Eating Disorders (Obesity, Anorexia Nervosa, Bulimia Nervosa), Immunity, and Infection

A. Marcos, A. Montero, S. López-Varela, and *G. Morandé

IN PURSUIT OF A DESIRABLE WEIGHT

Obesity, anorexia nervosa, and bulimia nervosa are significant public health concerns affecting a large section of the population; they are even considered to be epidemics. These disorders have a common problem—the failure to maintain a desirable weight. Treatment focused on making obese people thin is clearly not working and might even cause more harm than good (1). Many obese people give up attempting to lose weight because most of them fail in their efforts to achieve and maintain their desired weight (2). At the other extreme, overemphasis on thinness is contributing to an increasing incidence of anorexia nervosa and bulimia nervosa (3), which can present greater risks than obesity. The desired weight goal of patients with anorexia nervosa and bulimia is very far from the ideal body weight, and the medical complications of these conditions can ultimately be very serious.

OBESITY

Obesity, defined as an excess of body fat relative to lean body mass, is the consequence of a chronic imbalance between energy intake and energy expenditure; evidence also indicates that obese people have an increased tendency to deposit dietary fat as body fat (4). A high intake of fat may be important in both the cause and the maintenance of obesity; in fact, obese individuals have a preference for eating fatty foods and they consume a higher proportion of fat in their diets than normal weight individuals (5). Despite this well-defined cause of obesity, it is not yet clearly established whether the main abnormality responsible for the increase in body fatness is a
chronic excess intake of energy, a defect in energy expenditure, or perhaps a combination of both (6).

Obesity can be classified in a clinically useful way according to the body mass index (BMI) (7): grade 0, BMI 20 to 24.9 (normal weight); grade I, BMI 25 to 29.9; grade II, BMI 30 to 40; grade III, BMI more than 40.

The BMI range of 20 to 24.9, classified as normal, coincides well with the normal mortality ratio derived from the Metropolitan Life Insurance tables (8). The mortality ratio begins to increase at BMI levels above 25, at which point health professionals should be concerned. Although the increase in mortality in grade I is not great, it is of importance because it is transitional to grades II and III, which create more serious health risks for the individual (5).

**ANOREXIA NERVOSA**

Anorexia nervosa is a syndrome that includes three particular features: a marked fear of fatness, a disturbed perception of body size (body image), and an obsessive desire to lose increasing amounts of weight (9). Other symptoms and characteristics of this disorder are shown in Table 1. Anorexia as such is not usually associated with the syndrome of anorexia nervosa, and appetite in this condition remains normal or is even increased until late in the course of the illness (10).

**BULIMIA NERVOSA**

As in anorexia nervosa, patients with bulimia pursue thinness. However, in bulimia the distinguishing feature is binge eating, which is the rapid consumption of a large quantity of food in a short period of time, usually less than 2 hours, invariably followed by purging. Table 1 summarizes the main features of patients with bulimia nervosa according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (11).

Anorexia nervosa and bulimia nervosa are psychiatric illnesses characterized by abnormal eating patterns. People with these disorders respond in a different way from normal individuals to the macronutrient content of food (fat, carbohydrate, and protein). These abnormal responses seem to reflect the development of particular attitudes toward the macronutrient profiles of foods (12).

**INTERACTIONS BETWEEN NUTRITION, IMMUNITY, AND INFECTION**

The complexity of the interactions between nutrition, immunity, and infection is well recognized (13). Nutrients are known to play an important role in the appropriate maintenance of the immune mechanisms involved in host defense systems (14).

Epidemiologic data also suggest that the incidence and severity of infectious illness are higher in obese than in nonobese individuals (15). The mechanisms respon-
TABLE 1. DSM-IV diagnostic criteria for anorexia nervosa and bulimia nervosa

<table>
<thead>
<tr>
<th>Anorexia nervosa</th>
<th>Bulimia nervosa</th>
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<tbody>
<tr>
<td>A. Refusal to maintain body weight over a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight 15% below that expected), or failure to make expected weight gain during period of growth, leading to body weight below 15% of that expected.</td>
<td>A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:</td>
</tr>
<tr>
<td>B. Intense fear of gaining weight or becoming fat, even though underweight.</td>
<td>1. Eating in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time in similar circumstances; and,</td>
</tr>
<tr>
<td>C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or denial of the seriousness of current low body weight.</td>
<td>2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).</td>
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<tr>
<td>D. In postmenarchal females, amenorrhea (i.e., the absence of at least three consecutive menstrual cycles). (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen administration.)</td>
<td>B. Recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.</td>
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Restricting type: During the episode of anorexia nervosa, the person does not regularly engage in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives or diuretics).

Binge eating/purging type: During the episode of anorexia nervosa, the person regularly engages in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives or diuretics).

Bulimia nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

1. Eating in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time in similar circumstances; and,

2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. Recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.

C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively doing episodes of anorexia nervosa.

Purging type: The person regularly engages in self-induced vomiting or the misuse of laxatives or diuretics.

Nonpurging type: The person uses other inappropriate compensatory behaviours (e.g., fasting or excessive exercise), but does not regularly engage in self-induced vomiting or the misuse of laxatives or diuretics.

It is also necessary, however, to take into account the fact that weight reducing diets are the most common treatment for obesity and, therefore, most obese persons are subjected to energy restricted diets. The effects of such restricted diets on immune competence have not been widely reported, which is the reason why the effects of weight reduction on immunity are still disputed (18). Some investigators have speculated that a decrease in nutrient intake during weight loss might explain subsequent
TABLE 2. Body mass indices (in kg/m²) frequently used to define desirable and obese weights in adults

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommended* Males</th>
<th>Females</th>
<th>Overweight or obese† Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Life 1959‡</td>
<td>22.0</td>
<td>21.5</td>
<td>26.4</td>
<td>25.8</td>
</tr>
<tr>
<td>Metropolitan Life 1983‡</td>
<td>22.7</td>
<td>22.4</td>
<td>27.2</td>
<td>26.9</td>
</tr>
<tr>
<td>NHANES I§</td>
<td>24.5</td>
<td>23.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NHANES II§</td>
<td>24.3</td>
<td>23.2</td>
<td>27.8</td>
<td>27.3</td>
</tr>
<tr>
<td>NHANES III§</td>
<td>24.9</td>
<td>24.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Guidelines for Americans‖</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>19–25</td>
<td>19–25</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&gt;35</td>
<td>21–27</td>
<td>21–27</td>
<td>25.8</td>
<td>22.8</td>
</tr>
<tr>
<td>US Army‖</td>
<td></td>
<td></td>
<td>26.4</td>
<td>23.5</td>
</tr>
<tr>
<td>17–20</td>
<td></td>
<td></td>
<td>27.1</td>
<td>24.1</td>
</tr>
<tr>
<td>21–27</td>
<td></td>
<td></td>
<td>27.5</td>
<td>24.9</td>
</tr>
</tbody>
</table>

* Midpoint of desirable range for Metropolitan Life Insurance height and weight tables in 1959 and 1983; 50th percentile for NHANES (National Health and Nutrition Examination Survey) I, II, and III, phase 1; and healthy weights in the dietary guidelines for Americans.
† One hundred twenty percent of midpoint for Metropolitan Life Insurance tables in 1959 and 1983, 85th percentile for NHANES II, and discharge weights for obesity by the US Army, provided certain fat percentages are not met.
‡ Metropolitan Life Insurance, 1959; 1983.

Changes in immune function (15). Diets for weight reduction should optimally provide adequate amounts of all necessary nutrients except energy. It is very difficult, however, to maintain an adequate intake of micronutrients with energy intakes below 1,000 kcal/d unless supplements are provided (15).

Weight reduction, if adequate, has been reported to restore immunity in obese persons, although other effects secondary to the diet itself, or to stress during a very low energy diet, cannot be excluded (16).

Obese individuals have underlying impairment of lymphocyte responsiveness, although this can be reversed with adequate weight reduction. In those who are obese, this impairment, in conjunction with the risks incurred by a restricted diet (19), can cause further deterioration in immune function and ultimately produce manifestations of disease (20).

By contrast, many reports have suggested that anorexic patients, even though severely malnourished, remain relatively free of infectious disease (21) and show an unexpectedly high resistance to malignancy (22), at least until they enter the advanced stages of debilitation (23).

On the basis of various clinical observations, an association between refeeding and infection (24) has been suggested, in that starvation may suppress and refeeding may activate certain infections. The fact that the usual anorectic diet is deficient in carbo-
hydrate and energy while being relatively sufficient in protein and fat (25) could ex-
plain the apparently low likelihood of infection, with only a moderate deficiency of
copper, zinc, and iron-binding proteins, and, rarely, vitamin deficiency (26). These
conditions, therefore, are different from primary protein-energy malnutrition, al-
though affected individuals have been classed as being "relatively protein-calorie
malnourished" (27).

Studies of immune function of patients suffering from eating disorders have shown
them to have multiple impairments similar to those occurring in simple malnutrition
(27,28). Thus, although some of the immune impairments found in anorexia nervosa
are similar to those observed in primary malnutrition, they are less common and less
severe, and immune function seems to be better preserved than would be expected,
considering the highly undernourished state of these individuals (29). The difference
between simple starvation and anorexia nervosa may reflect the individual variabil-
ity in the micronutrient and macronutrient intake in the latter (22).

CHANGES IN THE IMMUNE SYSTEM

Nutrient excesses and deficits affect immune responses both directly and indirectly
through their effects on metabolism (17). It is also important to take into account
that both obesity (30) and anorexia nervosa or bulimia (29) are associated with in-
creased plasma cortisol. Epidemiological, clinical, and experimental evidence now
indicate that obesity, weight reduction treatment for obesity, and anorexia nervosa
and bulimia are all associated with impairment of immune function, although this
has received relatively little attention. The results, however, are controversial
(15,31,32).

Obesity and dieting are associated with altered intake and metabolism of nutrients
that are known to affect immune responses (6,14,15). Although B- and T-lymphocyte
counts, polymorphonuclear (neutrophil) phagocytosis, and serum immunoglobulins
and complement components have been found to be normal in obese adolescents, im-
paired delayed type hypersensitivity (DTH) testing responses, mitogen-stimulated
proliferation, and bactericidal capacity of neutrophil phagocytosis have been re-
ported in more than 30% of these individuals (14). The impaired immune function in
obesity could be a result of micronutrient deficiencies, even when relatively mild
(17). A high prevalence of vitamin deficiency, especially of the antioxidant vitamins,
has been found in obese women (33). However, immune responses can be enhanced
in obese children on supplementation (34).

With respect to anorexia nervosa and bulimia, little information is presently avail-
able on alterations to the immune system, and the results obtained so far suggest a large
between-patient variability in the effects of these disorders on immune response (32).

These observations imply that the protocol used for restricting energy intake or
refeeding, depending on the pathology, can affect many variables. This shows the im-
portance of investigating the interactions between metabolic, biochemical, and immu-
nologic factors with respect to diet, weight loss or gain, and, most importantly, nu-
tritional status (35).
In addition, nutritional and neuroendocrine status are among the factors likely to be involved in modulation of immune responses, both in obesity, as a result of dieting and weight reduction during obesity treatment (15), and in patients with anorexia nervosa because of their abnormal eating behavior (22).

**IMMUNOCOMPETENT CELLS**

Immunocompetent cell populations are well known to be affected by nutritional status, and either an excess or a deficient dietary intake, as in dieting to lose weight or refeeding to gain weight, can affect their number and function.

Obesity has been related to higher blood cell counts of total leukocytes, neutrophils, lymphocytes, and monocytes; these have been identified as independent risk factors for cardiovascular disease and cancer (36). Thus, decreases in numbers of these cells with weight loss could be interpreted as being consistent with lowered risk status. In fact, a decrease in total leukocyte, neutrophil, lymphocyte, and monocyte counts has been found in obese subjects during dietary treatment or following weight loss, although this is relatively modest. However, these altered white blood cell values are not outside the normal range (18,36), and no changes have been found in the leukocyte pattern of obese subjects after the ninth week on a very low energy diet or by the end of the program (37).

Studies of immune function in anorexia nervosa and bulimia nervosa, on the other hand, have provided additional information on the immunologic consequences of long-term dietary energy deficits and large weight losses in humans. Although it is currently accepted that hematologic values in patients suffering from these syndromes are within the normal range, studies on immunohematologic variables suggest an aberrant immunologic status (32). Thus, low values have been found in anorexia nervosa, and a tendency is seen to leukopenia together with a relative lymphocytosis in both anorexia nervosa (27) and bulimia, especially when the diagnosis is delayed (> 3.5 years) (28). However, when the diagnosis of bulimia nervosa is early (< 1.5 years), neither an alteration in the neutrophil or monocyte counts nor a relative lymphocytosis occurs. Nevertheless, lymphocyte counts are lower than in controls, which is a sign that malnutrition is occurring in the bulimia patients (38). It is important, therefore, to diagnose such patients early to lessen the likelihood of their becoming seriously malnourished and to avoid prolonged damage to their immunocompetent cells (32).

**IMPLICATION OF LYMPHOCYTE SUBSETS IN THE DETECTION OF SUBCLINICAL SITUATIONS OF MALNUTRITION**

The percentage of T-helper (CD4) cells has been shown to decrease in obese dieters at weeks 4 and 6 of dieting (370 kcal/d), with no change in the number of T suppressor (CD8) cells; this outcome results in a fall in the CD4:CD8 ratio. On refeeding, however, the percentage of T-helper cells and the CD4:CD8 ratio return to baseline values (18). Nevertheless, normal CD4$^+$ counts have been reported in obese subjects
after 6 months of dieting (800 kcal/d for 3 months followed by 3 months of food reintroduction). Although the numbers and percentage of CD8 lymphocytes in obese dieters do not differ significantly from the values in controls, significant decreases occur during and after dieting, reaching levels below controls at the end of the study period (39). One of the lymphocyte subsets that is most affected by dieting is the natural killer (NK) cells, which do not return to prerestriction levels after refeeding on an adequate dietary energy intake (40).

In contrast to other types of starvation characterized by low CD4⁺ counts (14), however, some investigators have found normal CD4⁺ counts in patients with anorexia nervosa and suggest that this could explain the lack of increased infection risk in affected individuals (39).

Cytofluorometric studies of immune function do not show a significant impairment of the immune system in adolescents admitted to the hospital for anorexia nervosa (29). On the other hand, significant reductions in the numbers of T lymphocytes and CD4, CD8, and CD57 cells have been found in comparison with controls (41,42). Some of these differences could be explained by the characteristics of the populations chosen for study, reflecting variations in age and the duration of illness. It is very important to take into account not only the degree of malnutrition in the patient but also the evolution of the illness, the time after diagnosis, and whether the patient has received adequate treatment (32).

In early studies, no modifications in CD4 cells were observed in outpatients suffering from anorexia nervosa who had received inadequate treatment at the onset of the illness. However, the CD8 subset was increased, leading to a lower CD4:CD8 ratio (27), which is considered to be an index of malnutrition (43). On the other hand, in a 1 year follow-up study of patients diagnosed early, admitted to the hospital, and submitted to both psychiatric and nutritional therapy from the onset of the illness, the CD4:CD8 ratio remained unmodified in comparison with controls, even though the numbers of CD2, CD3, CD4, CD8, and CD57 cells were lower than in the control group. However, an increase in CD2, CD3, and CD4 subsets was observed after the period of hospital admission (which lasted ~1 month), although curiously this was less when the patients had been living at home for a month (41) (Fig. 1).

Naive cells have been shown to be particularly sensitive to malnutrition (42). Thus, a reduction in naive CD4⁺CD45RA⁺ cells and an increase in cytotoxic CD8⁺ cells have been reported in patients with anorexia nervosa (age range 14 to 18 years) by Allende et al. (44). According to these investigators, although the CD4⁺ subset is altered in malnourished patients with anorexia nervosa (BMI < 17.5), the percentage of CD4⁺ cells increases after refeeding when the patients tested have a BMI greater than 17.5; the increase particularly involves naive CD4⁺CD45RA⁺ cells, with no significant change in the memory (CD⁺CD45RO⁺) cells. Obviously the CD45RA⁺:CD45RO⁺ ratio reached its lowest value in the group with a BMI of less than 17.5. The CD4:CD8 ratio was also particularly reduced in the patients with the lowest BMI (< 17.5), although higher values were restored when BMI increased to more than 17.5, becoming similar to controls.
As mentioned, it is important to specify the age range of the patients tested. Thus, in patients with anorexia nervosa (aged between 14 and 42 years), with a great variation in duration of illness (from 1 to 21 years), the most affected cells were memory CD4⁺ and CD8⁺ (CD45RO⁺RA⁻) cells, which increased after refeeding. This finding could be related to the perceived lack of common viral infections in underweight anorexic patients, and their return with weight recovery (45). In our research group, we consider the development of a febrile illness during hospital treatment of anorexia to be a sign of improvement and a reason for congratulating the patient (32).

With regard to bulimia, CD2 and CD4 counts have been shown to be reduced by 39% and 56%, respectively, compared with control in patients with illnesses lasting 3.5 years or more and with a normal BMI (28). This might reflect a deterioration in cell-mediated immunity (43). However, CD8 levels have been found to be unaltered, so the CD4:CD8 ratio reaches values below 57% of those in the controls. If the disease evolves over a shorter time course (<1.5 years), the CD4:CD8 ratio appears to be within the normal range, although the lymphocyte subsets show lower values than in controls (41). Vomiting has also been shown to affect lymphocyte subsets (38) (Fig. 2).

As well as the T-lymphocyte subset count findings cited above, it is important to take into account thymocyte function in these eating disorders, which will depend on weight fluctuation, diet restriction, and malnutrition status.
Unstimulated and mitogen-stimulated proliferation of lymphocytes decreases significantly in obese dieters after being on a 6-week, all protein, very low energy diet (370 kcal/d), and except for the response to one mitogen combination, this returns to baseline on refeeding (18). A decrease in the intracellular incorporation of [³H]-thymidine on stimulation of T lymphocytes with either phytohemagglutinin or concanavalin A (Con A) has been found in obese subjects compared with nonobese controls, with an increase in T-lymphocyte response to both these mitogens after weight reduction (16). Similarly, a significantly lower phytohemagglutinin-stimulated proliferative response has been reported in obese than in nonobese children and adolescents (34). However, exercise may enhance the impaired immune system in obese persons, and it has been reported that exercise reverses the impaired mitogen-stimulated lymphocyte proliferation and NK-cell activity in obese Zucker rats (46).

Delayed type hypersensitivity test responses to six antigens in obese dieters were not affected by the diet, although a trend was seen toward an increase in the size of the cutaneous response (18). However, in a study carried out in middle-aged obese women before and 2 months after a weight loss of 21 kg achieved over a 6 month period, reduced cutaneous responses were found after the weight loss. The change in DTH response may be directly related to changes in BMI (the more weight lost, the greater the decrease in average induration size). This outcome suggests that large

![Graph showing lymphocyte subsets in controls and patients with bulimia with and without vomiting.](image)

* : NO VOM/VOM vs C (Student's $t$ test, $p < 0.05$)
weight losses in obese persons result in a decrease in the functional capacity of the cell-mediated immune system (15). An impairment of the cutaneous DTH responses has been found by other investigators (36). Nevertheless, according to Chandra and Kutty (34), all the obese patients tested in their study showed a DTH response to at least one antigen.

When the DTH response to seven recall antigens was determined in overweight women after energy restriction, following a high fat or a low fat diet, no changes were found (40). According to the authors of that paper, the reason was likely to be that the women were all healthy, which is the reason why it is important to stress that prolonged or drastic energy restriction should obviously be supervised by physicians.

Similar hemagglutination inhibition titers against different viral antigens (and in the tuberculin test) have been found in patients with anorexia nervosa in comparison with a control group (47). A normal reactive skin test response has been reported in anorexic patients where *Candida albicans* was one of the five antigens used (48). Likewise, cellular immune function (evaluated by means of an anergy panel including candida, streptokinase/streptodornase, and mumps antigens) has been shown to be preserved in patients suffering from anorexia nervosa until weight loss is far advanced (23). However, reduced cutaneous reactions against other antigens have been reported (21). Our group (49) observed reduced responses to a delayed hypersensitivity skin test in patients with anorexia nervosa and bulimia compared with a control population (839 women aged from 16 to 25 years): it seemed that the most severe impairment of the cellular immunity occurred in patients with bulimia; however, this could be a reflection of the longer period of illness in the bulimia patients (3.75 years) in comparison with the anorexia nervosa patients (1.77 years).

Cell-mediated immunologic reaction to stimulation, as expressed by T-lymphocyte proliferative response to the phytohemagglutinin stimulus, seems to be well preserved in anorexic patients, as an unmodified T-lymphocyte proliferative response is seen to this stimulus, both under basal conditions and after the acute administration of corticotropin-releasing hormone in comparison with a control group (22). This is in contrast with the blunted responses observed in simple starvation (43) and might be one of the factors explaining the resistance to infection and malignancy observed in patients with anorexia nervosa (22).

The basis of these contradictory results could be qualitative nutritional differences reflecting different degrees of malnutrition. Patients with anorexia nervosa, although severely malnourished, usually have a relatively well-preserved protein intake (22), and it is well known that in primary malnutrition the blunted proliferative response to mitogens is related more to protein deficiency than to a globally reduced energy intake (18).

**CYTOKINE REGULATION AND THE IMMUNE RESPONSE**

Cytokines are modulated by nutrients and their participation is essential in triggering certain mechanisms involved in the infection process (50). Interesting data suggest that expression of at least one cytokine, tumor necrosis factor (TNF), is af-
fected by adiposity. Thus, increased expression of TNF mRNA in adipocytes from fat biopsies has been found in obese subjects, possibly related to the degree of adiposity. Interestingly, the levels of TNF mRNA fall consistently with a reduction in body weight (51). It is important to stress that obese subjects do not comprise a homogeneous group and significant differences can be found, depending on the degree of adiposity, the distribution of body fat (which is affected by sex), and the origin of the obesity (17).

The Interrelationship Between Leptin and Cytokines in Obesity

Leptin, the protein encoded by the ob gene, is known to regulate appetite and energy expenditure. Obese (ob/ob) mice fail to produce leptin and show hyperphagia, decreased energy expenditure, and obesity. When such mice are treated with recombinant leptin, their food intake decreases and they lose weight (31).

An interrelation is also seen between cytokines and leptin levels. Thus, exogenous leptin has been reported to stimulate phagocytic function and activate macrophages to produce proinflammatory cytokines, such as TNF-α, interleukin (IL)-6, and IL-12 in ob/ob mice (31). This implies a novel function for leptin as an upregulating factor in inflammatory immune responses.

In addition, ob/ob mice are known to show increased sensitivity to endotoxin-induced liver injury and lethality, suggesting a potential link between leptin deficiency and the dysregulated expression of endotoxin inducible cytokines (52).

In a recent hypothesis of body weight control and the regulation of metabolism, it has been established that adipocytes secrete leptin, a molecule that has a secondary cytokine structure correlating with the amount of fat tissue. In addition, adipocytes express TNF-α locally, which also reduces lipoprotein lipase activity in white adipocytes. Moreover, increased leptin levels downregulate appetite and increase sympathetic activity and thermogenesis in the hypothalamus. Diet-induced weight loss reduces adipose TNF-α expression and serum leptin levels (53).

Cytokine Changes in Anorexia Nervosa

Lymphocytes of anorectic patients have been shown to display major functional defects related to cytokines (54). Thus, an impairment of lymphocyte production of interferon has been reported during protein starvation (55). However, no substantial differences in the 2′-5′ oligoisoadenylate synthetase activity or interferon system activation have been reported in anorexia nervosa patients in comparison with healthy controls on a regular diet (56).

It is important to stress that infection-induced malnutrition, the most common form of cytokine-induced malnutrition, results from the actions of proinflammatory cytokines (TNF, IL-1, IL-6), which are capable of activating the hypothalamic-pituitary-adrenal axis (57). These cytokines are known to be capable of initiating an acute phase reaction that is stereotyped, including loss of appetite (35), fever, cellular hypermetabolism, and multiple endocrine and enzyme responses (58) (Fig. 3). How-
However, we are reporting specific types of malnutrition here, and patients with anorexia nervosa and bulimia do not show the same stereotyped reaction observed in infection-induced malnutrition.

Synthesis of TNF has been found to be inhibited in anorexia nervosa (56). The lack of detectable levels of TNF-α in the serum of anorexic patients could be a result of the short plasma half-life of this cytokine (54). Others have reported raised TNF-α levels when lean body mass is depleted (59), and then normalizes after weight gain (35,56).

The production of IL-1 has been shown to be impaired in protein-energy malnutrition (60); however, synthesis of IL-1, whether spontaneous or after lipopolysaccharide stimulation, has not been found to differ significantly between patients with anorexia nervosa and a control group (61). The clinical significance of such in vitro laboratory observations is unclear, as patients with anorexia nervosa tend to be free of infectious disease, at least until they enter the advanced stage of debilitation (41).

Transforming growth factor-β (TGF-β) is an anti-inflammatory cytokine that can act as a brake on the immune system and suppress immune responses (10) by inhibiting proinflammatory cytokine-induced immunologic or inflammatory processes. As a persistent state of hypercortisolism is found in anorexia nervosa (29) and as glucocorticoids may trigger TGF-β production and release (62), the undetectable serum levels of TNF-α found in some studies (54) may be explained by the actions of TGF-β. This could be the reason why immunosuppression is one of the characteristics of patients with eating disorders.

Raised serum IL-6 concentrations have been found in patients with anorexia nervosa, which may partially be attributable to the increased TGF-β levels (54). IL-6 has been detected in high concentrations in the serum of some tumor-bearing animals with cancer-associated cachexia (63). Interrelations exist between IL-6 and other cytokines: not only is IL-6 capable of modulating IL-1 (64), but the release of IL-6 is
also modulated by a variety of stimuli, including cytokines such as IL-1 (65), TNF-\(\alpha\), and TGF-\(\beta\) (66). In addition, IL-6 has been shown to play a major role in the pathogenesis of postmenopausal osteoporosis (66). Thus, a raised IL-6 concentration could contribute to osteoporosis in anorexia nervosa (54).

Phytohemagglutinin-stimulated peripheral blood mononuclear cells from patients with anorexia nervosa show a lower capacity to produce IL-2 than cells obtained from healthy subjects. However, an enhanced stimulatory effect of the patients' serum has been shown on the secretion of IL-2 by blood mononuclear cells from healthy controls (61). This supports the hypothesis that the patients' plasma not only contains inhibitors of immune function but also sufficient nutrients to sustain a normal lymphocyte transformation response (22). This is the reason why the presence of a stimulation factor in the serum of patients with anorexia nervosa has been suggested, which could compensate for the reduced capacity of their own peripheral blood mononuclear cells to produce IL-2. Such a mechanism provides a relatively normal immune response and could explain why patients with anorexia nervosa are not susceptible to infections despite reduced cytokine production by their peripheral blood mononuclear cells (61).

CONCLUSIONS

Because of the controversial results in published reports, research in this field should be focused on groups of patients who are as homogeneous as possible. Thus, any studies in this area should be undertaken only after careful selection of patients on the basis of their age at the time of study and at the onset of the disorder; their psychological and physiologic characteristics; and the duration of the appropriate treatment and the illness. Furthermore, as there are different types of anorexia nervosa and bulimia, different degrees of obesity, and different applications of very low energy diets, the frequency and length of weight fluctuations must be taken into account because of their important role in prognosis, disease evolution, and cure.

In this chapter, we have tried to update research related to immunocompetent cells and cytokines involved in infectious processes. Although the literature consulted has been vast, assessment of correlations between the immune system and other systems in the organism, such as the central nervous system and the endocrine system, would be of great interest in exploring the mechanisms involved (Fig. 4). This information could be important in determining appropriate therapy and avoiding lengthy treatments that may even interfere with the possibility of early recovery from these eating disorders. Professionals involved in the field should take into account the fact that anorexia nervosa and bulimia, and very often obesity, are psychological disorders that result in adverse somatic consequences, causing chaos throughout the organism. Thus, both psychotherapy and pharmacotherapy should be used appropriately according to what is known about the psychological characteristics of these disorders but also about the disturbances in function related particularly to their neuroendocrine and immunologic effects.
REFERENCES

DISCUSSION

Dr. Zoppi: It is important to stress that anorectic infants and children also have high levels of cholesterol in the blood. Dr. Suskind reported these results in his book on infant nutrition. It is possible to have such a lipid pattern in anorexia nervosa as well. The reason is that if the dietary energy intake is low, the percentage of fat may be relatively high compared with the calories ingested.

Dr. Marcos: Rather than the percentage of fat being relatively high, it is the percentage of protein which is high. In fact, patients with anorexia nervosa eat almost no fat but still have high levels of cholesterol. I think their metabolism is completely altered.

Dr. Chandra: One of the possible explanations for high cholesterol in these patients is the reduction in lipoprotein synthesis and also the mobilization of fat from the liver, and reduc-
tion in lipoprotein lipase activity. All these factors could be responsible for the higher cholesterol levels.

**Dr. Suskind:** You mentioned the difference between the anorectic and the marasmic child in terms of the factors that may play a role in their maintaining their immune response. You pointed out a very important point relating to the intake of vitamins and minerals helping to maintain the immune system, which otherwise would be compromised by starvation. I was wondering if you might elucidate that a little bit further.

**Dr. Marcos:** Differences are seen between the situation of a child with protein-energy malnutrition (PEM) and the adolescent suffering from anorexia nervosa. The most important thing to take into account is that the children with PEM do not have the opportunity to eat enough, because they cannot. In anorexia nervosa, the patients can eat whatever they want, but they do not want to eat; they only want to lose weight. That is why I believe you have to take into account the role played by neurotransmitters, as these have to be involved in all these mechanisms. Cytokines must be involved in the food behavior too, because in the end all of these factors are interlinked.

**Dr. Suskind:** Could that information be valuable in terms of the treatment of anorexia, as far as the cytokines or leptin are concerned? Have leptin levels and TNF-α been measured in anorexia and bulimia? And if they have, do you happen to know what the values are?

**Dr. Marcos:** Leptin levels have been measured in anorexia nervosa (1), and the results are the opposite to obesity (2)—TNF-α has been shown to be higher in anorexia nervosa than in control subjects (3). In one study, TNF-α was similar to the control group (4), but if measured in vitro the production is much higher than in controls.

**Dr. Marini:** I was impressed by the figures that Dr. Suskind gave yesterday concerning the number of babies who become obese after being malnourished—maybe as many as 20%. I think this may be related to the genetic constitution of these subjects. I believe they are more efficient at conserving energy: their membrane sodium-dependent adenosine triphosphatase works better than in other individuals, so they can save energy. Thus, when they resume a normal diet, they become obese. It is just a genetic selection of these cases.

Another point is about leptin. When you look to the intrauterine growth retarded babies (and this fits very well with Barker’s theories), these babies have very high levels of leptin, despite the fact that they are very thin. Maybe this high level of leptin causes downregulation of receptors, so that later on they develop obesity (5). We have recently evaluated the outcome in babies born from diabetic mothers kept under very tight metabolic control (6). These women had very low glucose blood levels, which was maintained very carefully to avoid the usual fetal complications. The newborn infants appeared to be perfectly normal, with no macrosomia at all. When we followed-up these subjects, some of whom are now 30 years old, we found an extremely high rate of obesity (≈55%). This is very high compared with other series of babies born from diabetic mothers managed conventionally (7), where the incidence of obesity is usually around 20%. Thus, it appears that if the supply of glucose to the fetus is reduced too much during fetal life, a risk may be incurred of developing obesity in later life. A possible explanation, involving the IGF-system has recently been suggested (8).

**Dr. Wasantwisut:** You said that the eating disorders group remained mainly free of infection. I wonder whether this is because that group is more likely to come from the well-to-do end of society and so has reduced exposure to infection. Most eating disorders occur in the well-to-do communities.

**Dr. Marcos:** Regarding the lack of infection in anorexia nervosa patients, the ones we studied were admitted to the hospital, usually for between 1 and 3 months, so they had the opportunity to become infected because they were in a hospital environment. Another find-
ing was that, although some of the patients had suffered from allergies before the onset of anorexia nervosa, when the anorexia began their allergies disappeared. It is as though anorexia was a cure for allergy. We believe the reason why they were not infected is that there was a modulation of the immune system. We have recently measured T-helper 1 and T-helper 2 cells and found a decrease in T-helper 1 but no decrease in memory T cells. We think that may be the reason why the patients in the study did not get infected. Related to the high socioeconomic levels, today, at least in Spain, anorexia nervosa patients come from all levels of society. However, some years ago, the professionals involved in this field thought that they came mainly from high socioeconomic levels as they were the only people who could afford private psychiatric treatment.

Dr. Woodward: With regard to the lesser impact on immune competence of anorexia nervosa in the adolescent than in the marasmic infant or child, it seems to me that this is more likely to be related to different stages of immune system development at which the nutritional stress is imposed rather than to micronutrient intake differences, which I know are often suggested as a cause. I have no precise idea why imposing such a stress earlier in the development of the immune system might make the situation worse, but intuitively that makes sense. Could you comment on that?

Dr. Marcos: As these people eat fruit and vegetables their intake of micronutrients could be at a reasonable level. However, as their intakes are extremely low, not more than about 500 kcal/d at most, their micronutrient intakes are also correspondingly very low. That is why I think that other factors must be involved in the apparent resistance to infection.

Dr. Woodward: It seems to me that a critical difference in the response to a somewhat similar nutritional stress at a different stage in development is the important factor here; that is, the infant responds with a much more profound depression of immune function than the adolescent. So, it strikes me that rather than trying to explain that difference in terms of nutritional intake, we need to understand it in terms of the individual's stage of development.

Dr. Tontisirin: What are the major causes of death in patients with anorexia nervosa and bulimia? If it is infection, that suggests a similar response to infants and young children with malnutrition.

Dr. Marcos: The mortality is caused by suicide and sudden death from heart failure. These patients do not usually die of infections; in fact, they have to be really cachectic to get a fatal infection. That is why this condition is so different from other types of malnutrition in developing countries.

Dr. Farthing: Are there any similar groups that have been studied with regard to their immune function, such as prisoners on hunger strike? They would comprise a similar group to anorexics: they would be adults and probably come from a similar cultural background.

Dr. Marcos: I believe they have been studied but I am not aware of any data about alterations in the immune system in such populations.

Dr. Farthing: Could I just ask you a question then about the mechanisms of anorexia nervosa. Some years ago, a study suggested that cholecystokinin (CCK) was increased, both basal levels and in response to food, in these individuals. I wonder today whether you think CCK is an important mediator of the continuing anorexia, because it is an important satiety peptide?

Dr. Marcos: We measured this too, and it was really high but I cannot explain why.

Dr. Suskind: As a pediatrician, and not knowing very much about anorexia, it is hard to believe that such a vast difference exists between a marasmic child and an anorectic adult or teenager. I just wonder if this is primarily because we have not studied anorexia in enough depth in relation to the immune system, gut flora, and so on. Maybe sudden death in these patients could be caused by endotoxic shock from septicemia, with no fever but usually an ele-
vated white count. We have studied the malnourished child in depth over the years, but have we studied the malnourished anorectic adult in sufficient depth?

**Dr. Marcos:** It is true that not many studies have been done in this field, and even fewer on the immune system. But I think that there are great differences between the two situations: a malnourished child is malnourished from around the time of birth, whereas the anorexia nervosa patient usually develops the condition at around 11 or 15 years of age. So, during their first 10 years at least they are well nourished. Then they lose approximately 10 to 15 kg in a very few months. The mechanisms involved in the adaptation of the organism to that new situation must be different from the situation in the malnourished child. Besides not finding any cases of fever, we found low white blood counts showing even a tendency to leukopenia.

**Dr. Chandra:** Although it is true that patients, mostly girls, with anorexia have fewer infections, once they get infections they can be devastating. Many report patients dying, not only of heart failure, or so-called heart failure (for which not much objective evidence is seen), but also of severe terminal infection. I would agree with Dr. Suskind that if an autopsy is done on these patients, endotoxin levels and other evidence of possible infections should be measured and documented. A small additional nutritional point is that zinc has been measured in patients with anorexia nervosa and found to be somewhat low, and many centers use zinc supplements in an attempt to improve taste and appetite. No controlled trials have been done, but the clinical impression is that it might be helpful.

I know of at least two other situations wherein voluntary starvation has been associated with impaired immune response. These are people who for religious or other reasons stop eating for periods of from 7 to 15 days; and secondly, in patients with rheumatoid arthritis, where it has been recommended that periodic starvation might help the clinical symptoms. Indeed, studies have shown that after about 6 to 7 days of almost total starvation, a reduction in the immune response occurs, which may have beneficial effects on symptoms. Cell-mediated immunity and complement levels fall in these patients.

I would support Dr. Woodward's suggestion that perhaps the age at which starvation occurs may be critical. Many of the patients we were talking about yesterday have had malnutrition from birth or soon after, when the immune system is developing, and that could be quite different from a mature individual with well-established immune responses.

**Dr. Marcos:** I agree with Dr. Chandra; however, when we measured zinc levels they were very high in the serum, three to four times as high as in controls and the zinc-dependent enzymes were low, so the whole metabolism is very altered. More research should be carried out to elucidate which mechanisms are involved.

**Dr. Keusch:** I was trying to recall the studies by Cerami and his group when they rediscovered TNF and called it cachectin (9). When TNF, or cachectin, was administered to mice on a daily basis, a reduction in food intake and loss of weight occurred, which continued for several days. However, the effect then dissipated, and I think the weight began to increase again, which suggested that a counter-regulatory cytokine network of interactions might have occurred to counteract the initial effect of TNF on food intake and weight loss. In relation to the question that Dr. Farthing was raising about CCK as being a possible factor in the sustained anorexia in those patients, tachyphylaxis of the cytokine-induced appetite suppression and weight loss might require the added effect of, for example, CCK to reverse it.

**Dr. Kennedy:** Just a comment on immunology and the cytokines: I agree with Dr. Keusch and some of his comments, but a recent paper reported on Bosnian concentration camp survivors. They found that the immunologic changes were very similar to marasmus, and different from anorexia, so I would not be surprised to find that the infection rates in patients with anorexia were different. Probably what we are dealing with here is a very interesting model of
neuroendocrine influences on immune function and the ability to manipulate cytokines by neuroendocrine inputs.

Dr. Marcos: I agree with you. Elite gymnasts comprise another group that is similar in a way to patients with anorexia nervosa. Their physical exercise is on a very high level, 48 hours a week, that is 8 hours a day including Saturdays. Their behavior is very similar to that of anorexics and their food intake is very low. But for some reason these people get many more infections than anorexics. So it is not only the starvation—it is more than that.

Dr. Suskind: One thing that you mentioned with regard to the anorexics that may explain this difference is the fact that they take supplements. Perhaps what you are seeing is the impact of severe malnutrition on the immune system being mitigated by the vitamin and mineral supplements they are taking, so they do not have the same changes in their immune system as, for instance, a severely malnourished adult or child would have. In relationship to obesity, I agree with you that it is important to make certain that any child or adult who is on a weight reduction program is on one that is safe in terms of maintaining lean body mass as well as immune function. I do not think we look at that seriously enough, but the fact is that if you put a child or an adult on a very low energy diet—500 or 600 kcal, high protein, low fat, low carbohydrate—it is also critical that these patients have vitamin and mineral supplements. I think that those of us who are working in the area of adult and childhood obesity should be looking at what happens to the immune system. We have been looking at lean body mass and how it is maintained on these low energy diets, but we have not looked at the immune system.

Dr. Marcos: We carried out a trial of supplements on our anorexic patients, and the most important result was that they gained more lean body mass than patients without supplements. The delayed hypersensitivity skin test was improved as well, but nothing else. We think that they probably needed more supplements than we gave, so we are going to start another trial giving more.

REFERENCES