

Chapter 6

Adjusting Food Intake to Meet Homeostatic Demands: Implications for Anorexia Nervosa

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INTRODUCTION

All living organisms continually monitor and adjust a multitude of internal variables in order to keep their biological processes operating at consistent and optimal levels. The 19th-century physiologist Bernard paid cogent tribute to the significance of a stable internal environment when he noted that "The constancy of the 'milieu interieur' is the condition of a free and independent existence" [1]. Early in the present century, Cannon introduced the word "homeostasis" to refer to the complex biological responses necessary to maintain a steady state in the body [2].

Food intake plays an essential role in homeostasis. Virtually all of an organism's functions ultimately depend on food, and a multitude of biological and psychological factors exert an influence on feeding and metabolic activity. These include hormonal level, body temperature, neurotransmitter activity, fluid levels, metabolic fuel reserves, past experience, psychological mood, and others. All of these factors have specific requirements for optimal function, and all of them exert some influence on food intake to achieve this end.

Under ideal conditions, the needs of different bodily functions place compatible demands on the food control system, and the consequences of food intake resulting from these demands are almost uniformly beneficial. This ideal does not always hold, however, and

homeostasis often involves compromise. In a situation where a food-deprived individual wishes to lose weight, for example, or when eating causes gastrointestinal disturbance, there is pressure both to eat and to abstain. The amount of food consumed in such cases reflects the combined effects of all feeding pressures, both positive and negative, acting on the individual at that moment, and this can be seen as an attempt to maximize overall function in accord with current needs and resources.

Anorexia nervosa is an example of a disorder in which different needs make conflicting demands on the food intake system. On the one hand, body weight drops so low that death from starvation may be imminent, and there is an urgent need for additional metabolic fuel. On the other hand, a number of powerful factors can act to inhibit feeding. Some of these inhibitory factors may be primary to anorexia nervosa, and others are a secondary consequence of starvation. Nevertheless, they all act to inhibit food consumption and weight gain.

The remainder of this chapter provides an overview of some of the factors known to exert a controlling influence on food intake, with particular reference to those that may play a role in the symptomatology of anorexia nervosa. These include osmotic pressure, body temperature, gastric emptying rate, food palatability, learned food aversions, zinc availability, and cognitive determinants. Other factors could have been included in this list, but those presented here will serve to il-

illustrate the concept that homeostatic constraints may limit food intake, even in individuals whose body weights are critically low. Each factor is discussed in two parts: The first summarizes its role in feeding, and the second explores possible implications for anorexia nervosa.

FACTORS INFLUENCING FOOD INTAKE

Osmotic Pressure

Water is required for the metabolism of most foods, and the regulation of food and water intake are closely related. Ingestion of hypertonic foods causes the movement of extracellular fluid into the stomach, and if this shift becomes excessive, the organism protects itself from further loss by decreasing its food intake. This protective mechanism is particularly noticeable under conditions of total water deprivation, which drastically reduces eating in most species [3]. Also, concentrated foods, regardless of their caloric content, are more filling than foods with lower osmotic pressure [4]. Overhydration affects food intake in an opposite manner, so that increased eating occurs following dilution of plasma salts or excessive water loading [5].

The duodenum is particularly sensitive to changes in osmotic pressure. Hypertonic stimulation in this area reflexively triggers release of enterogastrone, a hormone that slows the rate of gastric emptying [6] and reduces hunger [7]. These actions both protect against further fluid loss.

Osmotic Pressure and Anorexia

Rapid changes in body fluid levels are typical of malnutrition [8], and anorexic patients are often severely dehydrated. The abuse of diuretics, which occurs commonly in anorexia nervosa, can by itself lower weight by as much as 10 kg [9]. Partial diabetes insipidus, leading to excessive loss of body water through the urine, is also common in anorexia nervosa [10]. To the extent that dehydration is present, anorexic patients are subject to a compensatory pressure to avoid food to protect against further fluid loss. Until re-hydration is achieved, efforts to increase food intake operate in opposition to this osmotic defense mechanism.

Body Temperature

Regulation of body temperature has a high priority for warm-blooded animals, and a variety of mechanisms ensure that temperature stays within narrow limits. During heat stress, for example, mammals may sacrifice needed water to lower their body temperatures through evaporative heat loss.

Food consumption generates a considerable amount of heat. This occurs not only because heat is released by

the chemical activity of digestion, but also because feeding causes a sympathetic activation of brown fat [11]. This tissue, which is specialized for heat production, is very sensitive to alterations in nutritional state, undergoing rapid increases in weight and thermic activity after even a single meal [12]. Food is refused when body temperature is elevated, which helps to avoid additional thermal stress, and food intake increases when mammals encounter a cooler environment [13].

Several years ago Brobeck [14] formulated a "thermostatic" theory of food intake regulation, which suggested that maintenance of a stable and optimal body temperature is so important for survival that it forms an essential basis for making the decision whether or not to eat. One component of this theory is that a rise in body temperature serves as a satiety signal. Recent investigations have suggested that the thermogenesis caused by dietary activation of brown fat may be part of such a signal. Meals are terminated quickly if they generate a high respiration rate in brown fat, whereas meals that induce a lower rate of brown fat activity continue for a longer period of time [15].

Body Temperature and Anorexia

A common symptom of anorexia nervosa is decreased basal temperature. Patients complain of constant chilliness, and their extremities are often cold and blue. In one study of 100 anorexic patients, 80 had rectal temperatures of 96.6 degrees F or below, and some had temperatures as low as 93.0 degrees [16]. This reduced temperature may reflect a last-ditch effort to apportion metabolic fuel that ordinarily would be spent on heat production to other functions critical for life [17], although in extreme cases hypothermia itself becomes life-threatening for anorexics.

Normally, one would expect an unequivocal pressure to increase thermogenesis, and therefore food intake, in response to reduced body temperature. In anorexia nervosa, however, there is an impaired ability to activate heat loss mechanisms when temperature rises too far, and any heat source, internal or external, can rapidly produce hyperthermia. Wakeling and Russell [18] have reported that when one forearm is immersed in warm water, anorexic patients develop an abnormally high, and subjectively uncomfortable, elevation in central body temperature before peripheral vasodilatation begins, and even then the response progresses very slowly. This reduced ability to dissipate excess heat disappears after patients gain weight. It probably reflects an effort to conserve needed water by minimizing evaporative heat loss, because normal subjects who become dehydrated also exhibit abnormally slow vasodilatation in response to heat [19].

A rapid rise in body temperature during feeding, coupled with an impaired ability to dissipate excessive heat, may trigger a premature satiety signal in some anorexic patients. Wakeling and Russell [18] have reported that ingestion of a meal causes the temperatures of anorexic patients to quickly reach or surpass those of normal controls, whose temperatures remain constant during feeding. When otherwise-normal subjects lose weight from food deprivation, an unusually large meal is required to produce satiety, and hunger reappears rapidly. In contrast, subjects with anorexia nervosa feel full after consuming a 400-calorie lunch, and postprandial satiety persists as long, or longer, than it does in controls who eat a similar meal [20].

Gastric Emptying

Several converging lines of evidence suggest that gastric emptying rate may serve an important function in the control of food intake. Appetite typically is reduced when there is a reduction in the rate that food leaves the stomach. Thus, the anorectic drug fenfluramine, which reduces meal size and prolongs the duration of satiety [21], produces a profound inhibition of gastric emptying in rats [22]. In addition, tolerance to the gastric slowing produced by fenfluramine follows a time course that closely matches tolerance to its anorectic effects.

A number of factors can act to slow gastric emptying. One is simply the presence of hypertonic food [6,23]. This causes the release of enterogastrone, which in turn slows passage into the duodenum of any remaining stomach contents [24]. Other factors that reduce gastric clearance rate include strenuous physical exercise [25], high environmental temperature [26], and an excessive accumulation of body fat [27].

Moderately increased gastric clearance rates are associated with increased food intake, but if the emptying rate becomes too rapid, an opposite effect occurs. This is particularly evident after damage to the vagus nerve, which causes a disorder known as the "dumping syndrome" in man. The premature emptying of food into the duodenum after vagotomy is accompanied by epigastric discomfort, early satiety, and nausea. Patients usually learn to avoid it by taking small, frequent meals [28].

Gastric Emptying and Anorexia

Recent evidence suggests that abnormal gastric clearance rates may contribute to the accelerated onset of satiety often reported by patients with anorexia nervosa. In otherwise healthy humans, low body weight tends to be associated with moderately rapid gastric clearance and an associated increase in appetite. However, the gastric clearance rates of patients with anorexia nervosa are often abnormally slow, typically requiring

more than twice the usual time [29]. This disturbance may be primary to anorexic symptoms in some patients, because abnormally slow emptying rates have been reported to persist even after significant weight gain [29]. In other patients, reduced clearance rates may be secondary to dehydration [23] and strenuous exercise [25], which slow gastric emptying and are common symptoms of anorexia nervosa.

An occasional anorexic patient may exhibit a greatly accelerated rate of gastric emptying. Dubois [29] reported that one of his patients, out of a group of 15, exhibited an abnormally rapid gastric clearance, with rates in various test situations ranging from two to eight times faster than control values. This is reminiscent of the so-called "dumping syndrome" seen after vagotomy [28], and it raises the possibility that some anorexic patients may suffer from a vagal abnormality.

Food Palatability

Palatability is an important determinant of food intake, and a reduction in the sense of taste causes a corresponding reduction in appetite. Thus, gustatory deafferentation causes a decrease in both food intake and feed efficiency, and the body weights of rats that are deprived of their sense of taste will drop even when the diet remains unchanged [30].

Other things being equal, the less pleasant a food tastes, the more satiating it is. When rats are restricted to a diet that has been made unpalatable by the addition of a disliked taste, body weights may drop substantially [31], whereas a diet of highly palatable foods will elevate energy intake and induce obesity [32].

Palatability influences food intake and utilization through its effect on the "cephalic" phase of digestion. Cephalic reflexes, which are triggered by the sensory aspects of a meal, serve to ready the gastrointestinal tract to move and absorb food, prepare the viscera to metabolize and store nutrients, and provide the organism with immediate feedback about the ultimate postingestional consequences of food [33]. Included among these reflexes are changes in gastric motility and in the secretions of saliva, gastric juices, pancreatic enzymes, and insulin. One example of a potential consequence for body weight is that the better a food tastes, the greater the peak insulin release during the first minutes following meal onset [34]; this in turn delays the onset of satiety and increases the proportion of a meal that is stored as fat.

Sweet foods usually taste less pleasant after a meal. Cabanac [35] has called this phenomenon "alliesthesia," meaning "changed sensation," and he has reported that normal subjects rate sweet tastes as less pleasurable after ingesting a glucose solution than they do when they are hungry.

Food Palatability and Anorexia

Anorexic individuals exhibit a severe reduction in their sense of taste. Compared with controls, they have difficulty both in differentiating a test solution from water and in correctly identifying a taste quality as bitter, sour, sweet, or salty [36]. Food intake drops when the sense of taste is impaired [30], and hypogeusesthesia probably contributes to the lowered body weight of anorexia nervosa.

Patients with anorexia nervosa also experience less alliesthesia than controls after a meal. This defect appears to be independent of their reduced body weight, because differences between anorexic patients and controls persist even after any contribution of body weight is statistically removed by covariance analysis [20]. It also seems unlikely that the reduced alliesthesia of anorexic patients is due to a lower satiety level following a glucose preload, because evidence indicates that anorexic individuals feel just as full as controls immediately after a meal [20]. Interestingly, the absence of any decrease in postmeal taste sensation appears to be related to a tendency for anorexic patients to overestimate their own body size. Garfinkel and his associates [20] reported that impaired alliesthesia occurred more often in anorexics who overestimated their body size than in those who did not (see Chapters 10 and 11 in this book). This suggests a pervasive self-perceptive deficit.

Learned Food Aversions

Taste preferences decrease rapidly for foods associated with illness, and learned food aversions are adaptive in helping the organism avoid poisons and correct dietary deficiencies [37]. There is a biological predisposition to associate tastes with any feeling of malaise that develops within a few hours after ingesting food, regardless of whether the food actually caused the disorder [38].

Numerous treatments have been demonstrated to initiate a taste aversion. For example, hypotensive agents produce a conditioned aversion to tastes with which they are paired in rats [39], and human cancer patients exhibit a diminished taste preference for foods eaten immediately before receiving a chemotherapy treatment in which nausea is a side effect [40]. Damage to the vagus nerve causes an abnormally rapid rate of gastric emptying and, because of the ensuing malaise, rats develop an aversion to new foods consumed after vagotomy [41].

A learned association with malaise causes the abandonment of many diets that lack an essential nutrient or that are eaten during a long-term illness. In rats, the decline in food intake during terminal cancer is accompanied by an aversion specific to the diet consumed

during tumor growth, and food consumption increases immediately if a different diet is introduced [42]. Similarly, rats fed a diet that lacks an essential nutrient such as thiamine soon avoid that diet, preferentially selecting almost any available novel food rather than continuing to eat the diet that is deficient [43].

Learned Food Aversions and Anorexia

Many of the conditions necessary to acquire taste aversions are present in anorexia nervosa. Food consumption produces unpleasant physiological sensations and affective responses in many patients, and feelings of being bloated or nauseated are often reported [44]. Whereas control subjects usually feel more "relaxed" after a test meal, anorexic patients describe themselves as more nervous, tense, depressed, and irritable [20]. Anorexic individuals consistently suffer from low blood pressure [45] and disturbances in gastric emptying [29]. These symptoms are of interest in light of experimental studies that have demonstrated a tendency to avoid foods associated with hypotensive drugs [39] or vagotomy [41].

Nutrition deficits involving zinc, copper, and total iron-binding capacity are common in anorexia nervosa [36]. It may be that these deficiencies initiate dietary aversions that contribute to the reduced intake of anorexia patients.

Zinc Availability

Zinc is an essential element in humans and animals. It is important for the function of some 70 metalloenzymes, which play key roles in RNA and DNA activity, protein synthesis, energy metabolism, and vitamin utilization [46]. Zinc deficiency has been associated with impaired appetite, taste loss, growth retardation, gastrointestinal malfunction, dermatitis, depression, decreased sexual activity, impaired immune function, delayed puberty, and an increased level of circulating corticosteroids [47-50].

There is growing concern that there may be a chronic borderline zinc deficiency in the United States. In a recent study of 22 self-selected diets in the United States, 18 contained less than the minimum daily requirement of zinc [51]. Sandstead [52] reviewed the status of zinc nutrition in middle and upper income families in the United States and concluded that zinc deficiency is common, due primarily to poor eating habits and lack of meat in the diet. Individuals at particularly high risk for zinc deficiency include diabetics, those undergoing rapid growth, people on prolonged intravenous therapy, and those suffering from gastrointestinal disorders or in chronically debilitated states [53]. Corticosteroids cause an increase in urinary zinc excretion [54], and stress of

any kind will magnify a borderline zinc deficiency.

Zinc Availability and Anorexia

Numerous symptoms are common to both zinc deficiency [47-50] and anorexia nervosa. Included among these are impaired appetite, growth retardation, taste loss, gastrointestinal malfunction, delayed puberty, low sexual activity, and depression.

As noted above, borderline zinc deficiency may be present in a sizable portion of the population. The nutritional impairment associated with anorexia nervosa magnifies this risk, because weight loss lowers zinc stores, and depressed appetite reduces zinc intake. Additional factors that might predispose anorexic patients to a zinc deficiency include poor glucose tolerance [16], gastrointestinal abnormalities [29], and onset of anorexic symptoms at a time normally associated with rapid physical growth.

At least one clinical study has provided direct evidence for a zinc deficiency in anorexia nervosa. In a study of 30 patients, Casper and associates [36] reported that plasma zinc levels and taste acuity were significantly depressed compared with control levels. After several weeks of treatment, which included zinc supplementation, patients exhibited increased plasma zinc levels and weight gains. Taste function also improved substantially, although it still was abnormal.

The clinical symptoms of zinc deficiency may be less readily apparent in anorexic patients than in normals, since an abnormally low metabolic rate in anorexic patients [55] probably reduces tissue requirements for zinc. However, Casper's [36] data suggest that zinc supplementation may be a useful adjunct to treatment, since patients in this study usually regained their appetite within a few days after treatment began. The possibility that insufficient zinc contributes to the symptoms of anorexia nervosa needs further investigation.

Cognitive Factors

Physiological stability usually receives the focus of attention in any discussion of homeostasis, but psychological equilibrium is equally vital to the organism. All of an organism's functions are interrelated in an inseparable manner. Many, if not all, physiological changes affect psychological state, and cognitive processes exert a direct effect on physiological function.

Cognitive factors play an important role in determining what weight levels should be maintained. This is especially true in societies where good food is plentiful, but obesity is considered unattractive. Our national preoccupation with dieting and a lean figure sometimes leads to behaviors that conflict with optimum physiological function. Nisbett [56] has marshaled evidence that obese people who perceive themselves as over-

weight share many behavioral and physiological similarities with organisms that are semistarving, including emotional lability, increased levels of plasma free fatty acids, low interest in sex, and reduced energy. He suggests that this occurs because most obese individuals persistently try to maintain a weight below that dictated by purely physiological considerations, and in this sense, are "starving." In these cases homeostatic balance requires a trade-off between the benefits associated with increased social acceptance and the reduced function resulting from an inadequate supply of easily available metabolic fuel.

Cognitive Factors and Anorexia

There is little question that cognitive factors play an important motivational role in the dogged pursuit of thinness that is characteristic of anorexia nervosa. Anorexia is overrepresented in the upper social classes [57], where the sociocultural pressures for women to maintain a thin shape are especially compelling [58]. The likelihood of developing anorexia also is high among dance and modeling students [59], whose careers often demand thin figures.

The adoration of thinness in our culture mitigates against the recognition of low body weight as a disorder and provides a source of reward for the anorexic individual. In one study of college females, only 5% thought that they were too thin, even though 38% were statistically underweight [60]. Branch and Eurman [61] found that at least half of a sample of friends and relatives of anorexic females "admired" the "patients' appearance" and "envied" their "self-control and discipline" around food.

Patients with anorexia nervosa are abnormally dependent on cognitive factors in determining when they feel full. Garfinkel and his associates [20] found that the feeling of satiety following a standard test lunch persisted much longer in anorexic patients than in controls when the lunch appeared to contain many calories, but not when the caloric content appeared low. This unusual reliance on cognitive factors may be fostered in part by an impaired sensitivity to other satiety cues. For example, anorexic patients are less accurate than controls in estimating the amount of food given them through a stomach tube [62], and they often complain of feeling unable to rely accurately on internal sensations as a cue to stop eating.

CONCLUSIONS

For most healthy individuals, a drop in body weight triggers a set of compensatory events that work in synchrony toward rapid recovery of the lost weight. Hunger increases, edible substances are actively sought, food

utilization becomes more efficient, and satiety is difficult to attain.

A different picture is presented by patients with anorexia nervosa. Although these individuals exhibit some of the expected weight-gain responses, such as increased feed efficiency, others are notably absent. In fact, the net sum of homeostatic pressures often leads to a downward spiral of weight loss that can persist to the point of starvation.

Numerous factors can reduce food intake, and several of these may contribute to the symptoms seen in anorexic patients. In this chapter we have discussed evidence that decreased food consumption occurs in response to a loss of body fluids, a rise in body temperature, an abnormally slow (or precipitous) rate of gastric emptying, a diminished capacity to taste food, dietary aversions triggered by illness or nutrient deficiency, low zinc availability, and cognitive pressures to avoid food or lose weight. All of these phenomena may operate to some degree in anorexia nervosa.

Given the variety of factors that contribute to reduced intake and the awareness that these inhibitory mechanisms can be activated by multiple means, one would expect to find many differences among anorexic patients in the spectrum of inhibitory pressures that are present, the degree to which they operate, and the extent to which they are primary or secondary to the disorder. Concerning this last point, some causes of decreased food intake may be both primary and secondary to anorexia. An example of this would be a patient whose low food intake is aggravated by a dehydration that derives both from a partial diabetes insipidus (primary dehydration) and from an abuse of diuretics (secondary dehydration). Another example would be an individual in whom reduced intake follows an impaired taste function that is due both to a defect in the gustatory system and to a zinc deficiency resulting from inadequate intake. It is becoming increasingly clear that anorexia nervosa is not a single disorder. Unraveling its mysteries will require a multifaceted approach.

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