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Understanding eating disorders

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Abstract

The outcome in eating disorders remains poor and commonly used methods of treatment have little, if any effect. It is suggested that this situation has emerged because of the failure to realize that the symptoms of eating disorder patients are epiphenomena to starvation and the associated disordered eating. Humans have evolved to cope with the challenge of starvation and the neuroendocrine mechanisms that have been under this evolutionary pressure are anatomically versatile and show synaptic plasticity to allow for flexibility. Many of the neuroendocrine changes in starvation are responses to the externally imposed shortage of food and the associated neuroendocrine secretions facilitate behavioral adaptation as needed rather than make an individual merely eat more or less food. A parsimonious, neurobiologically realistic explanation why eating disorders develop and why they are maintained is offered. It is suggested that the brain mechanisms of reward are activated when food intake is reduced and that disordered eating behavior is subsequently maintained by conditioning to the situations in which the disordered eating behavior developed via the neural system for attention. In a method based on this framework, patients are taught how to eat normally, their physical activity is controlled and they are provided with external heat. The method has been proven effective in a randomized controlled trial.

Keywords: Eating disorders; Starvation; Neuroendocrine adaptation; Behavior; Treatment

Introduction

Almost all patients with eating disorders (95%) are women. The aim of research on these women is to improve their condition. If we fail to improve outcome, we most likely should change our strategy. And failure to improve outcome is the result when the field is reviewed. Hence, there is no evidence that outcome in anorexia nervosa has improved over the last 50 years (Steinhausen, 2002) and the outcome in bulimia nervosa also remains poor (Quadflieg and Fichter, 2003). Briefly, the chance of recovery from eating disorders is less than 50% in ten years, about 25% of the patients become chronically ill and the mortality varies between 0% and 25% in published studies. Bringing patients into partial remission, i.e., patient may still show some eating disorder symptoms, is considered easy, but 50% or more relapse within less than a year. For these reasons, eating disorders are considered chronic disorders.

Ben-Tovim et al. (2001) noted that when patients with eating disorders were evaluated five years after an initial examination, it was not possible to determine an effect of the treatments the patients had received in the intervening years. And when the effects of the treatment of eating disorders are reviewed, which has been done many times, it is clear that there is no compelling evidence that existing treatments are effective. Thus, there is no evidence that behavioral treatments have an effect on adult patients (Hay et al., 2003,2004) and the claim that family-based behavioral treatment of young anorexic patients is effective is based on weak evidence; the authors of the only study of its long term effect wrote that the improvement at follow-up could be "attributed to the natural outcome of the illness" (Eisler et al., 1997). It has been suggested that cognitive behavioral therapy is effective in bulimia nervosa, but a recent, very thorough, series of studies found that only 19% of a total of 194 bulimic patients who entered such treatment were in remission four months after treatment (Halmi et al., 2002). Treatment with psychopharmacological drugs has not been demonstrated to be effective on any type of eating disorder (Pederson et al., 2003).

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Why is it that all the efforts to understand the cause of eating disorders have yielded treatment strategies with such limited success? We suggest that the reason is that the physiological responses to shortage of food, which is the main evolutionary pressure under which human biology has evolved, has been ignored in clinical accounts of anorexia and bulimia nervosa.

Feast, famine and thrifty genes

It is estimated that presently one billion of the world's population (17%) is malnourished (Behrman et al., 2006). This number is decreasing and starvation has probably been even more common during early evolution. Most likely, humans have been exposed to erratic fluctuations in food availability and only those who have been able to cope have survived (Diamond, 2003). Those are bearers of "thrifty" genes that make intake of large amounts of food possible in times of plenty and hence make survival possible in the subsequent and inevitable periods of famine (Diamond, 2003; see also Schneider, this issue). It seems likely that the phenotypic expression of thrifty genes includes the capacity for intermittent high levels of physical activity as well (Chakravarthy and Booth, 2004). But "thrifty" genes are thrifty only under normal conditions and to our disadvantage in present day society where food is continuously abundant. Hence, the increase in body weight, reduction of physical activity, obesity and, eventually, obesity-induced diseases such type 2 diabetes (Diamond, 2003). However, while genes that are "thrifty" under certain conditions can facilitate the development of disease under other conditions it is questionable if such genes should be referred to as "disease" genes.

The phenotypic expression of anorexia nervosa

Anorexia nervosa starts by a reduction of food intake. An increase in physical activity then follows, a phenomenon that has been demonstrated in a wide variety of animal species (Mistlberger, 1987). This effect may be related to stimulation of dopamine transmission in the striatum (Bassareo and Di Chiara, 1999). Also, ovarian cyclicity ceases (Wade and Jones, 2004), and this can also occur in normal weight women who are excessively active, e.g., those engaging in athletic sports. Increased physical activity and amenorrhea are physiological responses to food shortage, not signs of disease. Subsequently, lowering of body temperature and slowing of heart rate occur as anorexia develops. No one disagrees that these physiological changes are caused by the shortage of food. But what about the psychiatric symptoms of anorexia nervosa? Patients suffering from anorexia are depressed, anxious and display obsessive behaviors and thoughts. Are these behaviors and cognitions also caused by starvation? We suggest that they are and explain why in the text below.

We will concentrate our discussion on anorexia nervosa, which is the prototypical eating disorder in patients who may subsequently develop other types of eating disorders, e.g., bulimia nervosa. There are more similarities than differences between the two conditions. For example, in her classical description of anorexia nervosa, Bruch (1962) described bulimic behavior as part of anorexia, and Russell (1979), who introduced bulimia nervosa as a separate eating disorder diagnosis, referred to it as a special form of anorexia. About 20% of patients with anorexia display bulimic behavior, i.e., bingeing and purging, and most bulimic patients have a history of anorexia and their bulimic behavior is preceded by brief episodes of starvation. We view anorexia and bulimia as two phases of the same disorder. There are two main reasons why they have been kept separate. Firstly, anorexic patients are underweight and bulimic patients are normal weight and so the patients are conspicuously, but only superficially, different. Secondly, the failure to treat eating disorders leads to the introduction of more diagnostic groups and the belief that they are all different.

The traditional explanatory model of eating disorders

Rather than viewing all symptoms of anorexia nervosa as signs of starvation, the psychiatric symptoms are often analyzed separately and thought of as causes of eating disorders. For example, Bruch (1962) noted hyperactivity in anorexia but no differences between anorexia and other forms of malnutrition, nor indications of organic damage. Yet, she chose to interpret her observations as indicating that the behavior of her patients was "closely related to schizophrenia". Probably for this reason, her attempts to treat her patients failed. In fact, Bruch (1962) reported that "patients got worse after treatment".

The model that Bruch (1962) used to explain and treat eating disorders remains essentially unchanged today. In that model, anorexia is considered a mental disorder, which is caused by another mental disorder, e.g., schizophrenia causes anorexia nervosa. The model is, however, quite difficult to understand. Is it for example, applicable to other, perhaps all, mental disorders, such that one disorder causes another? If so, the model must be expanded to: a mental disorder causes a mental disorder causes a mental disorder … etc. And the question arises: where does the "first" mental disorder come from? Clearly an uncomfortable situation.

Anorexic genes and the neurotransmitters that mediate the symptoms

A modern version of the explanatory model of Bruch (1962) has been formulated by Kaye et al. (2003, 2004), who hypothesize that there are genes that predispose individuals to develop a variety of anxiety disorders and that the time line of the phenotypic expression of these genes is (1) childhood obsessive–compulsive disorder (OCD), (2) anorexia nervosa and (3) anxiety disorders in adulthood. Thus, these hypothetical genes first *cause* OCD, then anorexia nervosa and, in adulthood, anxiety disorders. As a second part of this hypothesis, it is suggested that an increase in the turnover of brain 5-hydroxytryptamine (5-HT) mediates between the genes and the symptoms: "We hypothesize that people with anorexia nervosa have a trait related *increase* (authors italics) in 5-HT neuronal transmission that occurs in the premorbid state and persists after recovery … (which) … contributes to uncom-

fortable symptoms such as obsessionality, perfectionism, harm avoidance, and anxiety" (Kaye et al., 2003). While this hypothesis is formulated with admirable clarity, it will be difficult to test. It seems *a priori* unlikely that there are genes that first cause OCD, which is more prevalent in boys than in girls, then anorexia nervosa, which is more prevalent in girls than in boys, and then a wide variety of anxiety disorders, which are far more prevalent than eating disorders and more prevalent in women than in men (Yonkers et al., 2003). While this hypothesis is clearly a scientific hypothesis, it is not surprising that, so far, there is no evidence to support it. Most candidate gene analyses have yielded inconsistent or negative results (Gorwood et al., 2003).

We anticipate that genes that enable humans to tolerate prolonged starvation will be found. The search for such genes should, however, probably focus on other phenotypes than anxiety, e.g., those that are capable of a high level of physical activity because of their obvious survival value (Diamond, 2003; Chakravarthy and Booth, 2004). Anorexic patients are likely to have such genes, which should not be labeled "disease" genes.

The second part of the hypothesis, that overactivity in the 5-HT system in the brain *causes* anorexia nervosa (Kaye et al., 2003), is also unsupported by most published papers. We argue that the physiological, psychological and other changes in anorexia are epiphenomena to starvation. The change in brain 5-HT synthesis, which has been measured by the level of 5-hydroxyindol acetic acid (5-HIAA), the metabolite of 5-HT, in the cerebrospinal fluid (CSF), provides an example of this. Thus, starved anorexic patients have a low level of 5-HIAA in the CSF, because they eat only little protein (tryptophan is the amino acid precursor of 5-HT which is derived from dietary intake of protein) (Kaye et al., 1988). When food intake is gradually restored and, as a consequence, body weight is normalized, the level of 5-HIAA in the CSF is also normalized (Kaye et al., 1988). While one paper found that 5-HIAA was increased above normal levels in the CSF of weight restored anorexics (Kaye et al., 1991), the effect was very small and, probably for this reason, other studies have failed to replicate this finding (Mantzoros et al., 1997).

5-HT is one of the best-known inhibitors of food intake (Hayes et al., 2004). It seems highly unlikely, if at all possible, that the synthesis and turnover of an inhibitor of food intake increases in the brain when anorexic girls eat more food and increase their body weight. It is not surprising that there is no evidence that drugs affecting brain 5-HT are helpful in treating eating disorders (Pederson et al., 2003) and such drugs are best withdrawn from clinical practice (Södersten and Bergh, 2004).

The cause of eating disorders is known

Most texts on eating disorders begin by stating that anorexia and bulimia are "multifactorial" disorders of unknown etiology (Kaye et al., 2003). This lack of clarity is unsatisfactory and unnecessary because the cause of eating disorders is known.

We call attention to the semi-starvation study carried out by Keys et al. (1950). Healthy male volunteers, who had never been ill, were asked to eat less food during a period of three months. As a result, they showed not only the expected physiological changes but also the psychiatric symptoms of patients with eating disorders. These included depression, OCD- and psychosis-like symptoms, theft and many more. The effects of the experimental semi-starvation were not unlike what had previously been reported to occur under conditions of enforced starvation in humans, which also include disintegration of family and social life (Keys et al., 1950), which is very common also among patients with eating disorders.

It is surprising that these results are only seldom brought up in discussions of eating disorders. Only rarely can a hypothesis can be said to be "proven", but the study by Keys et al. (1950) more or less proves that eating too little food for a prolonged period of time *causes* most of the symptoms that are shown by eating disorder patients. There is no need to postulate that there is a mental or a non-mental predisposing illness, which is a likely reason why none has been found. A common critique is that the subjects in the semi-starvation study were male volunteers and therefore very different from young women. An alternative interpretation is that the effects of starvations are so strong that even healthy males will develop the symptoms of anorexia nervosa when starving.

Young women who develop anorexia are often thought to voluntarily starve themselves. If true, this adds to the similarities between anorexia nervosa and the semi-starvation study of Keys et al. (1950) because the men in that study volunteered to participate.

Also, both male and female athletes voluntarily eat less food to reduce their weight in forthcoming competition. The lower the required weight the more severe eating disorder symptoms they develop (Kiningham and Gorenflo, 2001; Loucks and Nattiv, 2005).

Why women?

The marked sex difference in eating disorders has not been explained but it is long known that women can stand starvation better than men, possibly because of the sex difference in body fat content (Keys et al., 1950; Hoyenga and Hoyenga, 1982; Cortright and Koves, 2000). In addition, sex differences in the metabolic responses to short-term food deprivation have been reported (Corssmit et al., 1994). On the basis of this limited information, it seems possible that men and women may respond differently to a short period of food deprivation, i.e., the initial challenge that may trigger the development of anorexia nervosa. We tested this possibility by asking high school students to come to the laboratory at noon and eat a meal. Seventeen women, who were 16.4±0.4 (mean±SEM) years old and had a body mass index (BMI) of 20.1±0.5 kg/m^2 and 13 men, who were 16.2±0.5 years old and had a BMI of 22.1±0.7 kg/m^2, participated. They were allowed to eat as much food (Nasigoreng, Findus, Bjuv, Sweden, 400 kJ, 4.5 g protein, 1.8 g fat and 15 g carbohydrate/100 g) as they wanted on one day and they returned seven days later to eat again after having omitted dinner the day before and breakfast in the morning of the day of testing. Food intake was measured using

the procedure described below (Mandometer®, omitting the training curves used to treat patients). The procedure was approved by the ethics committee of the Karolinska Institute.

As expected, men ate more food than the women (Fig. 1A). More interesting, whereas the men ate even more food after deprivation the women did not (Fig. 1A). In fact, the women ate less food after deprivation. Thus, the men ate about 30% more food when deprived, but the women ate about 20% less (Fig. 1B). Fig. 1C shows that the men ate at a higher rate than the women and that the rate of eating increased after deprivation of food in the men but not in the women.

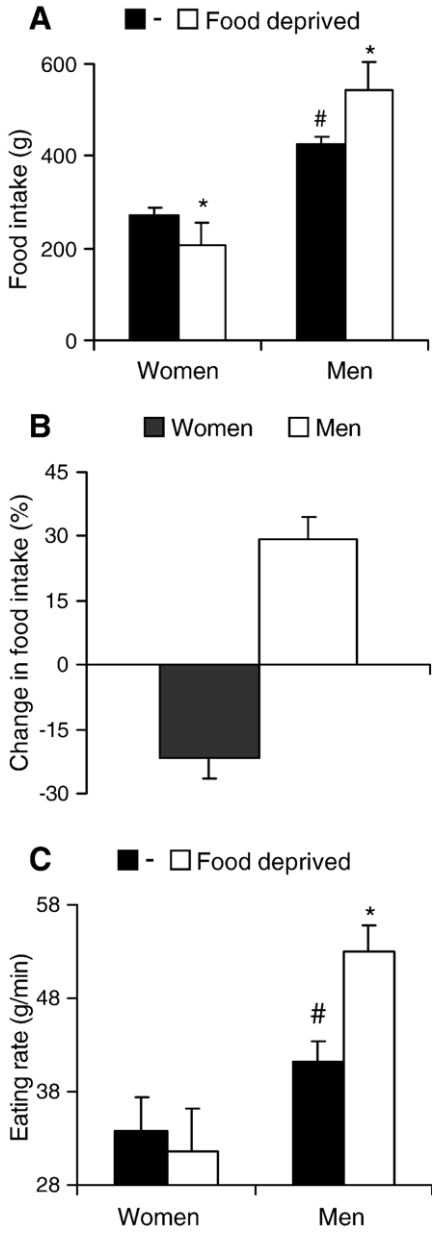

Fig. 1. Food intake in 17 female and 13 male high school students with normal body weight. The students ate a meal at lunch time (-) and returned one week later and ate another meal after omitting dinner and breakfast (food deprived) (A). Food intake after deprivation is expressed as percent of intake in the non-deprived condition in panel B. The rate of eating under these conditions is in panel C. $^{\#}P<0.01$ compared to women, $*P<0.01$ compared to non-deprived (t tests).

This experiment suggests that women have difficulty in compensating by eating more when deprived of food. In other words, dieting may be dangerous in women and in particular in those who are physically active and therefore need to eat more food, e.g., athletes (Loucks and Nattiv, 2005). However, in view of the scarcity of data on the effects of short-term food deprivation on sex differences in metabolism, the effect awaits an explanation.

The psychiatric symptoms in eating disorders

On the hypothesis that the symptoms of eating disorder patients emerge as a consequence of starvation it is easy to explain why patients, in addition to physiological symptoms, also show psychiatric symptoms, e.g., depression, OCD and anxiety. Depression is one of the best-described consequences of starvation in man. Keys et al. (1950) even found that, during nutritional rehabilitation of their starved subjects, there was a linear relationship between depression scores and the level of caloric intake. An interesting, subjective description of the feeling of depression and the other effects "on the mind", e.g., fatigue and loss of sexuality is given by a participant in a study by Dr Ansel Keys of the University of Minnesota School of Public Health (http://www.asph.org/document.cfm?page=793). The description includes the expected effect that starving subjects concentrate more and more on food, such that they eventually become "obsessed" with it. Concentrating on food, however, is obviously necessary when food is scarce. Just as it is inappropriate to refer to the amenorrhea of starvation as a sign of disease, it is a misunderstanding to label other physiologically useful responses as psychiatric symptoms (e.g., OCD).

Patients with eating disorders are anxious and fear becoming fat. We suggest that this cognitive aspect of both anorexia and bulimia is realistic rather than pathologic. Concentrating on food all the time anorexics realize that eating all the food they think about would make them overweight. In fact, Bruch (1962) reported that some of her anorexic patients became obese. Obesity is an aversive, highly undesirable condition. Aversive events are avoided and, as a cognitive concomitant, create a state of anxiety. A continuously avoided unpleasant event causes a progressive increase in anxiety and, unless the individual faces the aversive event, progressively more, similar events will elicit anxiety. These are very well-studied phenomena (Domjan, 1998) and rather than being signs of psychopathology they can be referred to as adaptive (Deakin, 1991).

On a physiological framework, the symptoms of eating disorder patients are understandable rather than "inexplicable" (Kaye et al., 2003), as they may appear if one works within the conventional model.

Neuroendocrine adaptations to changes in food availability

The neuroendocrine concomitants to increases in food intake and body weight are now intensely studied because of the worldwide increase in obesity. The focus is on leptin, a signal from peripheral fat stores to peptide-synthesizing neurons in the

arcuate nucleus (ARC) in the medial–basal hypothalamus and on its peptidergic connections to the hypothalamic lateral (LH) and paraventricular (PVN) nuclei and a few other subcortical nuclei (Cone, 2005). In addition, peptides such as cholecystokinin octapeptide are released from the duodenum in response to the ingestion of food and activate vagal afferents that terminate in the nucleus of the solitary tact in the brain stem thus making up the neural network of satiety (Cone, 2005). These neuroendocrine systems mediate the behavioral adaptations necessary to cope with the marked fluctuations in food availability that have characterized mammalian evolution. Thus, during starvation, body fat stores are depleted, blood levels of leptin are decreased and the synthesis of "orexigenic" peptides, e.g., neuropeptide Y (NPY) and agouti gene-related protein (AgRP), are increased while that of "anorexigenic" peptides, e.g., the proopiomelanocortins (POMC) are decreased in the ARC. POMC-, NPY- and AgRP-containing neurons project from the ARC to the PVN, LH and extrahypothalamic areas. These synaptic inputs are rapidly rearranged in response to leptin and other metabolic signals (Horvath, 2005). Thus, the neural networks of food intake are anatomically versatile and display synaptic plasticity, i.e., features that allow the flexibility needed to adapt to drastic changes in the supply of food. We suggest that many of the reported changes in the anatomy and neurochemistry of the hypothalamic circuitries of food intake are responses to environmental change, not causes of the ensuing behavioral adaptations.

While some forms of extreme human obesity can be related to genetic disruptions of the leptin signaling pathways (Farooqi and O'Rahilly, 2005), there is no compelling evidence that these pathways are irreversible changed in anorexia (with the possible exception of the AgRP–melanocortin system (Adan et al., 2003), an observation that needs to be replicated). Instead, the neuroendocrine changes in anorexia nervosa are most likely responses to the reduction in food intake and depletion of body fat. Thus, the level of leptin in the blood is decreased (Södersten et al., 2003) and the synthesis of NPY by the brain (Goldstone et al., 2002) and the level of NPY in the CSF are increased in anorexic patients (Gendall et al., 1999). These changes are reversed as the patients eat more food and regain body weight (Södersten et al., 2003; Gendall et al., 1999). Rather that merely assuming a role as an "orexigen" in a situation of food shortage, a hypothalamic peptide may take on different roles depending on physiological need. Recent evidence suggests that NPY, one of the best known "orexigens", actually inhibits the intake of food and facilitates hoarding, i.e., behaviors needed for finding and collecting food (Ammar et al., 2000; see also Schneider, this issue). Such food-anticipatory activities are very common in anorexic patients (Tappe et al., 1998).

An alternative framework

The neural substrates of food intake interact with the reward pathways in the brain (Volkow and Wise, 2005) although the anatomical neurochemistry that makes this interaction possible is not yet defined. A high level of physical activity causes dependence and, if prevented, ethanol-like abstinence in experimental animals (Werme et al., 2002). In his description of anorexia nervosa, Gull (1874) noted that the high physical activity of his patients seemed "agreeable". Physical activity and a reduction of food intake not only activate brain systems of reward but also those concerned with attention, i.e., the capacity to attend to sensory stimuli. The reward systems extend from the mesencephalic dopamine cell bodies in the ventral tegmental area to the nucleus accumbens in the ventral striatum and the attention system is the noradrenalin-containing cell bodies in the locus caeruleus in the brain stem that project to many forebrain regions (Bergh and Södersten, 1996). There is no need to postulate that these brain mechanisms are somehow changed in subjects who develop an eating disorder, only that they are engaged. Thus, we have suggested that eating disorders develop because it is rewarding to eat less food and be active (dopamine–reward system). Any clinician familiar with eating disorder patients have heard her/his patients say how good it felt to eat less and move more. As body weight gradually decreases and physical activity increases the experience of reward is replaced by an urge be active to avoid the symptoms of abstinence, just as when any other dependence develops. We have suggested that in this situation, anorexic behavior is maintained because it is conditioned to the stimuli that originally provided the reward (noradrenalin–attention system) (Bergh and Södersten, 1996). This neurobiologically plausible framework will probably need modification and, eventually, replacement by a better one.

Effective treatment of patients with eating disorders

Teaching patients how to eat is the main intervention in managing eating disorders. Many years ago, an anorexic patient told us: "I don't know how to eat, I don't know how to feel full",

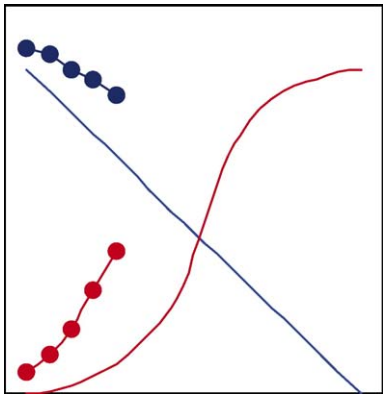

Fig. 2. Patients with eating disorders re-learn how to eat by adapting their intake of food to a curve displayed on a computer screen during their meal. This is possible because a patient sees her rate of eating (blue dots) appearing on the screen as she eats and can adapt her intake to a training curve that is simultaneously displayed on the screen (blue line). A rating scale for satiety appears on the screen at regular intervals and the patient rates her level of fullness by pressing on the screen. Patients re-learn how to feel full by adapting their ratings (red dots) to the sigmoid curve that mimics the development of satiety in normal weight people (red curve). There are no numerical values on the axes and the display looks the same throughout treatment. The figure displays an anorexic patient who fails to keep up with the eating rate and overestimated her level of satiety. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

when she first used Mandometer®, a system that gives feedback via a computer screen on how much to eat and at what rate and how to experience a proper level of fullness.

Mandometer® is a scale connected to a computer. The patient puts a plate on the scale and then she puts food on the plate. The computer stores the weight loss of the plate during the meal. This yields a curve of eating rate. At regular intervals, a scale (values ranging from 0 to 10) appears on the computer screen and the patient rates her feeling of fullness. The computer stores the ratings. This yields a curve of the development of satiety. During training, patients are asked to follow curves that are displayed on the computer screen (Fig. 2). A linear curve is used for practicing how to eat and a sigmoid curve is used for learning how to feel full. The patient is able to follow the training curves because she sees her own eating rate and satiety ratings on the computer screen during the meal (Fig. 2). The amount of food to be eaten is gradually increased and the duration of the meal is gradually decreased during treatment to make the patient re-gain a normal level of food intake, which is 300–350 g food consumed in 12–15 min (data generated by healthy volunteers). Satiety ratings start at 0 and end at about 6 on the 10-point rating scale (data generated by normal volunteers). The patients should eat ordinary food, and four changes in the parameters of the training curve for eating are made during the course of treatment. The sigmoid curve used to practice the perception of satiety (generated by healthy volunteers) is the same throughout treatment.

Mandometer® is used during the first part of treatment. Patients are also trained to eat under normal conditions and eventually, they should be able to eat most food items in normal social circumstances. On their way to recovery, patients may use Mandometer® in restaurants and other settings.

To facilitate re-learning how to eat, the patients rest in warm rooms after eating. This reduces the level of anxiety and prevents compensatory hyperactivity. The level of physical activity is carefully monitored and gradually reduced. In this treatment, it is hypothesized that the disordered eating behavior controls the anorexic or bulimic state. In support, the physiological and psychiatric symptoms are often normal only after the eating behavior is normal (Court et al., 2005). A description of our patients' condition at admission and at remission and an evaluation of the method of treatment by a randomized controlled trial has been published (Bergh et al., 2002). The evaluation also includes data on relapse during a five year period of follow-up (Bergh et al., 2002). Briefly, the chance of going into remission is about 75% in on average one year and the risk of relapse is about 10%. Patients in remission must be free of symptoms and they must be back in school or professional activities. Using strict remission criteria probably reduces the rate of relapse and may also explain why the patients who relapse do not relapse into as severe a condition as they were in at admission.

Conclusions

Overemphasis on the psychiatric symptoms of starvation and the belief that these are causes, rather than consequences, of eating disorders has not been beneficial to patients. Neither has the hypothesis that eating disorders are genetic disorders and that irreversible changes in brain neurochemistry mediate between genes and eating disorder symptoms been useful. We offer an alternative according to which anorexia and bulimia emerge as consequences of starvation. Eating disorders are considered eating disorders and training patients how to eat is therefore essential. Combined with interventions to facilitate normal eating, this method has been found effective in bringing 75% of patients into remission and keeping relapse at a relatively low 10% during a five-year period of follow-up. Perhaps because this model represents a paradigm-shift it has been slow to catch the attention of clinicians and scientists working within the conventional framework.

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