

# An Auto-addiction Opioid Model of Chronic Anorexia Nervosa

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*The phenomenology of chronic anorexia nervosa is compared with that of addictive states. A model is proposed in which brain opioids mediate the elation, neuroendocrine changes, and down-regulation of metabolism that occur in adaptation to dieting. The physiology of opioids is reviewed, and clinical and animal data are marshalled to support an auto-addictive model. Opiate blockade together with therapeutic approaches used in the addictions may prove helpful in this stubborn disorder.*

Chronic anorexia nervosa remains a stubborn, intractable disorder that does not yield to diverse psychotherapeutic and drug approaches. In this paper we propose that the pathophysiology of the chronic disorder may be of greater importance than the psychopathology. Opioid systems in the brain are assumed to play a fundamental role in adaptation to starvation and the down-regulation of metabolic set points. There is now substantial evidence that opioids are mobilized in states of prolonged food deprivation, and we are hypothesizing that they are the substrate for an auto-addictive process responsible for the relentlessness of chronic anorexia nervosa. In the auto-addictive model, anorexia nervosa involves a three-phase process. In the acute or initial phase there is a phobic fear of eating that evolves out of broader anxieties about maturing into the body of a woman with all of the associated responsibilities and role expectations. The anorexic patient then develops ritualistic, obsessional be-

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havior organized around dieting and exercising in order to restrict or burn calories. Fifty percent of patients then move into a phase of chronicity, which in our model cannot be understood solely in psychological terms and requires a corollary biological explanation. Anorexia nervosa may then be understood as a psychobiologic process in which dieting to achieve a prepubertal weight will then initiate a series of central nervous system changes that then perpetuate the disorder and in some instances make it irreversible. An auto-addiction may evolve over time to the pathophysiology of weight loss. Clinicians have long observed that the longer anorexic patterns exist, the more likely it is that the disorder will become irreversible (Crisp et al., 1977; Halmi et al., 1977). Our hypothesis is that the opioid systems are of fundamental importance in the biology of the disorder and in its chronicity and intractability. Relevant opioid physiology will be reviewed and then discussed in light of this hypothesis.

## **ANOREXIA NERVOSA AND ENDOGENOUS OPIOIDS**

Increased endogenous opioid activity in the cerebrospinal fluid (CSF) of anorexia nervosa patients was recently reported by Kaye et al. (1982). It was found only in patients who were severely underweight at the time and not in those in whom body weight was being maintained or restored. Total endogenous opioid activity was measured by a radioreceptor assay, in which the endogenous opioids compete with labelled enkephalamide for binding to opioid receptors in crude brain membranes. Although Gerner & Sharp (1982) found normal  $\beta$ -endorphin levels in the CSF of anorexia nervosa patients, they used a radioimmunoassay specific for  $\beta$ -endorphin. Thus, some endogenous opioid other than  $\beta$ -endorphin itself may explain the difference between these two studies. Moreover, the body weight status of the patients was not indicated by Gerner & Sharp but was shown to be critical by Kaye et al. (1982).

The origin of endorphin in the CSF appears to be of hypothalamic, or at least brain, rather than pituitary origin (Herbert et al., 1982; Hosobuchi & Bloom, 1983; Jeffcoate et al., 1978; Kraft et al., 1983; Krieger et al., 1979). Pituitary origin would require a reverse circulation from the pituitary to get into the CSF, which is possible but not likely. CSF endorphin levels are not influenced by hypopituitarism. Conversely, brain lesions that lower endorphin levels in the brain do not affect the pituitary levels. Furthermore, the regulatory factors for brain and pituitary endorphin levels differ, indicating different independent pools and roles.

## **NARCOTIC ANTAGONISTS AND ANOREXIA NERVOSA**

The effects of narcotic antagonists in anorexia nervosa are also indicative of a role of endogenous opioids in this disorder. Although examined for a questionable antilipolytic activity, one study supports a therapeutic

effect of naloxone in anorexia nervosa patients. (Moore et al., 1981) Weight gain per week was dramatically increased 10-fold in 12 hospitalized anorexia nervosa patients given a constant intravenous infusion of naloxone (3.2–6.4 mg/day). When naloxone was stopped, the patients returned to the previous low weight gain per week. Patients were simultaneously treated with the antidepressant amitriptyline (50–200 mg/day). The authors said that "a dietary intake of 3000–4000 kcal was aimed for," but it is not clear if it was achieved and whether this was altered by naloxone. Whether naloxone altered the amount of food ingested, its utilization, or both is not known. The same group of investigators more recently discussed the beneficial effect of naloxone in terms of blocking compulsive behavior (Mills & Medicott, 1984). Compulsive behavior is certainly a critical component of drug dependence as well as the syndrome of anorexia nervosa.

Responsiveness of the reproductive system to naloxone is also altered in anorexia nervosa. A single intravenous dose (0.2 mg/kg) raises LH and FSH in normals but was less effective in doing so in anorexics, particularly those in whom the amenorrhea follows the weight loss (Baranowska et al., 1984). FSH was not raised and LH was raised in only about half the patients. Higher opioid levels might make the naloxone blockade at a given dose less competitive. Although this difference could be due to functional antagonism of nonopioid mediated abnormalities, these data are certainly suggestive of, and in accord with, the proposed opioid-mediated mechanisms.

## OPIOIDS AND OTHER EATING DISORDERS IN HUMANS

In addition to the studies of endorphin systems in anorexia nervosa, investigators have examined the effect of opiates in other clinical conditions of appetite dysfunction. Dunger et al. (1980) reported an association between the hyperendorphinemic state and obesity in a child. Fraioli et al. (1981) described a 17-year-old male with congenital unresponsiveness to pain and elevated total opioid activity in the CSF, who also was obese. Naloxone decreased food intake in obese humans (Atkinson, 1982). Two out of three obese patients with hyperphagia as part of the Prader-Willi syndrome responded to naloxone by reducing their food intake (Kyriakides et al., 1980). There are other individual case studies that suggest a relationship between high endorphin levels (measured directly or by pain sensitivity), hyperphagia, and obesity (Givens et al., 1980; McKendall & Haier, 1983; Morley et al., 1983b; Pradalier et al., 1981). Increased opioid peptide levels are reported, then, in both states of starvation and obesity. Endogenous opioids may play a homeostatic role

in appetite regulation in humans at both ends of the spectrum in a manner that remains to be explicated, but which might be expected in light of the variety of opioid actions discussed in the next section.

## RELEVANT OPIOID ACTIONS

A number of opioid actions are also manifestations of anorexia nervosa. The former will be reviewed here and their relationship to anorexia nervosa will be discussed in the later hypothesis section, "Theoretical Relationship of Anorexia Nervosa and Opioids". Two categories of opioid actions are useful adaptations to starvation. First, they increase food intake to correct the starvation. Second, they adapt the organism to survival in the face of starvation, until nutritional repletion can occur.

The first response is much more extensively documented and is well known. Narcotics and the endogenous opioid peptides increase food intake when injected systemically or locally into the CSF or hypothalamus (Brown & Holtzman, 1979; Gosnell et al., 1983; Levine & Morley, 1983; Marks-Kaufman, 1982; McLean & Hoebel, 1983; Marks-Kaufman & Kanarek, 1981; Morley & Levine, 1981, 1983; Morley et al., 1983a,b; Sanger, 1981; Sanger & McCarthy, 1980, 1981; Tannenbaum & Pivorum, 1984; Walker et al., 1980). There are multiple subtypes of opiate receptors, including mu, kappa, and sigma. Agonists preferential for all receptor subtypes have been demonstrated to increase food intake in at least rats (Gosnell et al., 1983; Levine & Morley, 1983; McLean & Hoebel, 1983; Morley & Levine, 1981, 1983; Morley et al., 1983a, b; Sanger, 1981; Sanger & McCarthy, 1981; Tannenbaum & Pivorum, 1984; Walker et al., 1980). The endogenous opioid peptides dynorphin and  $\beta$ -endorphin have the same effect (Morley & Levine, 1981, 1983; Morley et al., 1983b; Sanger, 1981). In summary, the opioid peptides have a stimulatory effect on caloric intake.

Secondly, Margules (1979) has proposed that an endogenous endorphin system mediates the homeostatic adaptations to starvation. The endorphins protect the organism against starvation by conservation of energy and bodily resources and by reduction of physiological and metabolic functions to the minimum essential for survival. The physiological changes that take place in starvation and in anorexia nervosa seem to parallel those that occur when endorphin systems are activated. They have a number of conservatory actions, summarized as follows:

1. Constipation—This slows the transit through the gastrointestinal (GI) tract, and hence increases the extraction of all nutrients and water.
2. Water retention and famine edema—This is promoted by stimulation of vasopressin release, decreased emptying of the bladder, and reduction of the digestive secretions. Interestingly, in anorexia nervosa, vasopressin in the CSF is increased (Gold et al., 1983).

3. Body temperature falls.
4. Thyroid hormone release and calorogenesis diminish.
5. Blood pressure and vascular sympathetic tone decrease.
6. Respiration and the sensitivity of the respiratory center to carbon dioxide and hypoxia become depressed.
7. Emotional reactivity (fear and rage) is less intense.
8. Lethargy, drowsiness, and passivity occur.
9. Reproductive activities are inhibited. Sexual activity is not essential for the minimum survival status. Sexual desire is low during starvation. Follicle-stimulating hormone (FSH) and lutenizing hormone (LH) are reduced by opioids. Interestingly, these are glycosylated hormones, and the carbohydrate is in short supply during starvation. In anorexia nervosa, LH and FSH are low and show a prepubertal pattern. This may be either secondary to the weight loss or may precede it. Anorexia nervosa most commonly starts at the time of adolescence and the associated hormonal changes. The disturbance of food intake and the reproductive hormones are clearly closely linked in this disorder.

Functions 1 and 2 conserve bodily resources. Functions 3 through 8 decrease the metabolic rate and hence the metabolic need. Function 9 reduces species survival functions, which are not necessary to the preservation of individual organisms. These homeostatic adjustments, together with opiate analgesia and inhibition of sympathetic arousal, seem to represent a broad adaptation to the stress of starvation.

Margules argues that the sympathetic nervous system and glucagon are activated during the initial adjustments to fuel shortage. Then an endorphinergic system assumes responsibility for the more severe and long term adjustments. It is known that starvation-related, enduring metabolic changes are not dependent on the sympathetic nervous system. For example, some glucoregulatory effects of morphine are known to be in the direction of fuel conservation, whereas others may not be so. These could be components of the metabolic adaptations to starvation and will be discussed below.

If the opioids down-regulate metabolism as well as activating food intake, it is not surprising that anorexia as well as hyperphagia can be produced by opiate agonists (Sanger & McCarthy, 1980; Yim & Lowy, 1984). Suppression of feeding responses may be followed by their arousal, and these two opposing phases can be selectively blocked by either tolerance development or naloxone. Corresponding changes in body weight can occur. Under certain conditions of food deprivation, naloxone prevents the resulting weight loss, possibly by blocking metabolic down-regulation, while morphine conversely inhibits the activation of ingestive behavior.

A number of glucoregulatory effects of narcotic drugs and endogenous opioid peptides are known and may be part of the opioid system's pro-

posed role in the adaptation to starvation. Hyperglycemia is a classic effect of morphine (Jaffe & Martin, 1980; Margules, 1979; Morley, 1981). Morphine and the opioid peptides modulate release of a number of glucoregulatory hormones from the pancreas, including insulin, glucagon, somatostatin, and pancreatic polypeptide (Giugliano et al., 1982; Helman et al., 1983; Ipp, 1984; Ipp et al., 1978, 1980; Kanter et al., 1980; Margules, 1979; Morley, 1981; Morley et al., 1980; Reid and Yen, 1981; Schusdziarra et al., 1981, 1983a-f). Although the direction of the changes is not entirely consistent among the studies, they all indicate an influence of endorphins on these hormones. These differences may depend on the exact conditions. According to the proposed role in the metabolic adaptation to starvation, the activity of endorphins would be highly dependent on the basal metabolic state. The direction of the change could also be contingent upon which subclass of opioid receptor ( $\mu$ ,  $\delta$ ,  $\kappa$ , etc.) predominates and the levels of various nutrients (see below). Opioid peptides also modulate insulin action on glucose fluxes and may thus serve a function in the redistribution of glucose during stress (Werther et al., 1984). Release of pituitary glucoregulatory hormones is also modulated by the opioid systems, including adrenocorticotrophic hormone (ACTH) and, hence, cortisol, growth hormone, and thyroid hormone (Giugliano et al., 1982; Halmi, 1978; Margules, 1979; Morley, 1981; Morley et al., 1980). Opiates increase glycogenolysis induced by epinephrine and increase gluconeogenesis via both glucagon and ACTH release (Margules, 1979). Lipolysis may be activated (Jean-Baptiste & Rizack, 1980; Margules, 1979; Schwandt et al., 1981), mobilizing available energy stores that need not be used when adequate fuel supplies are available. These findings provide metabolic mechanisms for maintaining fuel supplies during starvation.

The brain is critically dependent on blood glucose for its fuel supply. During starvation, the brain is protected against glucose shortage by the maintenance of blood glucose at the expense of other organs (Margules, 1979). Although the brain is not dependent on insulin for its glucose utilization, other organs are insulin dependent. Glucose utilization in insulin-dependent organs is reduced by decreased sensitivity of the insulin-receptors and by decreased glucose-stimulated insulin release. Thus, glucose is directed away from the insulin-dependent organs to the brain. The metabolic set point is readjusted for protection of the brain. Although the role of opioids in this mechanism is not known, an unidentified pituitary substance related to ACTH, which could be an opioid peptide, is involved (Margules, 1979).

Generalized alteration of chronic metabolic set points after food deprivation is supported by several rat studies (Armstrong et al., 1980; Boyle et al., 1978; Coscina & Dixon, 1983; Hill et al., 1984; Levitsky et al., 1976). The efficiency of food utilization is enhanced after food deprivation. For example, after food deprivation, a return to ad libitum feeding restores

usual body weight without unusually high caloric intake (Boyle et al., 1978; Coscina & Dixon, 1983; Hill et al., 1984; Levitsky et al., 1976). An altered metabolic setpoint is indicated by a greater weight gain for a given hyperphagic response to increased food palatability. (Coscina & Dixon, 1983). In some experimental paradigms, body weight may not be totally regained despite a return to ad libitum feeding (Armstrong et al., 1980; Kanarek & Collier, 1983). In one study, after a prolonged period of food deprivation, body weight did not return to usual even with a return to ad libitum feeding (Armstrong et al., 1980). This is particularly true under circumstances of "activity induced self-starvation". In a report by Kanarek & Collier (1983), hyperactivity prevented recovery from food deprivation when a running wheel was available. This was extraordinary because rats food-restricted to certain times of day initially lose weight that they recover after adjustment to the feeding schedule. However, when allowed to run on a wheel, the rat ignores the food and runs itself to death. The authors did not relate their work to anorexia nervosa, but there are striking analogies. Although opioid mediation of these effects has not been examined, their influence must be considered. There is the suggestion that endorphins enhance the efficiency of energy use (Mandenoff et al., 1982). In this regard, increased palatability of food produces hyperphagia, obesity, and greater oxygen utilization. All three responses are blocked by naloxone, indicative of an endogenous opioid substrate. The direction of this change needs to be reconciled with the greater efficiency of energy utilization proposed to be associated with starvation. However, involvement of the opiates in alterations of the efficiency of energy expenditure must be considered. Variation in the efficiency of food utilization in anorexia nervosa patients is suggested by the fact that weight gain in this disorder is not precisely related to caloric intake (Pertschuk et al., 1983).

The opiates also inhibit reproductive function by modulating the release of LH, FSH, and gonadal hormones (Adler & Crowley, 1984; Bodnar et al., 1978a; Ferin et al., 1984; Morley, 1981; Morley et al., 1980; Van Vugt & Meites, 1980; Van Vugt et al., 1982). Changes in hypothalamic  $\beta$ -endorphin levels occur during different stages of the estrous cycle (Knuth et al., 1983). Sex-related differences in the opioid system have been found (Hong et al., 1981, 1982; Mueller, 1980; Wilkinson et al., 1983), which could be a factor in the marked dominance of anorexia nervosa in females over males. Disturbances in feeding and the reproductive system are closely linked. Amenorrhea and a prepubertal endocrine pattern of LH, FSH, and gonadal hormones are key signs of the disorder. Weight loss below a critical body weight accounts for these signs in only some of the patients, whereas in others amenorrhea may actually precede dieting. The return to normal body weight does not necessarily correct the hormonal pattern or restore the menstrual cycle. Thus, in certain cases the reproductive system disturbances occur in parallel with, rather

than as a consequence of, the starvation (Boyar & Katz, 1977; Brown, 1977, 1983; Casper et al., 1977; Fisch, 1977; Halmi, 1978; Nillius & Wide, 1977; Sherman & Halmi, 1977; Vigersky & Loriaux, 1977; Wakeling & DeSouza, 1983; Warren, 1977; Weiner & Katz, 1983). The onset of anorexia nervosa is generally shortly after pubescence. Therefore, changes in the opioid systems may underly both reproductive and metabolic changes clinically observed in anorexia nervosa. In the context of anorexia nervosa, the speculation is particularly interesting that gonadotropins may be cleaved from the same large molecular weight precursor as  $\beta$ -endorphin, i.e., from pro-opiocortin (Margules, 1978). At different stages of development, the precursor may be split in different ways. During childhood the ingestive actions of the endorphins may be primary, whereas during adolescence the reproductive hormones may be favored.

### FOOD DEPRIVATION: CHANGES IN ENDOGENOUS OPIOIDS AND OPIOID SYSTEMS

Release of endogenous opioid activity during food deprivation is suggested by several studies in rats. Two studies directly measure hypothalamic  $\beta$ -endorphin levels by radioimmunoassay after food deprivation. Complete starvation for 2-3 days decreased  $\beta$ -endorphin in whole hypothalamus (Gambert et al., 1980). Food restriction to 50% of normal altered hypothalamic  $\beta$ -endorphin levels (Knuth & Friesen, 1983). Depending upon the particular hypothalamic nucleus,  $\beta$ -endorphin increased, decreased, or was unchanged. Most of the fluctuations occurred simultaneously with the starvation-induced anestrus, which is a model for the amenorrhea of anorexia nervosa. Food restriction may also be a better model for anorexia nervosa than complete starvation. Indirect measures of naloxone-sensitive actions also suggest release of an endogenous opioid during food deprivation. Analgesia is heightened after 12 hours of complete starvation (Bodnar et al., 1978c; McGivern et al. 1979). The hypotension induced by 4 days of complete starvation is blocked by naloxone, suggesting an endorphin effect (Einhorn et al., 1982). Food deprivation-induced analgesia may be biphasic in nature, contingent upon its duration (Bodnar et al., 1978c; Hamm & Lyeth, 1984). This biphasic response may cause pathophysiology in opposing directions, depending on the duration and/or severity of food restriction. In addition to food restriction, the metabolic glucoprivation effected either by 2-deoxyglucose (2DG) blockade of glycolysis or by insulin hypoglycemia is associated with endorphin release. Radioimmunoassayable plasma  $\beta$ -endorphin was increased by 2DG and insulin, in doses which would induce feeding (Davis et al., 1982; Yim et al., 1982). For comparable increases in food intake, the endorphin release was greater for 2DG than for insulin, but it was significant for both. Although the hyperphagia and  $\beta$ -endor-

phin release do not always occur together, the  $\beta$ -endorphin release is a significant response to 2DG glucoprivation. Analgesia is another concomitant of 2DG- and insulin-induced feeding (Bodnar et al., 1978a,b, 1979a,b, 1983; Spiaggia et al., 1979). Although the 2DG analgesia is not blocked by naloxone, an opioid factor is indicated by the development of tolerance to 2DG analgesia and the cross-tolerance of 2DG analgesia and morphine. Rats tolerant to morphine are also cross-tolerant to 2DG analgesia. Conversely, adaptation to 2DG results in a tolerance to the analgesia but not the hyperphagic effects. Analgesia was measured by the flinch-jump threshold to an electric shock. In a study in humans, naloxone blocked 2DG-induced increase in food intake but did not reduce the subjective feeling of hunger (Thompson et al., 1982).

The behavioral effects of food restriction are in harmony with fluctuations in endogenous opioid activity associated with food deprivation. Food restriction to maintain rats at 80–90% of their body weight on ad and libitum feeding increased the self-administration of a variety of addictive drugs (Atrens et al., 1983; Carroll & Boe, 1984; Carroll et al., 1981; Meisch & Kliner, 1979; Oei, 1983; Takahashi & Singer, 1979). Although the authors did not attribute these behaviors to opioid changes or fluxes, they seem to support the proposed association between altered opioid activity and food deprivation. Perhaps the opioid release associated with chronic food deprivation produces a tolerance that then stimulates the self-administration of exogenous opiates and sets the stage for other addictive behaviors. Moreover, repeated administration of naloxone results in a sensitization to the effects of naloxone in ad libitum fed animals. However, this sensitization was prevented by food restriction to maintain the animals at 80% of their free-feeding body weight or by complete starvation for 24 hours (Snell et al., 1982). Again, an interaction of the endogenous opioid systems and food deprivation is suggested by the differential between the ad libitum fed and food-restricted states. Repeated administration of naloxone enhanced a number of, but not all, naloxone effects. Naloxone effects that were sensitized include the suppression of shock avoidance in rats, suppression of motor activity in mice, and enhancement of morphine analgesia in mice. Sensitization did not occur to naloxone-induced hyperalgesia in mice. The mechanism of sensitization is not known, but no change in naloxone binding was found. However, the conclusion important to our hypothesis is that there is an interaction between the feeding state and naloxone, an indicator of the involvement of endogenous opioid systems. The precise nature of this interaction remains to be defined.

Food deprivation even alters the responsiveness of the opiate system to effects on food intake itself. Morphine increases food intake when rats are fed ad libitum but decreases it after 24 hours of starvation (Sanger & McCarthy, 1980). An actual qualitative, as well as quantitative, difference exists. Naloxone suppression of food intake is diminished with longer

periods of food deprivation, being less after 48 hours than after 24 hours starvation (Brown & Holtzman, 1979). Similarly, naloxone suppression of feeding does not occur if rats are adapted to a restricted feeding schedule (Sanger & McCarthy, 1982).

## **INTERPLAY OF DIETARY FACTORS IN THE OPIOID MODEL**

Dietary factors may influence opioid responses and hence play a role in the proposed mechanisms. The self-imposed dietary abnormalities in anorexia nervosa may be perpetuating the disorder or may be nutritional self-selection to avoid a psychologically aversive reaction. Carbohydrates affect the opioid system. Effects have been found on receptor binding, responses to exogenous opiates, and endogenous opioid mediated function (Davis et al., 1956; Schusdziarra, 1983a,e; Werther & Hogg, 1984). The hyperglycemia of diabetes can alter opioid-related analgesia, insulin release, and food intake (Giugliano et al., 1982; Levine et al., 1982a,b; Simon & Dewey, 1981, Simon et al., 1981). Another type of dietary interplay is suggested by the preferential effects of morphine and naloxone on fat intake over carbohydrate or protein intake (Marks-Kaufman, 1982; Marks-Kaufman & Kanarek, 1981). Thus the type of caloric restriction may also be a factor in the biological changes induced by dieting and the resulting susceptibility to long term anorexic consequences.

## **THEORETICAL RELATIONSHIP OF ANOREXIA NERVOSA AND OPIOIDS**

There appears to be not only a psychopathology of anorexia nervosa but also a pathophysiology. Psychodynamic concepts suffice to explain the initial and acute stages of the disorder. They are insufficient to account for its chronicity, its stubborn resistance to treatment, and sometimes lethal course. The compulsive and relentless nature of the dieting, the subjective sense of loss of control over weight loss, dieting in the face of medical and social contraindications, and patient reports of dieting-associated elation all suggest an auto-addictive process. In this paper we have proposed that endogenous opioid systems somehow mediate this auto-addiction, and clinical experience and animal data are marshalled to support this hypothesis. Total endogenous opioid activity is increased in the CSF of anorexia nervosa patients. Food deprivation alters the levels of endogenous opioid peptides and endogenous opioid systems. The activation of endogenous opioids in starvation serves functions of both increasing food intake and down-regulating physiological and metabolic processes in an adaptation for survival. There is evidence that these are

opioid-mediated metabolic effects and that starvation may reset metabolic set points for prolonged time periods. Naloxone, a narcotic antagonist, produced a dramatic improvement in weight gain in anorexia nervosa patients in one study. The auto-addiction model allows for potential interactions with diet composition, other neurotransmitters, and the relationship between weight loss, gonadotropin inhibition, and amenorrhea.

The elevated total endogenous opioid activity in the CSF of anorexia nervosa patients who are markedly cachectic may result from starvation-induced opioid release. It is proposed that these endogenous opiates are the substrates for an auto-addictive state that reinforce anorexic behavior and perpetuate it over time. In anorexia nervosa, the increased endogenous opioid activity in the CSF may be a maladjustment of the internal homeostatic adaptations to starvation, as a result of prolonged dieting initially determined by psychodynamic forces. The patients may become psychologically and physically dependent on an altered energy expenditure and mood mediated by the endogenous opioid peptides. A maladaptive set point may become self-perpetuating. Opioids down-regulate metabolism in adaptation to starvation while the anorexic suppresses their concomitant appetite-stimulating properties. The binge eating and the intense craving for food that occur in anorexia nervosa may be due to a periodic breakthrough of the appetite-stimulating properties of opioids. Anorexic patients have a universal fear that any lapse of discipline will result in a total loss of appetite control and horrid obesity. These fears may be of excessively high drives rather than excessive fears of normal drives.

Hyperactivity is a characteristic sign of anorexia nervosa, which does not initially appear to fit the opioid addiction hypothesis and will require further resolution. Physical exercise is known to stimulate endorphin secretion, which may be additive to the opioid release from dieting. Alternatively, although narcotics usually produce sedation, under some circumstances they can cause hyperactivity. In anorexia nervosa these special conditions may exist. Although not linked to the opiate systems, interaction of hyperactivity and dieting is further indicated by the "activity induced self-starvation" discussed above (Kanarek & Collier, 1983). Moreover, increased activity can result from food deprivation in some conditions (Armstrong et al., 1980).

Many of the classic neurotransmitters modulate feeding behavior, and it has been proposed that they play a role in anorexia nervosa (Morley, 1981; Morley et al., 1983b). For example, noradrenergic drugs such as the tricyclics and monamine oxidase inhibitors, which stimulate appetite even in normal subjects, seem useful in treating anorexia nervosa. Decreased noradrenergic activity is found in anorexia nervosa but may be secondary to the weight loss and depression (Gross et al., 1979; Halmi et al., 1979). However, opiate interactions with these other neurotransmit-

ters exist, although their exact nature is not clear. The proposed opiate model is highly compatible with other neurotransmitter hypotheses but better explains the addictive-like behavior and compulsive drive in anorexia nervosa. As mentioned above, there is an interplay between the noradrenergic system that mediates short term adjustments to minimal starvation and the endorphin system that is activated over the long term. Margules further suggests that the endogenous opioids inhibit the sympathetic activation associated with the "fight or flight" response. Opiate receptors are present on noradrenergic presynaptic neurons in the locus coeruleus. Opiate withdrawal results in sympathetic arousal, which may be therapeutically damped by blocking noradrenergic activity with clonidine (Jaffe & Martin, 1980). Opioids may also have antianxiety effects by this mechanism. Both opioid peptide modulation of noradrenergic activity and, conversely, noradrenergic modulation of opioid activity are indicated (Morley, 1981; Morley et al., 1983b; Palmer et al., 1983). The opioid receptor also inhibits the noradrenergic receptor activity (Tsang et al., 1978). The details of these interactions will not be reviewed here except to indicate the relevance of such interactions to our hypothesis.

Chronic anorexia nervosa seems unresponsive to the spectrum of psychotherapies. Current psychological hypotheses purporting to explain the evolution of the disorder are relevant to the understanding of its onset but are of limited utility in reversing its course when it has stubbornly persisted for years. An auto-addiction model may not only provide a basis for further biological research but contribute to alternative therapeutic approaches as well. Recovering anorexics are increasingly being employed in treatment programs having some resemblance to Alcoholics Anonymous. Opiate antagonists maybe expected to prove helpful in the management of anorexia nervosa, and more selective receptor blockers than those currently available may prove to be even more efficacious. We are now undertaking such research.

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