Endocrine

MEDICAL GRAND ROUNDS

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ANOREXIA NERVOSA

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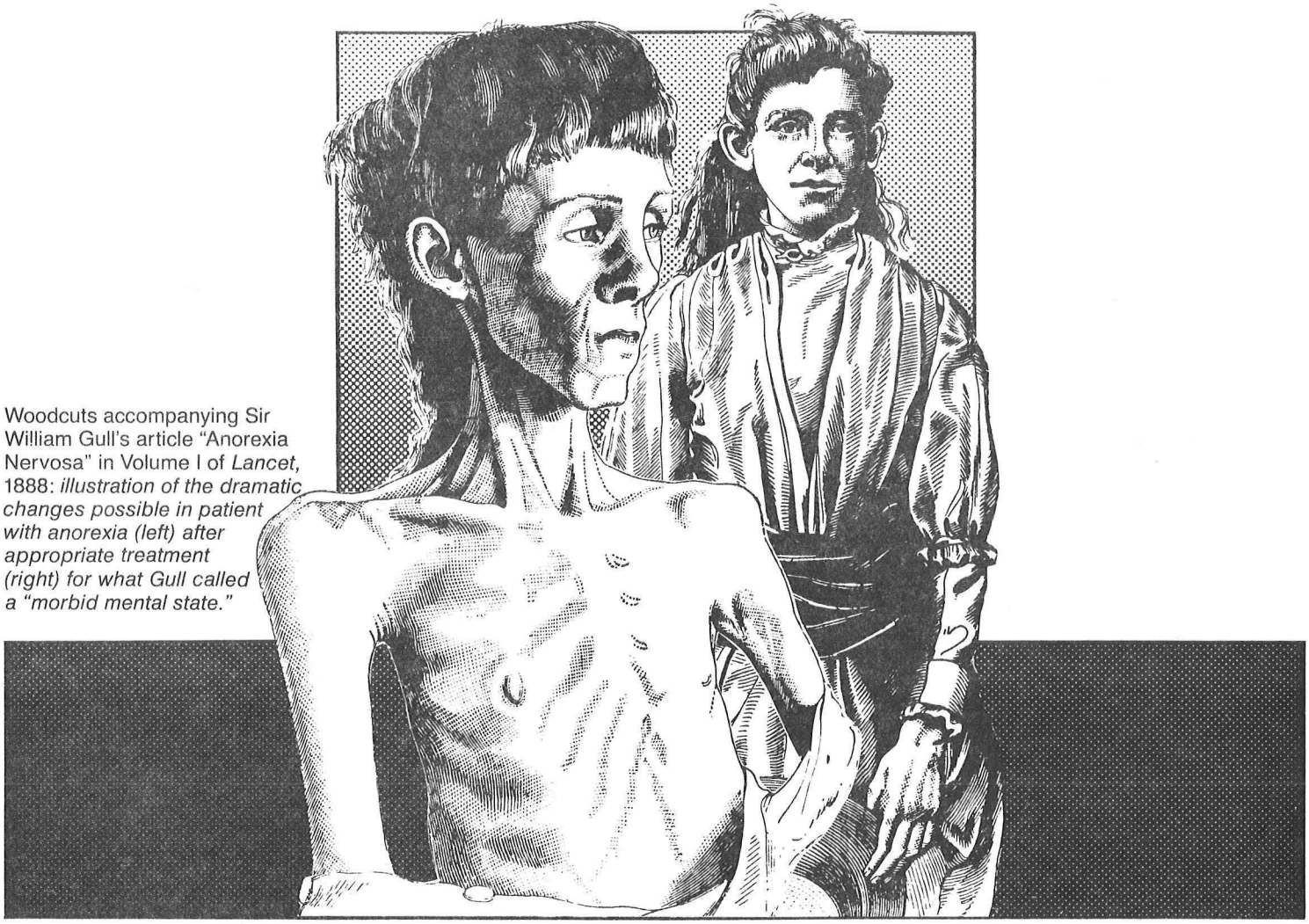


Woodcuts accompanying Sir William Gull's article "Anorexia Nervosa" in Volume I of *Lancet*, 1888: *illustration of the dramatic changes possible in patient with anorexia (left) after appropriate treatment (right) for what Gull called a "morbid mental state."*

Anorexia nervosa was named in 1874 by Sir William Gull who observed the presence of hyperactivity in some emaciated patients whose *want of appetite is due to a morbid mental state.*

Anorexia nervosa is a disorder of previously healthy adolescent girls who become emaciated as a result of voluntary starvation. The term is actually a misnomer, since patients do not actually show a true loss of appetite. They confess to severe cravings for food and sensations of hunger. However, they fear that if they give in and indulge in eating they will lose control and will not be able to stop.

An operational set of criteria has been established by Feighner (1) as shown in Table 1.

TABLE 1. *Feighner criteria for anorexia nervosa*

Anorexia nervosa. For a diagnosis of anorexia nervosa, A through E are required.

A. Age of onset prior to 25.

B. Anorexia with accompanying weight loss of at least 25% of original body weight.

C. A distorted, implacable attitude toward eating, food, or weight that overrides hunger, admonitions, reassurance, and threats: e.g., (1) denial of illness with a failure to recognize nutritional needs; (2) apparent enjoyment in losing weight with overt manifestation that food refusal is a pleasurable indulgence; (3) a desired body image of extreme thinness with overt evidence that it is rewarding to the patient to achieve and maintain this state; and (4) unusual hoarding or handling of food.

D. No known medical illness that could account for the anorexia and weight loss.

E. No other known psychiatric disorder with particular reference to primary affective disorders, schizophrenia, obsessive-compulsive and phobic neurosis. (The assumption is made that even though it may appear phobic or obsessional, food refusal alone is not sufficient to qualify for obsessive-compulsive or phobic disease.)

F. At least two of the following manifestations: (1) amenorrhea, (2) lanugo, (3) bradycardia (persistent resting pulse of 60 or less), (4) periods of overactivity, (5) episodes of bulimia, (6) vomiting (may be self-induced).

Since the cause and mechanism for anorexia nervosa is not known, the diagnosis has to be made through a constellation of symptoms. However, as is the case in many conditions, not every patient has every symptom so that we can have multiple categories as shown in Table 2.

ATYPICAL ANOREXIA NERVOSA

TABLE 2. *Categories of anorexia nervosa*

Clinical features	Conceptual implication
Typical presentation, typical syndrome	Classic patient
Atypical presentation, typical syndrome (type 1 atypical)	Problem of recognition
Typical presentation, atypical syndrome A. Quantitatively atypical: mild or incomplete B. qualitatively atypical (type 2 atypical)	Problem of classification
Atypical presentation, atypical syndrome (type 3 atypical)	Problem of weight loss of unknown origin

GENERAL FEATURES:

Anorexia nervosa is a form of semi-starvation. Semi-starvation is a synonym for chronic caloric deficiency. Famines have occurred endemically and epidemically. Semi-starvation has been inflicted on others as during wars and catastrophes or are self-inflicted from religious zeal or, as in our current discussion, in anorexia nervosa. Semi-starvation can also occur as a complication of disorders such as cancer, emphysema, and malabsorption (Table 3).

TABLE 3

CLASSIFICATION OF SEMISTARVATION

Primary semistarvation—lack of food in the environment

1) Natural causes—spontaneous famines
2) Man induced
   a) War, military occupations, concentration camps, blockade, etc.
   b) Experimental

Secondary or conditioned semistarvation

1) Psychological—anorexia nervosa
2) Organic
   a) Cancer
   b) Emphysema
   c) Malabsorption
   d) Other

A classical study of experimental semi-starvation was conducted in the mid-1940's at the University of Minnesota by Ancel Keys and collaborators. Significant amounts of our knowledge on the physiology and psychology of semi-starvation came from those studies. In this study 32 non-obese conscientious objectors to military service voluntarily underwent 24 weeks of semi-starvation preceded by a control period of 12 weeks and followed by a rehabilitation period of 12 weeks. In addition, 12 of the subjects remained for an additional 8 weeks of unrestricted diet, and follow-up studies were made on about half the patients after 8 and 12 months of recovery. Semi-starvation or starvation has been used clinically in the treatment of obesity. However, the clinical and metabolic consequences of caloric deprivation in obese patients are somewhat different from those in the lean patients.

Clinical picture: Semi-starved patients are usually very conscious of their physical condition and are well aware of changes in the looseness of clothing and shoes and the presence of protruding wrists and bones. However, in patients with anorexia nervosa, there is a distortion of body image in which they actually see themselves as being either adequately proportioned or even fat in spite of the emaciation. Sitting on any hard surface becomes uncomfortable, and they frequently complain of muscle soreness and cramps. Nocturia is also a frequent problem. The nails grow slowly and the hair falls out in increasing amounts. Their extremities go to sleep very easily, and they do not tolerate cold

temperatures well. The individuals suffer from dizzyness and syncopal episodes when rising from the reclining position. Commonly, they start losing coordination because of weakness, and they begin to have difficulties while walking around obstacles.

Semi-starved persons usually complain bitterly about the constant hunger. In contrast, totally starved people frequently stop feeling hungry after a few days. Patients with anorexia nervosa deny hunger, but when questioned carefully they will admit to it. They cherish the newly-found will to resist eating as a manifestation of being in control. Subjects in the Minnesota studies, after a few weeks of semi-starvation, became obsessed with food and related subjects. The conversation invariably centered around eating, cooking, and farming. Their ideation and dreams were frequently occupied with the various aspects of food. Patients with anorexia nervosa frequently get involved in cooking and preparing very elaborate meals for the rest of the family which they will not eat. Not infrequently, they will hoard food. They are frequently involved in collecting recipes and are constantly preoccupied with the caloric content of foods--an area in which they usually become expert. A semi-starved patient frequently complains of weakness, irascibility, drowsiness, and depression. Patients with anorexia nervosa frequently complain of these symptoms. However, they tend to get involved in strenuous and ritualized exercising programs even when weak and tired. There is a loss of libido. On observation, semi-starved patients appear haggard and emaciated. The face is thin and pallid with prominent zygomatic arches. The hair is dry and irregular, and areas of dirty brown pigmentation are often present in the face--particularly around the mouth, under the eyes, and on the malar imminences. Eyes are dull and the sclera frequently resemble unglazed porcelain. The lips tend to be dry, peeling, and cracked, and the tongue frequently shows edema with dental impregnation in the inferior margins. Sometimes there is edema of the eyelids and cheeks which may mask the degree of emaciation. Table 4 shows the changes in mass of different organs and tissues in semi-starvation.

TABLE 4

CHANGES IN MASS OF DIFFERENT ORGANS AND TISSUES IN SEMISTARVATION

Organ or tissue	*Gross changes*	*Changes in mass relative to decrease in total body weight*
Brain and nervous system	Minimal or absent	Lose very little weight in starvation (up to 10% in severe emaciation)
Bones	Unremarkable	Much less than that of body as a whole
Kidneys	Some thinning of cortex on inspection	Less than that of body as a whole
Adrenal Glands	Often normal in appearance; sometimes enlarged, with cortical hypertrophy	Conflicting reports: some instances of decrease in size but much less than decrease in body weight. Some hypertrophy also described.
Skeletal musculature	Marked atrophy	Proportional
Heart	Heart appears soft, pale, and flabby	Loss of heart volume about 70% of body weight losses.
Thyroid gland	Atrophy	Roughly proportional
Pancreas	Atrophy	Roughly proportional
Liver and G.I. tract	Marked atrophy	Exceeds that of body as whole
Skin	Appears dry, scaly, thin, and unelastic	Not known

The neck is thin and seems long. The clavical and ribs are prominent. The scapula has the characteristic wing appearance. In general, all bone prominences--such as the vertebral column, iliac crest, and ischial tuberosity--become very prominent. The buttocks are thin and sagging. The arms and legs are stick-like. Women develop amenorrhea and atrophy of the breasts. For unknown reasons, patients with anorexia nervosa usually lack the breast atrophy seen in semi-starvation of other causes. Skin tends to be thin, cold, dry, rough in texture, and inelastic. It is reminiscent of the skin of old people. Skin fold shows marked loss of subcutaneous fat. The muscle tone is poor and frequently peripheral edema is noted. On neurological examination, deep tendon reflexes are diminished and may be absent. Blood pressure tends to be low and pulse pressure narrow. The heart is small, but the heart sounds are usually prominent because of the thinness of the chest wall.

Systemic and morphologic changes: In general, the changes in body composition observed during starvation reflect the body's attempt to adapt to undernutrition. Fat stores are used to spare structural protein. Body fat diminishes at a considerably more rapid rate than does muscle. Skeletal muscle, thyroid, and pancreas diminish in roughly the same proportion as the body as a whole. More extensive losses occur in other soft tissue organs--mostly in liver and intestine. The brain and skeleton show minimal gross changes, but the heart and kidneys exhibit proportionately less weight loss than the total body. Central nervous system and circulation are maintained at whatever the cost to less essential portions of the organism. Moderate anemia is commonly associated with semi-starvation and the severity gradually increases with the degree and duration of caloric restriction. In the Minnesota experiment, a decrease of hemoglobin from 15.1 to 11.7 gm/dl after 24 weeks of semi-starvation was noted. In this experiment plasma protein concentration diminished only slightly during semi-starvation. Patients frequently complain of polyuria of 2-3 liters/24-hours and nocturia. Vigerski and co-workers found abnormalities in water conservation comparable to those of patients with partial diabetes insipidus in 38% of the semi-starved patients. However, these patients responded well to vasopressin.

Starvation edema: Edema that occurs in starved persons usually does not result from either hypoproteinemia or congestive heart failure. In general, intravenous pressure is lower than normal. Edema fluid is very low in protein, and the edema occurs slowly--usually after the first month of semi-starvation. At the beginning it tends to be vespertine. Loss of elasticity and other changes in the tissue structure are thought to have an important role in the pathogenesis of famine edema.

Tables 5 and 6 describe findings in a study of 65 patients with anorexia nervosa.

TABLE 5

Historical data of 65 patients with anorexia nervosa

A. Sex: female, 59; male, 6
B. Race: Caucasian, 64; Oriental, 1
C. Religion: Jewish, 27; Roman Catholic, 22; Protestant, 15; none, 1
D. Social class: upper, 16; middle, 45; lower, 4
E. Residence: suburban, 54; urban, 10; rural, 1
F. Family history of emotional illness: 32 (49%)
G. Age at onset of anorexia nervosa: 9–20 years
H. Age of presentation: 10–21 years
I. Interval between onset and presentation: 2–30 months
J. Intellectual ability: average, 60 (IQ 90–110); superior, 4 (IQ 110–130); below average, 1 (IQ under 90)
K. Educational level of parents: college, 104[a]; high school, 22; primary school, 2
L. Psychiatric aberration: behavioral disorder, 44; neurosis, 2; schizophrenia, 19
M. Menarche prior to onset of illness: 43 of 59
N. Amenorrhea: 100% of those who had reached menarche
O. Constipation: 100%

TABLE 6

Abnormalities noted on physical examination of 65 patients with anorexia nervosa

Abnormality	No. affected	% Affected
A. Skin (hairiness, scaliness, dirtiness, desquamation)	57	88
B. Hypothermia (rectal temperatures <96.6°F)	55	85
C. Bradycardia (<60 beats per min)	52	80
D. Cachexia	47	72
E. Bradypnea (<14 breaths per min)	43	66
F. Hypotension (systolic pressures below 70 mm Hg)	34	52
G. Heart murmurs	25	38
H. Peripheral edema	15	23

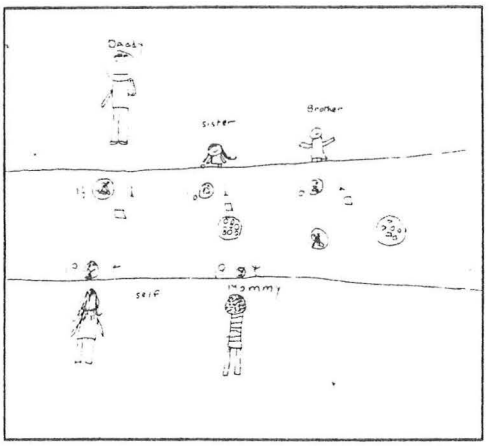
Psychosocial features: As we have reviewed above, there are at least two aspects to the patients with anorexia nervosa. On one side is the consequence of semi-starvation. The other aspect is related to perceptual and behavioral abnormalities. Table 7 summarizes the psychological behavior and perception of features in anorexia nervosa. Among the perceptual abnormalities there are three major areas. (1) Disturbance in body image: Patients with anorexia nervosa consistently underestimate body width--particularly the face, chest, waist, and hips--relative to the self-perception of control groups of normal and thin subjects. As these patients improve clinically and begin to gain weight, their image of their own bodies returns to normal. An example of this is shown in the drawings in Figure 1.

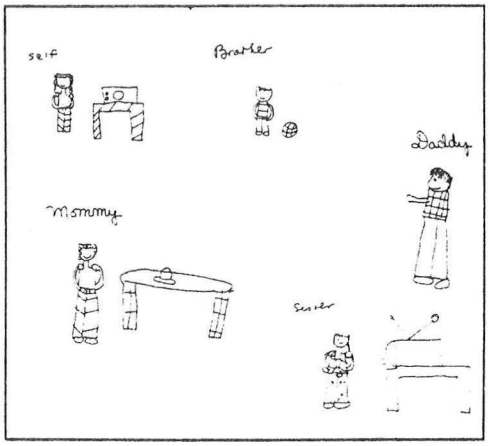
TABLE 7

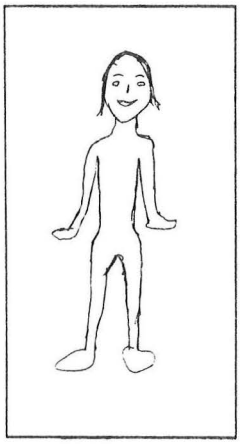
Psychologic, Behavioral, and Perceptual Features in Anorexia Nervosa

PSYCHOLOGIC
No predominant psychiatric diagnosis
Features of depression, anxiety, and obsessional thoughts may exist.
Lowered self-esteem and social anxiety
Perfectionistic
Average intelligence but high achievement
BEHAVIORAL
Preoccupation with food
Willful semistarvation
Bulimia
Vomiting and purging
Hyperactivity
Maintenance of personal appearance
Decreased sexual interest
PERCEPTUAL
Disturbed body image
Overestimation of face and torso sizes
Misperception of bodily sensations
Distorted hunger awareness
Denial of fatigue
Sense of ineffectiveness
Poorly developed autonomy
Feeling controlled by rather than controlling of environment

Figure 1

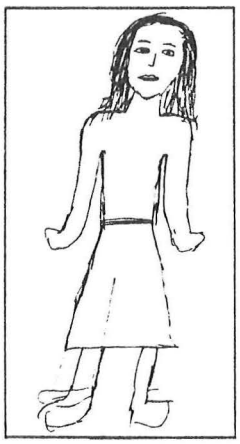






Above:
Drawing made by a preadolescent girl with anorexia nervosa prior to treatment: *responding to a request that she picture herself and family doing something, the girl drew them eating. The drawing indicates the patient's preoccupation with food and the extent to which she sees the family organized by her symptoms, Dr. Bernice Rosman says. The seating arrangement and the distance between the child and her father show the divisions within the family, she adds.*

Left:
Pretreatment self-portrait of a 24-year-old woman with anorexia nervosa: *lack of detail and smallness of figure indicate a constricted psychological life, developmental immaturity, and lack of sexual differentiation.*



Above:
Drawing made one year after therapy: *the family is more realistically differentiated and proportionately sized. "There is no longer the feeling of divided camps, and activities are no longer organized around the child's illness," Dr. Bernice Rosman says.*

Left:
Self-portrait after successful treatment: *drawing reflects a less fearful and constricted psychological life, more maturity, and sexual differentiation.*

(2) Misperception of body sensations: These patients have either a disturbance in the perception or the interpretation of enteroceptive stimuli. They either have a distorted hunger awareness, denial of fatigue, or failure to recognize emotional states such as anxiety, anger, and depression.

(3) Sense of ineffectiveness: Anorexic patients frequently see their choices of actions as response to the demands of others. Their environment controls them. The following poem portrays a perceived inability to initiate actions of consequence in the environment (2).

THE MISSING LINK

There is a basic
connection
my spirit lacks
threading
action to consequence.

My body swelled
too monstrous
ravenous hunger
consuming.

I clipped it out—
precise
neat
reversing the process.

Appetites
seizing control
without warning
block my relationship
with self
with God.

Any feeling
which races me away
arms flung
round the neck
must be halted
before I lose
all touch
with earth
and sky
that soft silence
which opens my life
petal
by petal

J.H.E., 5/11/78

Some people believe that there is an abnormality in the relationship between the patient and the family. There are four characteristics which are frequently encountered.

(1) Enmeshment
This refers to families in which people are over-involved with each other and too close. This leaves the family members with insufficient autonomy at the crucial development stage.
(2) Overprotectiveness
(3) Rigidity in the relationships
(4) Inability to negotiate conflict

Endocrine studies in anorexia nervosa: Endocrinologists have been interested in anorexia nervosa ever since the description by Morris Simmonds of pituitary cachexia. It is well known that there is no global failure of the pituitary in anorexia nervosa. However, it must be remembered that most patients with anorexia nervosa are women, and one of the most prominent manifestations is amenorrhea which is secondary and frequently happens before there is any decrease in body mass. Basal plasma LH and FSH tend to be low (17,18). Frisch and collaborators (22) presented evidence that onset of menses in women depends on obtaining an ideal body weight or fatness during puberty. Data from non-anorectic female patients showed that a loss of body weight in the range of 10-15% of normal weight for height, which represents a loss of about one-third of body fat, results in amenorrhea. On the basis of a study of 181 girls followed from menarche to the completion of growth at age 16 to 18, they were able to build a nomogram for the prediction of the onset of menstrual cycles (Figure 2). They were also able to build another nomogram for the restoration of menstrual cycles in cases of secondary amenorrhea when amenorrhea is due to weight loss. The weight at which menstrual cycles resume in post-menarchial patients aged 16 and older are about 10% heavier than the minimal weights for the same height observed at menarche. They have observed that some patients have a surprisingly sharp threshold at which there is resumption of cycles (Figure 3). When the ideal amount of fatness is achieved, the hypothalamus apparently becomes sensitive to the inhibitory effect of circulating estrogens and, consequently, its secretion of LHRH becomes disinhibited. LHRH, in turn, regulates in cyclical fashion the production and secretion of FSH and LH by the pituitary. Unfortunately, the Frisch hypothesis fails to explain the 25-50% of women who develop amenorrhea even before the onset of weight loss. Moreover, on recovery from anorexia nervosa and reestablishment of normal body weight, about half of the people failed to resume their menses. The measurement of a 24-hour sleep-wake cycle of LH and FSH will provide a more reliable index of maturation. Boyar *et al* (18,19,20) have established a set of criteria to evaluate the maturity of the circadian LH secretory patterns.

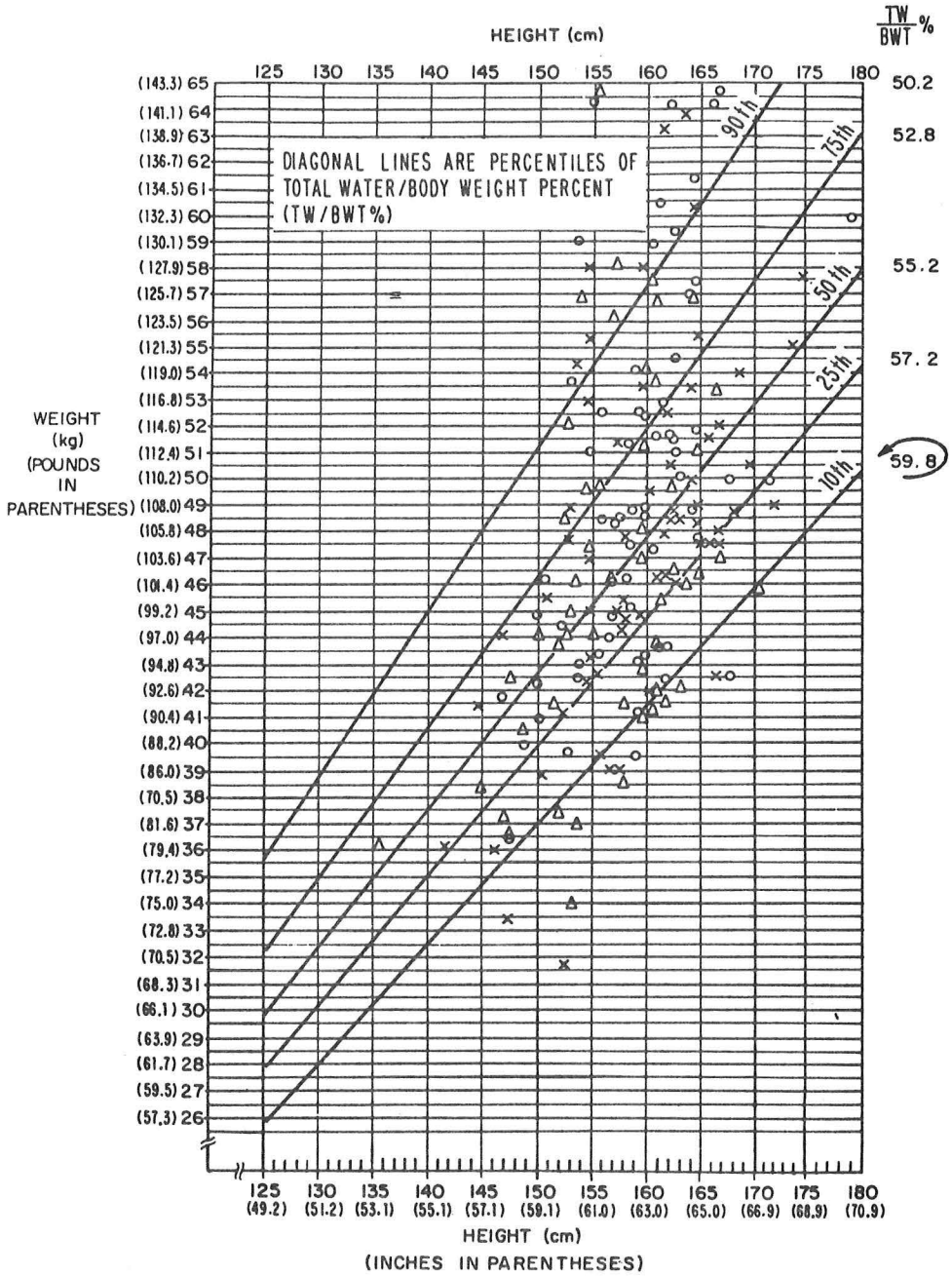


FIG. 2. Minimal weight necessary for a particular height for onset of menstrual cycles is indicated on the weight scale by the 10th percentile diagonal line of TW/BWt%, 59.8%, as it crosses the vertical height lines. Height growth of girls must be completed, or approaching completion. For example, a 15-year-old girl whose completed height is 160 cm (63 in.) should weigh at least 41.4 kg (91 lb) before menstrual cycles can be expected to start. Symbols are the height and weight at menarche of each of the 181 girls of the Berkeley Guidance Study, O; Child Research Council Study, X; and Harvard School of Public Health Study, △.

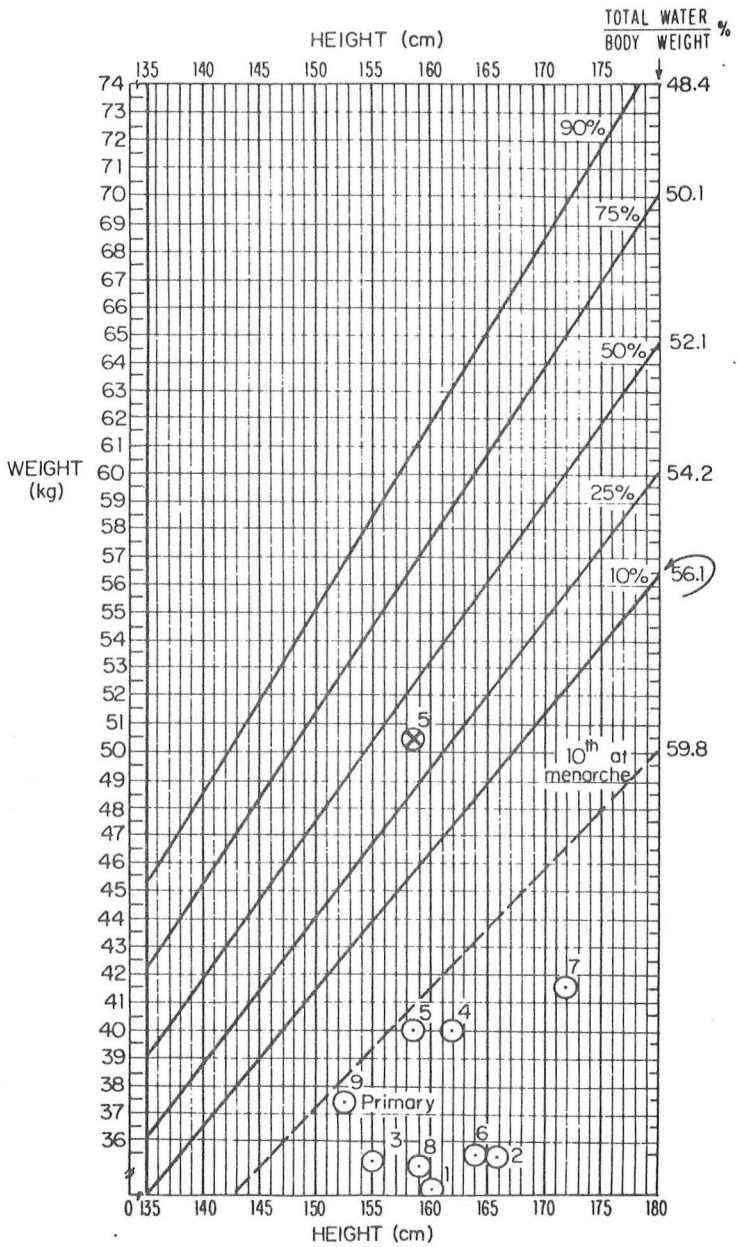


FIG. 3. Minimal weight necessary for a particular height for restoration of menstrual cycles is indicated on the weight scale by the 10th percentile diagonal line of TW/BWt%, 56.1%, as it crosses the vertical height line. For example, a 20-year-old woman whose height is 160 cm should weigh at least 46.3 kg (102 lb) before menstrual cycles would be expected to resume. (Modified from ref. 15.)

The 10th percentile at menarche (taken from Fig. 2) is shown by the dashed line.

⊙1–9: Amenorrheic, anorectic patients described in Boyar et al. (2) in comparison with normal, minimal weights. ⊗: Patient #5 at the time of resumption of normal cycles.

CRITERIA FOR MATURITY OF CIRCADIAN LH SECRETORY PATTERNS (20):

Based on the previous work by Boyar group with normal children, adolescents, and adults, the following criteria for classifying the maturity of circadian LH secretory patterns were used:

1. *Prebubertal Pattern.* LH pulses are small throughout sleep and wakefulness; there is no significant sleep-wake difference in the respective mean LH concentrations as both values usually fall between 2 and 6 mIU/ml.

2. *Early to Midpubertal Pattern.* LH pulses increase in amplitude during sleep (particularly slow wave sleep) so that the mean LH concentration during sleep increases to 7-12 mIU/ml, which is significantly greater than the mean concentration of 3-7 mIU/ml during the waking state.

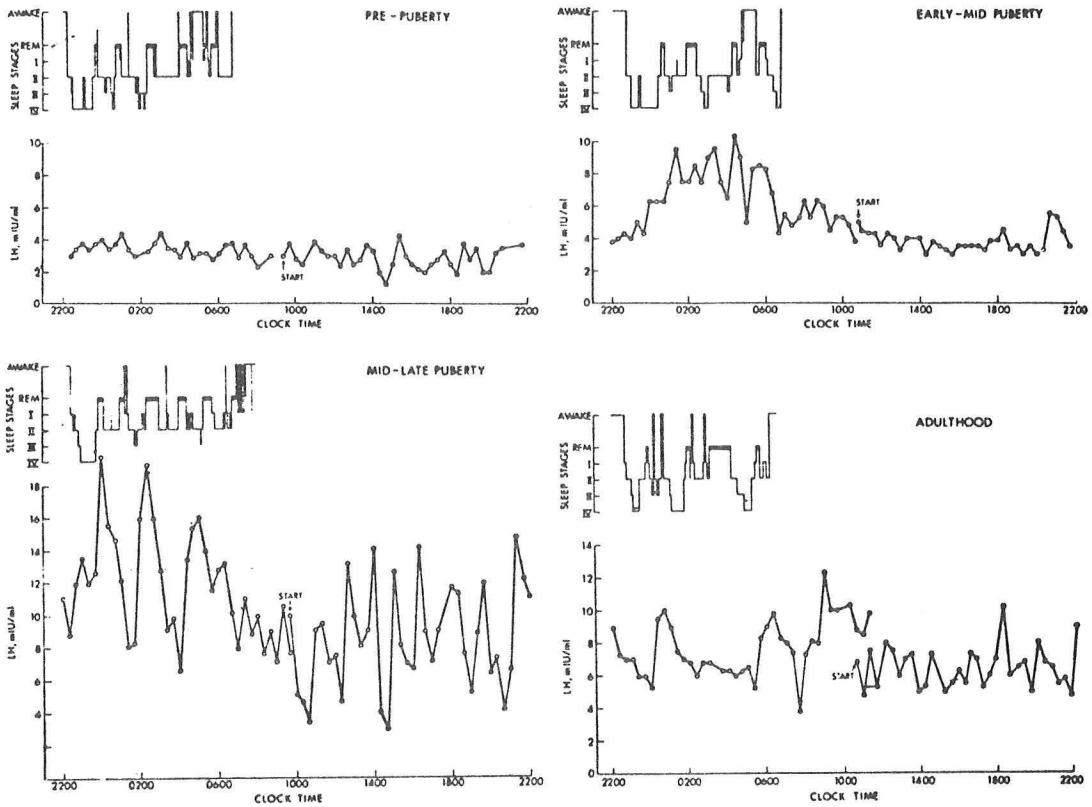
3. *Mid-to-late Pubertal Pattern.* LH pulses now show a marked increase in amplitude throughout sleeping and waking, but the mean LH concentration during sleep remains significantly higher than the mean concentration while awake; typical values are 16-24 and 7-12 mIU/ml, respectively.

4. *Adult Pattern.* Pulses moderate slightly in amplitude throughout both the sleep and awake phases, and the difference between the respective mean LH concentrations is again no longer significant; the typical 24-hr mean value is now in the range of 7-24 mIU/ml, with the phase of the menstrual cycle influencing where in this broad range the mean will be.

On the basis of this observation, Boyar studied the circadian variation of plasma LH concentrations in a series of patients with anorexia nervosa. They found that a significant number of them had immature patterns.

Figure 4 shows the ontogeny of the human circadian LH secretory pattern from prepuberty through early and late puberty into adulthood. Figure 5 shows one such pattern of a 21-year-old woman with anorexia nervosa (19). In the same figure it is compared to that of a normal prepubertal girl.

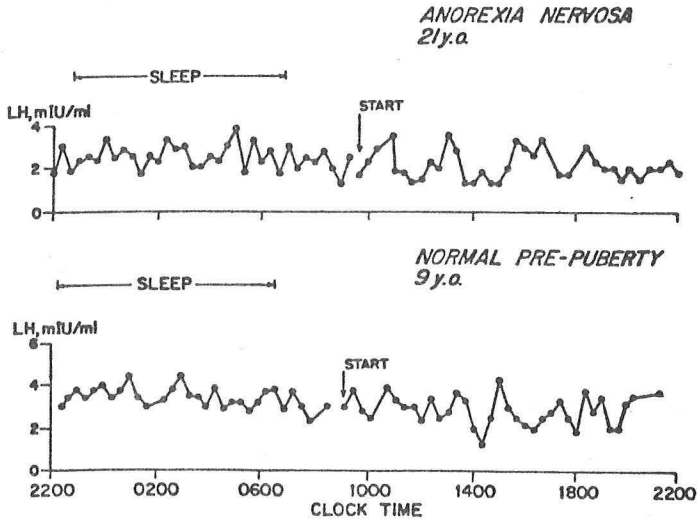
Katz (20) studied 8 women who had recovered from anorexia nervosa. In only two of these was the pattern of circadian LH secretion relatively mature. The first of these patients had studies done at six months when her weight was only 76% of the ideal. At that time, she had an early pubertal pattern. By the time of the second study, the patient's weight was 97% of ideal, and she had an LH secretory pattern that was virtually adult. Five patients who had regained sufficient weight to be very close to or at ideal value, but were still severely symptomatic, showed immature patterns. They ranged from prepubertal pattern to early midpubertal pattern.



Ontogeny of the human circadian LH secretory pattern from prepuberty, through early and late puberty, into adulthood

Figure 4

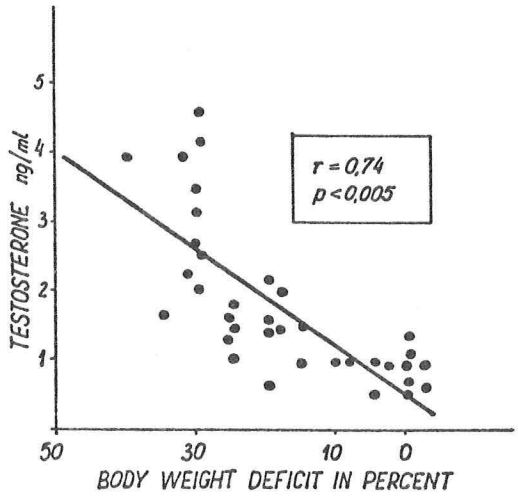
Figure 5



The 24-hour LH secretory pattern in a 21 year old girl with anorexia nervosa compared to a normal pre-pubertal girl.

The response of LH and FSH to the administration of synthetic LHRH has been studied by multiple investigators (23-28). LH response, in general, has been found to be impaired--especially peak LH response is significantly delayed. This finding is similar in patients with anorexia nervosa and in those with simple weight loss when compared to normals. The integrated response to LHRH is not abnormal. The FSH response in general has been found to be normal or the response has been found to be delayed or increased. The administration of clomiphene has been found to be abnormal.

Serum testosterone (28) has been found to be elevated in patients with anorexia nervosa (Figure 6). The explanation for this finding is not clear.



Relationship between serum testosterone and per cent of body weight deficit in anorexia nervosa.

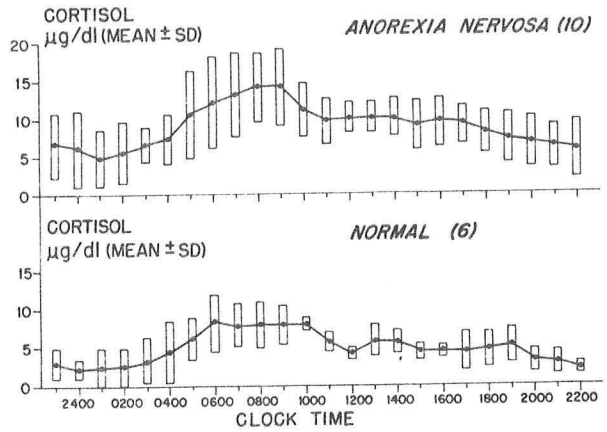
Figure 6

Thyroid function: Patients with anorexia nervosa frequently complain of unremittent cold intolerance. As described above, some of the skin changes suggest the possibility of hypothyroidism. Serum thyroxine is generally within normal levels even though it is on the lower side of normal. 3,3',5-triiodothyronine tends to be low, while reverse T_3 (3,3',5'-triiodothyronine) tends to be increased (29-31). TSH levels tend to be normal. The response to the administration of TRH tends to be similar to that of normal subjects (30). The above findings suggest that peripheral conversion of T_4 to T_3 is impaired. This probably is a protective mechanism to semi-starvation.

Adrenal function: Boyar *et al* (31) have studied cortisol secretion and metabolism in 10 patients with anorexia nervosa. They studied these patients by measuring plasma concentration every 20 minutes for a 24-hour period. The patterns were characterized by failure of plasma cortisol concentration to fall near zero values between 11 p.m. and 3 a.m. and the persistence of an elevated plasma cortisol level in the afternoon.

Figure 7 shows that in general the circadian rhythm was preserved, but at a higher level than that of the controls. The mean plasma concentration of these 10 patients was 8.9 μg/dl as compared to 4.9 μg/dl in normal controls. These elevations were not the consequence of elevation of corticosteroid binding globulin. They further studied these patients by administering to them radioactive cortisol to measure the production rate. They found that the mean values were similar to that of normal matched controls.

Figure 7



Hourly Mean Cortisol Level (Derived from the Average of the Sample 20 Minutes before the Hour, on the Hour and 20 Minutes after the Hour) in the 10 Patients with Anorexia Nervosa as Compared with Six Normal Controls Matched for Age and Sex.

Note that the preservation of the circadian variation in the patients is similar to that in the controls, although at a somewhat higher level.

Table 8 shows that the $t\frac{1}{2}$ of these patients were significantly elevated in comparison to controls--78 *vs* 60. Metabolic clearance rate was reduced (177 *vs* 359), suggesting that the production of cortisol was normal.

TABLE 8

Cortisol Production and Metabolism.*

Case No.	% Difference from Ideal Weight	[F̄] (μg/Dl)	CBG†	t½ (Min)	MCR (Liters/Day)	CPR (Mg/Day)	Urinary Cortisol (μg/Day)	THF/THE
1	40.5	11.7	21	64	190	16.5	61	1.9
2	38.6	5.7	22	80	278	31.5	—	1.1
3	31.1	10.8	20	57	199	20.0	75	0.6
4	26.5	7.8	18	86	138	15.6	—	1.0
5	23.8	8.5	22	88	146	22.1	—	0.9
6	37.1	8.7	18	61	190	19.0	73.0	0.7
7	33.5	13.7	—	110	94	16.0	60.0	1.5
8	35.1	3.7	11	76	260	12.8	50.4	1.4
9	24.1	9.5	17	79	139	24.7	—	1.2
10	30.0	8.6	20	74	132	16.1	—	1.5
Mean ±SD		8.9±2.9	18.8±3.4	78±15.4	177±55.5	19.4±5.2	63.8±9.2	1.2±0.4
Normal controls:								
Mean ±SD		4.9±0.97	19.9±3.5	60±7.0	359±83.7	19.5±4.0	44.1±13.8	0.65±0.15
(range)		(3.9-6.8)	(15 - 20)	(54 - 73)	(262 - 495)	(14.4 - 25.5)	(30 - 64)	(0.4-0.85)
Significance (patients vs normal controls)		P<0.01	NS‡	P<0.01	P<0.001	NS	P<0.05	P<0.01

*[F̄] denotes 24-hr mean cortisol, CBG cortisol-binding globulin, t½ half-life of plasma cortisol, MCR metabolic clearance rate, CPR cortisol production rate, & THF/THE tetrahydrocortisol/tetrahydrocortisone ratio.

†Expressed as cortisol-binding capacity in μg/dl.

‡Not significant.

However, its metabolism was abnormal. When they measured the ratio of tetrahydrocortisol to tetrahydrocortisone, they found that the ratio was 1.2 ± 0.4 in comparison to controls of 0.65 ± 0.15. This abnormal ratio is frequently seen in patients with hypothyroidism; and, therefore, they postulated the possibility that these patients behaved as though they were hypothyroid. To test this hypothesis, they administered T_3 and further studied the similar parameters. As can be observed in Table 9, the ratio of tetrahydro-F to tetrahydro-E was reduced toward normal.

TABLE 9

Effect of Tri-iodothyronine (T_3) on Cortisol Metabolism in Anorexia Nervosa.*

Case No.	% Weight Deficit	T_3 (Ng/Dl)	T_4 (μg/Dl)	THF/THE	t½ (Min)
11:					
Control	35	70	6.8	1.4	—
with T_3		307		0.8	
12:					
Control	14	96	5.8	1.2	81
with T_3		460		0.6	49
13:					
Control	39	71	6.0	1.6	110
with T_3		183		1.0	76
14:					
Control	19	62	5.6	1.38	116
with T_3		463		0.74	91
15:					
Control	35	102	7.2	0.82	82
with T_3		662		0.51	74
Normal mean ±SD		137.8±21	6.9±1.7	0.65±0.15	60±7.0

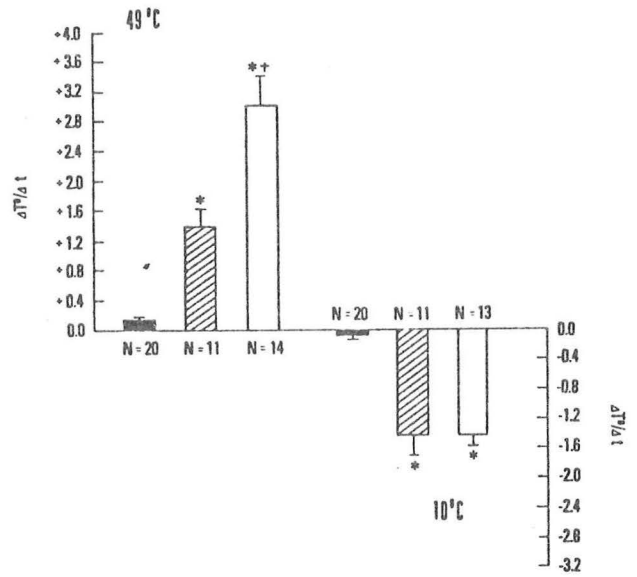
*T_4 denotes total thyroxine, THF/THE tetrahydrocortisol/tetrahydrocortisone ratio, & t½ half-life of plasma cortisol.

Further evidence of this hypothyroid state was provided by the study of urinary androsterone/etiocholanolone ratio (32) which was uniformly low in a range characteristic of hypothyroidism. Clinical remission of the anorexia nervosa was followed by concomitant increases of the A/E ratio. The administration of T_3 also resulted in a shift of the ratio toward normal.

Growth hormone: Patients with anorexia nervosa have normal growth hormone concentration. However, it has been found that growth hormone increases after the administration of TRH and frequently is not suppressed by glucose. This response is analogous to that seen in protein energy malnutrition (34,35).

Hypothalamic dysfunction: Water conservation. It has been shown that patients are unable to maximally concentrate the urine with dehydration and dehydration plus exogenous vasopressin, which suggests the possibility of partial diabetes insipidus (34). It has also been shown that a defect in temperature regulation exists. This abnormality is in relation to weight loss as can be seen in Figure 8. However, this is not a uniform finding (36).

Figure 8



Mean ± S.E.M. Rate of Change of Core Temperature per Hour ($\Delta T°/\Delta t$) at 49°C, 12 per Cent Relative Humidity (Left) and 10°C (Right) in Patients with Secondary Amenorrhea Associated with Simple Weight Loss (▨) and Anorexia Nervosa (□), and in Normal Woman (■).

Temperature was recorded at one-minute intervals via a rectal thermistor.

*P<0.01 for anorexia nervosa or simple weight loss vs. normal.

†P<0.01 for anorexia nervosa vs. simple weight loss.

Therapy: The treatment of this disorder is difficult and has to involve the combined efforts of an internist to deal with the physical changes secondary to anorexia and a psychiatrist to deal with the primary psychological events which cause the anorexia and subsequent cachexia. Psychotherapy is ineffective in the treatment of this disease while the patients have a marked diminution in the body weight. Some of the psychological disturbances seem to be due to the starvation by itself since they are very similar to the psychological disturbances found in patients who either have undergone starvation due to circumstances out of their control (i.e., in concentration camps) or because they were being experimental subjects in starvation experiments. It is not always easy to make the patient eat even in a hospital setting, and they use a series of subterfuges to avoid eating. The combination of an understanding physician and a gentle coercion into eating in a hospital environment tends to be helpful in the treatment of the disorder. In some circumstances intravenous hyperalimentation has to be administered in patients who are very sick and refuse to eat. In some cases tube feedings can be employed and, because of the discomfort caused by tube feedings, quite often patients start eating on their own. Fortunately, the treatment at least of gaining weight is successful in the hospital in most cases, but it is important to have some supportive mechanism when the patients are discharged from the hospital so that weight gain is maintained with time. Most patients only require one hospitalization, but there are patients who require multiple hospitalizations. It is at this stage that psychotherapy can be helpful--

especially when started early. The mortality varies between 2-10%, and in most cases a clearcut cause is not found except for just plain cachexia. Death usually occurs suddenly and autopsy is usually not revealing. Multiple drug therapy has been utilized in the treatment of these patients. These drugs are occasionally useful: Cyproheptidine, which stimulates appetite, has been used in double-blind studies with no significant advantage; antiemetic drugs can be helpful in patients who have prominent gastrointestinal symptoms.

Long-term prognosis: Most patients get better. However, a significant number of them retain psychological disturbances in the body image and a feeling of ineffectiveness even though their weight might remain more or less adequate.

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