patients with these eating disorders is a pathological fear of food and the consequences of consuming it (Woods & Brief, 1988). To the extent that food is a homeostatic threat, it is reasonable to expect some people to develop extreme affective reactions to it. Food may well have become a genuine stressor to sufferers of eating disorders. Broberg, Dorsa, and Bernstein (1990) recently reported that bulimic women report feeling nauseated and secrete vasopressin into the blood in response to the sight, smell, or taste of a palatable food. Vasopressin is recognized to be a marker of nausea in humans (Rowe, Shelton, Helderman, Vestal, & Robertson, 1979).

Conclusion

In this article, I have tried to make the point that whereas food itself is a necessity and operants to obtain it are successfully reinforced, the act of taking food into the body and assimilating it is not. On the contrary, food intake has many attributes of a particularly disruptive event. Just as people learn to tolerate the administration of dangerous drugs, so they learn to tolerate the intake of food. They make anticipatory responses that serve to minimize its impact on the body; they limit the total amount eaten at any one time so as to reduce the impact of individual meals; they limit their postprandial behavior so as to minimize the need to recruit endogenous fuels to interact with those that they have eaten; and they become sympathetically aroused when they eat. I have also suggested that defenses against overeating may become burdensome, perhaps contributing to the syndrome of reactive hypoglycemia.

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Received August 17, 1990
Revision received January 7, 1991
Accepted January 22, 1991 ■