Assessment of Protein–Calorie Malnutrition

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We critically review the various methods for assessing protein–calorie malnutrition. These tests are lacking in sensitivity and specificity, and currently no single one can be used as a reliable indicator of malnutrition. However, a combination of several of them can be used as prognostic indicators and are of help in selecting patients who may benefit from nutritional support. Body-composition analyses and functional tests hold the promise of greater applicability in the future. Newer and more nearly accurate tests for use in diagnosis of protein–calorie malnutrition as well as for objectively monitoring short-term changes in response to nutritional repletion are badly needed. Despite a lack of consensus on the desirability of objective nutritional assessment, we expect the use of these procedures in hospitals to increase.

Additional Keyphrases: nutritional status • albumin • prealbumin • retinol-binding protein • transferrin • nitrogen balance • potassium • 3-methylhistidine • parenteral nutrition • creatinine • fibronectin • lymphocytes • T-cells and B-cells • immunocompetence

Protein–calorie malnutrition (PCM), also referred to as protein–energy malnutrition, has long been recognized as a common problem—especially of children in the developing countries, whose inadequate nutritional intake is deficient for socio-economic reasons (1–3). The term PCM covers a wide range of deficiency states, from mild to severe, and has been defined as "a range of pathological conditions arising from coincident lack, in varying proportions, of protein and calories, occurring most frequently in infants and young children, and commonly associated with infections" (4). This definition emphasizes the important concepts that inadequate intake of both protein and energy-yielding food can lead to PCM and that various forms of malnutrition are inter-related. The individual initially responds to deprivation of protein or calories, or both, by adaptation, and only when the deprivation continues does an eventual physiological breakdown occur, marked by symptoms and clinical signs.

The severe and advanced stages of PCM, characterized by clear clinical signs and symptoms, are estimated to occur in 1 to 3% of the children from developing countries (5). However, at least 10-fold as many children may be suffering from less severe or "marginal" malnutrition (5). It has been suggested—on the basis of data on weight in relation to age—that as many as one-half to two-thirds of all children in some developing countries may be marginally malnourished (6). According to the well-known Gomez classification, "weight for age," is used as a basis for grouping the malnourished children into grade 1 (75–90% of the standard), grade 2 (90–75% of the standard), and grade 3 (less than 60% of standard) (7).

An accurate assessment of the extent of marginal malnutrition is hampered by the difficulty in defining this term and in diagnosing subclinical malnutrition. Be'har (8) characterizes marginal malnutrition as all subclinical forms of malnutrition in which nonspecific signs or laboratory indices may be present that are considered to be related to inadequate nutrient intake but are not clearly recognizable as a nutritional disease. This type of malnutrition may commonly present in the elderly and the poor in the United States, as well as in hospitalized patients.

PCM in Hospitalized Patients

Until a few years ago, it was assumed that the problem of PCM, so important for the developing countries, had little relevance to the population of western industrialized countries and was relatively rare in the United States, where it was thought to affect, if at all, only a very small segment of the poor and the elderly, who are more likely than others to be malnourished. As a result of this impression, medical school curricula paid little attention to the problem of diagnosis and treatment of PCM. Cannon et al. (9) had showed as early as 1944 that adequate protein intake and utilization was important in combating infection. That hospitalized patients may constitute a significant group of malnourished individuals was also indicated by Rhoads and Alexander (10), who showed that loss of nutrients as a result of disease led to cases of starvation in United States hospitals, and that the incidence and severity of infection and surgical complications was higher in such patients. However, not until the 1970s, as a result of numerous studies (11–15), did it become quite clear that the prevalence of PCM in the hospitalized population—characterized by depletion of body fat, muscle, and visceral protein stores—is close to 50%. PCM—either primarily or as a consequence of some other condition such as malignancy, trauma, or surgery—appreciably increases the morbidity, mortality, and susceptibility to infection generally associated with a given disease (14, 16–19). Moreover, with the advent of improved techniques for enteral and parenteral nutrition, malnutrition in the hospital setting has become a manageable problem, and the resulting improvement in the nutritional status of a patient may lead to a positive clinical outcome. Indeed, evidence now indicates that optimal nutritional status of a patient leads to better results with surgical procedures.

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3 Nonstandard abbreviations: PCM, protein–calorie malnutrition; MAMA, mid-arm muscle area; 3-MH, 3-methylhistidine; DCH, delayed cutaneous hypersensitivity.

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procedures and other forms of therapeutic interventions. However, total parenteral nutrition carries with it certain risks of metabolic derangements associated with the mode of feeding, and it should be administered judiciously.

As a result of the greater appreciation of the importance of the nutritional status of a patient in the overall prognosis, and to make the most effective and rational use of total parenteral nutrition only for those patients likely to benefit most, with minimal risk of adverse effects, there is clearly a need for an accurate, objective, and comprehensive means of evaluating a patient's nutritional status. Although it is possible to evaluate PCM clinically, especially when the condition is moderate to severe, lack of consistency in the clinical impression of a patient by different examiners or by the same examiner at different times is a major source of error. Nutritional assessment provides an objective picture of malnutrition, with its primary goal to identify the patient with "clinically relevant malnutrition, i.e., state of altered nutritional status which is associated with adverse clinical events" (14). Objective evaluation of nutritional status is also essential for adequate nutritional care, to monitor the progress of a patient on nutritional therapy, and for a prognosis. Identification of patients who may have greatly increased nutritional needs and are likely to become protein–calorie malnourished is also important. For example, the energy requirements of a burned patient may be more than twice normal, and failure to treat them will lead to weight loss and even death. Despite advances in this area, clinicians are not very clear as to which tests to use for nutritional assessment (20) and how best to use the available data for the proper management of the patient. In fact, one of the main reasons for the high incidence of malnutrition in hospitalized patients is that many health professionals cannot identify the patients at high risk.

As benefits of nutritional therapy are being more widely recognized, the need for nutritional assessment is gaining greater acceptance. However, there is no consensus as to its utility. Some investigators (21–24), believing that clinical judgment suffices in evaluating nutritional status, criticize the tests used in nutritional assessment for their lack of sensitivity and specificity and their insufficient validation (25). Nonetheless, nutrition-support teams of doctors, nurses, dietitians, and pharmacists are now commonplace in hospitals, and the trend is towards increasing hospital utilization of nutritional-assessment procedures. Future directions in this field would involve clinical chemists as well, to use the currently available laboratory procedures more effectively and to help develop more reliable indices of PCM.

In this review we primarily discuss methods for nutritional assessment and interpretation of data, with particular emphasis on critical discussion of tests done in the clinical laboratory. The topic of micronutrient malnourishment, which generally accompanies PCM, is beyond the scope of this article.

Several recent reviews (22, 26, 27) have addressed the subject of nutritional assessment. An excellent and comprehensive article (28) has appeared in a book on clinical nutrition, and a manual on the subject, based on the practices followed by Dudrick's group at one of the large hospitals and containing a wealth of theoretical and practical information, has recently been published (29). Nutritional assessment has also been the topic of several symposia (30–32).

Consequences of PCM

Before discussing nutritional assessment in detail, we will briefly describe the clinical syndromes that result from severe PCM.

Mild or moderate PCM diminishes the rate of increase in size and growth in young children, whereas the severe PCM resulting from prolonged nutritional deprivation comprises a range of conditions that can be put into three main classes: kwashiorkor and marasmus, which form the two extremes of the spectrum and are caused by protein and energy deficiency, respectively, and the intermediate class, marasmic kwashiorkor. Gopalan has suggested (33) that the syndromes of marasmus and kwashiorkor are two facets of the same disease entity, the final outcome being determined by the individual's capacity to adapt to nutritional stress. It has also been proposed that an adequate adrenocortical response is needed for satisfactory adaptation to the nutritional deprivation leading to marasmus, whereas failure to adapt gives rise to kwashiorkor.

Severe PCM in adults is analogous to the childhood syndromes, but in general many of the depleted adults are not as seriously affected as the use of these terms would suggest. Anthropometric methods are useful in distinguishing various forms of severe PCM and will be discussed in detail under Nutritional Assessment Procedures.

Kwashiorkor. The term "kwashiorkor," meaning the "disease the first child gets when the second is on the way" in the Gia dialect of Ghana, was introduced by Williams (34) in 1933 for a previously recognized syndrome linked to malnutrition. In contrast to marasmus, the child afflicted with this syndrome characteristically has edema. Growth is stunted and wasting of skeletal muscle is apparent, but subcutaneous fat is maintained. Kwashiorkor in children frequently leads to death, and terminal infections are invariably present.

Adult kwashiorkor is common in patients whose protein intake is inadequate and whose catabolism is increased—as in trauma or severe burns. This condition may develop rather quickly in response to protein deprivation, and in general is characterized by depressed protein concentrations in serum and subnormal immunocompetence. Anthropometric measurements are within normal limits. The concentrations of certain hormones, e.g., cortisol, vasopressin, insulin, and somatotropin, are affected in kwashiorkor. Endocrine changes in PCM have been reviewed by Becker (35). Aggressive nutritional support of such patients is needed; otherwise, their prognosis is poor.

Marasmus is a chronic condition resulting from a deficiency in total energy intake, whether the source of energy is protein, fat, or carbohydrate. The marasmic individual has consumed all the reserves of protein and energy and is thus severely wasted in skeletal muscles as well as fat depots. A child with this syndrome is generally inactive and underweight, with prominent ribs and a head that appears disproportionate in size. Vital muscle functions are impaired, as is immune function, and subcutaneous fat is absent. In adults also, anthropometric measurements are subnormal but serum protein concentrations are normal. The distinctive characteristic of marasmus is that edema is absent. Patients with wasting illnesses such as cancer commonly have marasmus and give a starved appearance. If the patient receives adequate nutritional support, the prognosis is good, but with additional stress the patient is prone to develop marasmic kwashiorkor.

Marasmic kwashiorkor is a condition characterized by features of both marasmus and kwashiorkor and is a form of severe PCM that occurs when stress is superimposed on a chronically ill, starved patient. Body-fat stores as well as both somatic and visceral protein stores are depleted. This condition is marked by a high incidence of life-threatening complications. Immunocompetence is lowered. The prognosis is very poor because of the high risk of infections and the poor wound healing.
Procedures for Nutritional Assessment

No single method currently available adequately assesses PCM. Instead, various methods and rather nonspecific tests are used to obtain such data. These can be grouped under anthropometric, biochemical, clinical, and dietary approaches, sometimes referred to as the ABCD of nutritional assessment. A stepwise approach to nutritional assessment is generally recommended. Subjective methods of evaluation, including the medical history, nutrition history, and a thorough physical examination, continue to be of great importance and should be used first, along with a routine screening procedure comprising some of the simpler methods, to identify high-risk patients. A partial list of those populations of patients who are at greater risk for developing PCM includes patients with cancer, liver disease, kidney disease, diabetes, pancreatic disease, or digestive or absorptive diseases; obese patients who may have protein malnutrition with caloric surplus; and elderly patients or those with chronic diseases. Also susceptible are patients with hypermetabolic states such as trauma or burns, those undergoing chemotherapy or radiation therapy, and patients who have lost more than 20% of their usual body weight. Physical examination of the patient may reveal certain signs of malnutrition such as changes in the hair and skin, and may provide indications for further evaluation. The nutritional status of high-risk patients hospitalized for lengthy stays should be assessed periodically, because patients who appear adequately nourished can become depleted very quickly as a result of complications of the disease or the treatment. Those patients identified by the screening procedure as being at high risk should be comprehensively assessed to quantify the degree of malnutrition and to provide a baseline for the nutritional therapy that follows. Additional subjective and objective data are collected for this purpose, including 24-h dietary recall to determine the adequacy of dietary intake. Energy requirements are calculated by the Harris–Benedict equation (36) for determining the basal energy expenditure and adding it to additional needs as defined by the nature of the physical activity and of the disease state. For more details concerning calculation of energy needs, consult the manual by Jensen et al. (29).

For the purpose of assessing PCM, one can think of the body protein in two compartments: somatic (that in skeletal muscles) and visceral protein (all the rest). Most commonly evaluated variables of PCM include measurement of these compartments as well as changes in body weight and assessment of fat stores and of immune status.

Before detailing the various factors used in assessing PCM, let us elaborate on the concept of "body cell mass," which is important in relation to the objective of nutritional assessment. Body weight consists of the skeletal mass, which is relatively inert; the body fat, which can be considered as the energy store of the body; and the energy-utilizing component, referred to as "the lean body mass" (26). In 1923 Moulton (37) emphasized the concept of "lean body mass," originally proposed by Rubner in 1902, as the component that has a constant composition and that, unlike neutral fat, is rich in both potassium and nitrogen. In 1963 Moore's group (38), using isotope-dilution techniques, showed the direct relationship of resting energy expenditure to the size of the lean body mass. These workers further pointed out that some of the tissues constituting the lean body mass are inert and they introduced the more precise term, body cell mass, defined as "the oxygen-changing, potassium-rich, glucose-oxidizing, work-performing tissue" (38). The measurement of the body cell mass is an ideal single parameter for assessing nutritional status, because the loss of this component as a consequence of hypermetabolic states such as burn or sepsis is representative of the increasing inability of the body to utilize energy to support vital functions and will therefore eventually lead to death. The preservation of body cell mass is thus the aim of nutritional therapy. We will discuss more sophisticated techniques for estimating the size of the body cell mass, not generally available in hospitals, in a later part of this article. Here we will discuss the commonly used indices of nutritional assessment.

Body Weight

Body weight is a simple but important index to malnutrition, although it does not provide any information about the nature of tissue loss. Therefore the practice in many hospitals of not routinely weighing their patients is to be deplored. Monitoring weight changes, fluid intake, and urinary output, the clinician can ascribe weight changes to dehydration or to a real weight loss in an adequately hydrated patient. Changes in body weight are related either to an individual's weight or to the "ideal weight for height" as derived from anthropometric tables. Comparison of weight with "ideal" body weight generally leads to unsatisfactory results because these tables are inadequate in many ways. Comparison with the individual's usual body weight is preferred, but this depends on accuracy of recall and is subject to considerable error (39).

It is important to accurately record the daily weight of the patient at the same time each day, to avoid the variations in body weight throughout the day. Weight loss exceeding 20% of the usual body weight may put the patient in a high-risk category for surgery (40). Seltzer et al. (41), in a study of approximately 5000 surgical patients, showed that a weight loss of 10 lb. (4.5 kg) or more was associated with a 19-fold increase in mortality.

Body weight provides information regarding malnutrition but, as pointed out by Buzby and Mullen (28), changes in body weight cannot be used as an indicator of "clinically relevant malnutrition" and a weight loss exceeding 10% should rather be used as a risk factor for malnutrition, prompting more thorough nutritional assessment. A patient may be malnourished without showing significant weight loss; conversely, the extent of weight loss does not necessarily correlate with the degree of malnutrition.

The increased energy requirements of the hypermetabolic or catabolic hospitalized patient are met by three major body compartments—fat stores, somatic tissue protein, and visceral protein stores—and assessment of these three components is important for interpreting changes in body weight.

Assessment of Fat Stores. Adipose tissue constitutes the primary caloric reserve of the body, providing energy during periods of starvation or depletion. Estimation of the body fat stores may indicate the extent of malnutrition and the ability of the individual to withstand additional starvation. Measurement of the skinfold thickness at the triceps of the nondominant arm with a caliper provides an estimate of subcutaneous fat, and thus an index of total fat, because more than half of the total body fat is subcutaneous, and changes in subcutaneous fat have been assumed to reflect changes in body fat (42). This measurement correlates somewhat better with total body fat than do results of ultrasound or radiographic techniques, but subcutaneous fat thickness is not estimated as well as by other techniques (43, 44). Although estimation of subcutaneous fat and of total body fat stores is subject to numerous errors and is relatively insensitive to short-term changes in tissue composition, serial measurements in a given patient performed by the same trained observer on the same side (usually right) are reproducible (45) and provide a good evaluation of the status of fat stores during depletion and repletion (46).
However, when different individuals make the measurement on different days, the coefficient of variation (CV) may be as high as 22% (47).

Proper skinfold thickness measurement is obviously limited to the sites where a proper fold can be raised, which creates a problem in obese individuals. It has been suggested that measurements should be made at a variety of sites (42). Most current data, however, refer to triceps and subscapular sites only, and indicate a good correlation between weight change and the sum of triceps and subscapular skinfold thickness (48, 49). After reviewing the published literature, Bastow (42) concluded that "overall the most practical method of assessing subcutaneous fat thickness is the use of skinfold skin calipers." Frisancho (50) has published skinfold percentiles standards, which can be used in estimating total body fat.

Interpretation of the decreased values of triceps and subscapular skinfolds varies according to the investigators involved. When the percentile values are used as a standard, values between the 35th and 40th percentile indicate mild depletion, between the 25th and 35th, moderate depletion, and below the 25th percentile, severe depletion (22). Changes in body composition owing to moderate malnutrition are mainly confined to a decrease in body cell mass, and body fat may remain normal.

**Anthropometric assessment of muscle mass.** In addition to fat stores, which serve as the primary source of energy by lipolysis during periods of nutrition deprivation, tissue protein reserves provide energy by conversion to glucose via gluconeogenesis. Skeletal muscle, which makes up about two-thirds of the total body protein, provides an indicator of the severity of PCM, whatever the underlying cause of negative nitrogen balance may be (51). There are several ways to determine muscle mass, the simplest and the least expensive being anthropometric, the measurement of mid-arm circumference and area (13), which has been correlated with other measures of total muscle mass (52, 53).

Both mid-arm muscle circumference (MAMC) and mid-arm muscle area (MAMA) are derived from mid-upper-arm circumference (MAC), determined at the same level as the triceps skinfold (TSF), and expressed by the equations (28):

\[ \text{MAMC (cm)} = \frac{\text{MAC (cm)} - \pi \text{TSF (mm)}}{10} \]

and \[ \text{MAMA} = (\text{MAMC})^{2/4} \pi \]

The calculations are based on the assumptions that both the mid-arm and the mid-arm muscle compartment are circular and that triceps skinfold is twice the average diameter of the fat rim. Heymsfield et al. (54), using computed axial tomography, found that the above approximations were in error, leading to about a 25% overestimate of the MAMA, and tended to underestimate the amount of muscle atrophy. In the corrected equations proposed by these authors, to arrive at the absolute amount of fat-free body mass, they subtracted 10 and 6.5 for men and women, respectively, from the above equation. These workers also defined a range of MAMA values that are compatible with survival, introducing another index, the "available MAMA." Available MAMA values were obtained by subtracting 9 cm² from the corrected equation for MAMA, because death usually resulted when the corrected MAMA fell below this value. Values for available MAMA between 0 and 5 cm² are considered indicative of severe PCM, whereas values of zero or less suggest life-threatening PCM.

To detect small changes that take place in corrected MAMA after nutritional therapy to a depleted patient, it is important that mid-upper-arm circumference and triceps skinfold be measured on a marked arm by the same observer. The main criticism of anthropometric measure of muscle mass is its lack of precision, so that the accuracy of the measurement for an individual patient is not very great. Also, muscle mass can change independently of changes in muscle composition, and there is poor correlation with concentrations of visceral protein (55). However, anthropometry of muscle mass, when applied serially by trained personnel with careful attention to some points such as those outlined by Heymsfield et al. (54), provides an easy, noninvasive, and inexpensive method for following changes in protein status.

**Some Clinical Chemical Measurements**

**Urinary creatinine and creatinine/height index.** Measurement of the 24-h urinary creatinine excretion is the most widely used biochemical index of muscle mass. Creatinine is produced from creatine by dehydrogenation in an irreversible reaction that takes place at a relatively constant rate in proportion to the muscle mass in individuals with normal renal function and sufficient fluid intake. Values for 24-h urinary creatinine excretion correlate with anthropometric measures of muscle mass, basal oxygen consumption (53, 56), and lean body mass as measured by isotope-dilution or 40K total body counting (57–59).

The creatinine/height index proposed by Bistrian et al. (60) is a composite anthropometric and biochemical indicator of protein reserves. This index exploits the ratio between the 24-h creatinine excretion observed for a subject and that expected for a normal healthy adult of the same sex and height (60). The expected creatinine excretion is obtained by multiplying the normal creatinine excretion (23 mg/kg per day for males and 18 mg/kg per day for females) with the ideal weight for height for medium frame. Published tables show the expected 24-h urinary creatinine excretions for both sexes (60–62). A decrease in muscle mass is assumed to be reflected in a proportionate decrease in the creatinine/height index. Index values of 40–90% are indicative of moderate depletion; values below 40% are evidence of severe depletion (61).

The fact that creatinine excretion is influenced by age, decreasing with increasing age, leads to a falsely high estimate of muscle-mass depletion in the elderly. Indeed, no standards for the elderly are available. Another problem in using creatinine/height index as an indicator of muscle mass is the difficulty in obtaining a reliable 24-h urine specimen; thus CVs for daily creatinine excretion are high (22).

The creatinine/height index does not accurately reflect muscle mass in patients with impaired renal function and urine output; moreover, it is affected by a diet high in protein (63). Because steroids and some other medications affect creatinine excretion, use of the creatinine/height index in such cases may be unreliable.

**3-Methylhistidine (3-MH).** 3-MH is an amino acid found mainly in myofibrillar protein. When the protein is degraded, 3-MH is released but cannot be re-utilized and is rapidly and quantitatively excreted in the urine. In light of suggestions (64, 65) that the rate of urinary excretion of 3-MH should reflect the breakdown of protein containing this amino acid, it has been used as another biochemical marker for evaluation of somatic protein mass. By using the excretion ratio of 3-MH to creatinine, one can calculate the fractional turnover of muscle protein.

3-MH can be measured with an amino acid analyzer, by liquid chromatography, or, as more recently reported (66), by a convenient fluorometric assay, which can be automated. Because 3-MH is also produced by breakdown of ingested muscle protein, it is necessary to exclude muscle protein from the diet three days before the analysis, a requirement.
that may be difficult to fulfill in the case of acutely ill patients but not for infants or patients receiving total parenteral nutrition. Fürst et al. (67) advocate the use of 3-MH excretion as the best indicator of skeletal muscle catabolism. In recent studies from this group (67), the urinary excretion of 3-MH has been used to monitor the increased muscle breakdown in severe trauma. Ballard and Tomas (68) also support the use of 3-MH as a marker of muscle-protein breakdown in hospitalized patients.

However, an opposing view is presented by Rennie and Millward (69), who consider 3-MH excretion a poor indicator of skeletal muscle breakdown. They believe that the condition that skeletal muscle contributes almost entirely to the excretion of 3-MH—a condition necessary for validating the usefulness of this indicator—is not met, because about 25% is derived from nonskeletal pools, which are in rapid turnover. According to these authors, changes in skeletal muscle breakdown as indicated by 3-MH excretion are in some cases in the opposite direction to those that actually occur. Furthermore, 3-MH excretion is influenced by several factors besides muscle mass—age, sex, and dietary intake. There are no standards available for comparison, and the difficulties in accurate collection of 24-h urine that pose problems for the creatinine/height index are also important for 3-MH. Thus, 3-MH has not found general acceptance and its measurement is not usually included in nutritional-assessment protocols.

From this discussion it is apparent that none of the anthropometric and biochemical methods for measurement of body protein stores can be considered entirely acceptable for clinical use. Anthropometric methods are more widely used but are of low accuracy and may not even be suitable for certain types of patients. Because of the uniqueness of muscle tissue in the evaluation of PCV, a more reliable, accurate, and easily used marker for evaluation of muscle-mass is greatly needed (51).

**Amino acid profiles.** The usefulness of analysis for amino acids in assessing the protein nutritional status is limited and controversial (70). Generally speaking, changes in amino acid concentrations do not sensitively indicate PCV, because the homeostatic mechanisms of the body tend to keep amino acid concentrations fairly constant unless the depletion is quite severe. Children with PCV have altered amino acid patterns during fasting, with subnormal concentrations of the essential amino acids leucine, isoleucine, and valine and an increase or no change in the nonessential amino acids, especially glycine (71, 72). The ratio of essential to nonessential amino acid concentrations changes with severe malnutrition in children, and has been used by several authors (70), but the depletion state can easily be recognized clinically before changes in amino acid patterns become clear. Harper (73) suggests that “an amino acid clearance test, standardized as for the glucose tolerance test, might serve as a guide to protein status” and is worth exploring. On the other hand, on the basis of other available data, Freund et al. (74) claimed that amino acid patterns predicted mortality with high accuracy in a group of patients with sepsis. Fürst (75) has suggested that, although plasma amino acid may be of no value, determination of intracellular free amino acid patterns in muscle may serve as a useful indicator for assessment and may help lead to better means of nutritional support in different catabolic conditions. However, determination of intracellular amino acids by muscle biopsy is a difficult technique and the research in this area is still rudimentary.

**Measurement of Visceral Proteins**

The preservation or restoration of the size of the protein compartment of the body is the primary objective of nutrition therapy, and assessment of this compartment is therefore very important. Measurement of certain proteins in serum has been used in assessing nutritional status. Ideally, the protein of choice should have a short biological half-life, should respond to a protein-deficient diet, and should reflect its deficiency by decreased concentrations in the circulation in most cases (76). The total amount of the protein in the body should be small, and it should have a rapid rate of synthesis and a fairly constant catabolic rate, responsive only to protein and energy restriction.

Data on both humans and subhuman primates (77) show that dietary protein deficiency must be prolonged and severe before there are any significant changes in the concentrations of serum proteins. Furthermore, these concentrations are affected not only by protein deficiency but also by other factors: zinc deficiency, energy deficiency, hepatic disease, renal disease, and, most importantly, infections. Therefore, measurement of the concentrations of individual proteins may not provide a sensitive index of protein status, but nevertheless is valuable as an indicator of morbidity (78, 79). Golden (77) has compared measurement of serum proteins to erythrocyte sedimentation rate; each allows the clinician to identify the sickest patient, whether from malnutrition or any of several other reasons.

**Serum albumin.** Of the circulating serum proteins, albumin is one of the first biochemical markers of malnutrition and has long been used in population studies as well as in assessment of the hospitalized patient. Various surveys of patients in both acute- and chronic-care facilities have identified hypoalbuminemia to be a common abnormality and one well-correlated with increased morbidity and mortality. Seltzer et al. (19) reported that hypoalbuminemia and decreased lymphocyte number correlated with a fourfold increase in morbidity in a large hospital population and a sixfold increase in mortality. Similar results have been found in populations of surgical patients (14, 80) as well as other groups of patients (81, 82). In a recent study (83) on patients admitted to a nephrology service, low serum albumin correlated with a longer stay in the hospital and increased incidence of infection. Serum albumin concentration also correlates with body cell mass (84).

Concentrations of serum albumin are the net result of albumin synthesis, degradation, and distribution into the serum compartment. The body pool of albumin is large, and about 60% of it is not included in the intravascular compartment. During periods of protein depletion, albumin from the extravascular pool may be mobilized, so that the concentration in serum will not decline for some time. Moreover, the fractional catabolic rate of albumin is proportional to the size of the extravascular pool, which means that the concentration in the serum will be kept fairly constant. Because of these processes, as well as the long biological half-life (20 days) of albumin, concentrations in the serum are affected at a later stage in malnutrition and are not a good indicator of short-term (within three to five days) protein and energy deprivation. However, chronic protein deficiency under conditions of adequate nonprotein caloric intake leads to marked hypoalbuminemia, owing to the net loss of albumin from both the intravascular and extravascular pools (kwashiorkor). On the other hand, in marasmus, which is caused by caloric insufficiency without protein insufficiency, serum albumin concentrations are normal but there is considerable loss in body weight. Serum albumin concentrations of 35 g/L or greater are considered normal; the values for mild, moderate, and severe depletion are 28–35, 21–27, and <21 g/L, respectively (22). A serum albumin value below 25 g/L was used in correctly predicting the survival prognosis in 93% of a critically ill patient population (85).
Transferrin. Transferrin is a transport glycoprotein with a relative molecular mass of approximately 76,000. It is synthesized in the liver and has a shorter biological half-life than albumin, 8.8 days. Transferrin binds and transports ferric ion, and more than 99% of the total serum iron is bound to about one-third of the transferrin pool.

Because its half-life is shorter and the size of the body pool is smaller for transferrin than for albumin, transferrin is more likely to respond to protein depletion before any alterations in serum albumin are manifest (86). There is almost conclusive evidence that transferrin concentrations decline in severe PCM, but its usefulness in diagnosis of subclinical, marginal, or moderate malnutrition is still open to question, because a wide range of values has been reported in various studies. Moreover, transferrin concentrations can be affected by factors other than protein and calorie deficiency, e.g., by iron deficiency, which leads to increased synthesis of transferrin, and by liver disorders, nephrotic syndrome, anemia, and neoplastic disease, which cause hypotransferrinemia. In the hospitalized patient the sensitivity of transferrin to nutritional status as well as use of this measurement as a prognostic tool has been shown in several studies. Transferrin determination is included in the prognostic indices of morbidity and mortality proposed by different workers (81, 87).

Serum transferrin can be measured routinely by radial immunodiffusion. Reported normal ranges are close to or more than 2.0 g/L; Values of 1.5-2.0, 1.0-1.5, and <1.0 g/L are considered to be indicative of mild, moderate, or severe depletion, respectively (22). If it is not feasible to determine transferrin directly, one can estimate it indirectly from measurement of total iron-binding capacity.

Several formulas proposed for estimating transferrin from total iron-binding capacity (27) vary according to the method used for determining total iron-binding capacity. Each laboratory is advised to establish its own formula relating its measurement of total iron-binding capacity to the results of radial immunodiffusion method for transferrin.

Thyroxin-binding prealbumin. Thyroxin-binding prealbumin, a serum protein with a relative molecular mass of approximately 54,000, transports about one-third of thyroxin in blood and is also a carrier for retinol-binding protein, the transport protein for vitamin A alcohol. These carrier proteins, because of their short half-lives, high tryptophan content, and small pool size, show promise of being better indicators of visceral protein status than albumin and transferrin and for following short-term effects of nutritional therapy (88). The concentration of prealbumin—retinol-binding protein complex is greatly decreased in PCM and changes towards normalcy on repletion (86, 89, 90). Prealbumin has a low concentration in serum, a half-life of 1.9 days (91), and a rapid response to a lowered energy intake—even when protein intake is adequate—in as little as three days (76).

The determination of prealbumin rather than retinol-binding protein is preferable in clinical use; both exhibit parallel responses to nutritional depletion, but prealbumin is present in much higher concentrations. Recent studies (92) support the use of prealbumin as a useful tool for diagnosis and as a prognostic indicator in surgical patients, as well as for assessing the adequacy of replacement therapy in both noninflammatory and stable inflammatory conditions. Bourry et al. (93) measured several serum proteins in the sera of cancer patients before and during parenteral nutrition. They found prealbumin to be the most valuable and sensitive indicator of nutritional status. Although it had no prognostic value when measured at the beginning of refeeding, prealbumin responded quickly to refeeding and thus allowed monitoring of response to repletion by parenteral nutrition in this group of cancer patients. Furthermore, a decline in prealbumin after two weeks of parenteral nutrition seemed to predict a poor prognosis for the short-term.

Moskowitz et al. (94) showed that, in premature infants, serum prealbumin concentration was a more sensitive indicator of nutritional intake than were various growth measurements and was also better than albumin in detecting PCM.

Recently, Farthing (95) suggested that prealbumin is an unreliable index of nutritional status, finding that it failed to reflect mild malnutrition as determined by anthropometric measurements in men with chronic intestinal disease. The interpretation of their data has been disputed by Carpentier and Ingenbleek (96). However, it appears that prealbumin may be restored to normal concentrations rapidly after repletion, although other evidence of undernutrition may persist. Thus, this protein may be an indicator of dietary intake rather than of nutritional status (97).

Prealbumin is measured by radial immunodiffusion. The normal ranges have been reported to be 160-300 mg/mL (22) and 200-360 mg/L (93). Values of 100-150, 50-100, and <50 mg/L indicate mild, moderate, and severe protein depletion, respectively (22). As with other serum proteins, prealbumin concentrations are affected by various physiological and pathological conditions and thus are not specific for protein deficiency. For example, assay of prealbumin has been suggested as a very sensitive liver-function test (98), and its concentrations are depressed by iron (99) and increased in renal disease. Prealbumin may not reflect protein depletion if energy intake is adequate for the first four days, especially in obese patients (100).

Retinol-binding protein. Retinol-binding protein, a protein of low relative molecular mass (21,000) may be even better than prealbumin for monitoring short-term acute changes because its biological half-life is about 12 h, and its pool size is smaller than that of prealbumin. It responds quickly to both energy and protein deprivation (100). Ingenbleek et al. (101), in a study of malnourished Senegalese children, reported a decrease in the concentration of retinol-binding protein, which returned to normal after three weeks of repletion. Shetty et al. (100) studied untrated obese patients with carefully controlled energy and protein intakes and found prealbumin and retinol-binding protein to be better indicators of long-term changes than albumin and transferrin. This group found that retinol-binding protein and prealbumin are more profoundly affected by energy restriction than by protein deficiency, observations supported by the finding that retinol-binding protein is still synthesized by children on a diet adequate in energy but deficient in protein (77).

Although these two rapid-turnover proteins, prealbumin and retinol-binding protein, indicate nitrogen balance during malnutrition and after refeeding, especially in primates, factors other than nutritional status also affect them. Thus, retinol-binding protein concentrations decline in vitamin A deficiency, which is frequently present in PCM (102), and respond quickly when patients with severe PCM are given vitamin A (90). Retinol-binding protein concentrations are markedly lowered in hyperthyroidism, chronic liver disorders, and zinc deficiency. Values also decrease in cystic fibrosis and increase in renal disease.

Retinol-binding protein has been measured by radial immunodiffusion, RIA, and a latex immunoassay (103). Recently two enzyme-linked immunosorbent assay methods have been reported (104, 105), and the normal range has been determined as 30-65 mg/L (100).
Fibronectin. Plasma fibronectin is an opsonic glycoprotein of high relative molecular mass. It has a half-life of about 4 h, and it has recently been proposed as an index of acute nutritional deficiency before severe depletion has taken place (106, 107). The complete physiological role of fibronectin has not been elucidated, but it is considered to be the primary nonspecific opsonin (108) and regulates phagocytosis of particulate matter. Fibronectin concentrations decrease after physiological insults such as shock, burn, trauma, and infection (108-111) and return to normal on recovery. Fibronectin is thought not to be synthesized in the liver, but it responds more rapidly to changes in nutritional status than the serum proteins discussed before. Scott et al. (107), measuring fibronectin by immunoassay every week in healthy obese subjects who had fasted for three weeks, and five days after enteral repletion, showed that fibronectin was clearly sensitive to both caloric deprivation and repletion. The concentrations decreased to a low, consistent value after a week of starvation, stayed there for the remaining two weeks, and were back to normal five days after refeeding. In contrast, albumin concentrations were unaffected throughout. The return of transferrin and retinol-binding protein to pre starvation concentrations takes considerably longer (112). Furthermore, fibronectin concentrations returned to normal before the body weight was restored to pre starvation status.

Other serum proteins have not been extensively studied as indicators of nutritional status. As better and more sensitive assays for the many other serum proteins become available, some of these may turn out to be more sensitive and specific tools for assessment of short-term changes, which may be of greater relevance to hospitalized patient populations.

Nitrogen balance. Nitrogen balance, the difference between nitrogen intake and nitrogen excretion, is one of the most widely used indicators of assessing relative protein change. In normal, healthy individuals, anabolic and catabolic rates are in equilibrium and the nitrogen balance is zero. During catabolic states such as sepsis, trauma, or burns, or when the nutrient intake is deficient, nitrogen excretion may exceed intake, leading to a negative balance. Nitrogen balance becomes positive during recovery from illness, and the aim of nutritional support is to have the patient in a state of positive balance.

Normally, 90 to 95% of the daily nitrogen loss is accounted for by elimination via the kidneys, about 9% of which is in the form of urea. Therefore, determination of 24-h urinary urea nitrogen serves as a fairly accurate method for determining nitrogen excretion. Nitrogen balance can thus be calculated (29) as:

\[ \text{Nitrogen balance} = \text{Nitrogen intake} - \text{Nitrogen excretion} \]

where 4 is the term used to account for other losses, either through skin, stool, or nonurea urinary nitrogen excretion. Nitrogen intake is estimated by dividing protein intake for a 24-h period by 6.25, the average nitrogen content of the amino acids.

Nitrogen balance as calculated by the above formula is not valid in patients with renal disease and may be difficult to determine in certain other clinical conditions involving abnormally high nitrogen losses.

Newer Methods of Body Composition Analysis in Nutritional Assessment

Precise methods for the measurement of body cell mass and total body fat by direct determination of body composition such as measurement of total body nitrogen and total body potassium have become available in recent years. These sophisticated methods are complex, require expensive equipment, and are at present limited mainly to experimental studies. However, they may become more common in routine studies in the future. Some noninvasive techniques such as measurements of total body electrical conductivity also hold great promise for future applications.

Computed tomography. Although radiographic methods were used in studies on body composition as early as 1920, the potential of radiographic analysis has been enhanced greatly by the recent use of computed tomography, mainly by Heymsfield's group (113). This technique has been used to estimate liver, kidney, and spleen volume (114) to within 5%, and may be useful for quantification of PCG (115). Technical limitations to its use in body-composition analysis are not serious and probably will be resolved in the next few years (113). However, the cost of the procedure and the radiation exposure to the patient may determine the extent of its future acceptance for use in nutritional assessment.

Total body potassium. Body cell mass cannot be directly determined by any of the currently available methods but a close estimate can be obtained by measuring total body potassium. \(^{40}\)K, a natural radioisotope of potassium, is present in very low concentrations in bone. Gamma emission from the decay of \(^{40}\)K can be measured with a whole-body counter, with use of sensitive detectors and heavy shielding to eliminate background radiation, to a counting error of about 3% (116). Difficulties in calibration of the whole-body counter do not entirely allow for differences in body build of subjects, and fat is overestimated in obese patients. The expense of whole-body counters currently limits the use of this technique to research.

Exchangeable potassium and the Shizgal index. An alternative to determination of total body potassium, measurement of exchangeable potassium (\(K_e\)), is accurate enough for a clinical setting, because \(K_e\) is linearly correlated with body cell mass. \(K_e\) can be measured directly by the isotope-dilution technique with use of \(^{40}\)K or, more conveniently, indirectly by multiple isotope-dilution techniques. Shizgal (117) worked extensively in this area, using simultaneous injection of four isotopes—\(^{131}\)I-labeled-albumin, \(^{40}\)Cr-labeled erythrocytes, \(^{22}\)Na, and \(^{18}\)O—for studies of body-composition analysis. After total body water is calculated from the equilibrium concentration of injected tritiated water, \(K_e\) is obtained from total body water and exchangeable sodium (\(Na_e\)) by the equation:

\[ K_e = (\text{total body water} \times R) - Na_e \]

where R is the sum of the sodium and potassium content of a whole-blood sample. Shizgal applied this method in numerous studies in assessment of nutritional status before and after nutritional support. On the basis of this experience with more than 1500 body-composition measurements, the \(Na_e/K_e\) ratio, termed the "Shizgal index," appears to be a sensitive marker of nutritional status. In well-nourished individuals, the body cell mass and extracellular mass are about equal in size and the \(Na_e/K_e\) ratio is close to unity, whereas in malnourished body cell mass decreases and the Shizgal index is >1.22.

Although the Shizgal index appears to be precise and provides useful information for the assessment of hospitalized patients, it is not sensitive enough to indicate early responses to nutritional support (118). The Shizgal index is not yet widely applied clinically, mainly because it involves radiation exposure to the patient and because changes in the \(Na_e/K_e\) ratio in some cases represent disease-related effects with no alteration in body cell mass (28).
determine concentrations of potassium, sodium, nitrogen, chloride, phosphorus, and calcium in the body (119, 120). This technique has also been used to evaluate changes in body composition in disease and to monitor responses to nutritional therapy. The newer technique of prompt gamma–neutron activation analysis measures gamma-rays from the interaction of fast neutrons with various elements (121). Cohn et al. (119), with the help of predictor equations and the use of ratios of nitrogen/potassium in muscle and nonmuscle lean tissue, have calculated the mass and protein content of both these compartments in normal subjects and cancer patients.

Prompt neutron activation analysis enables direct determination of total body nitrogen and total body potassium, and is therefore a definite improvement over such measurements as nitrogen balance. It also makes possible highly accurate sequential studies. However, this is still a relatively new technique and, as indicated by Hill (120), "a clear perspective of its value in nutrition and metabolic work is not yet possible." Future developments will be concerned with evaluation of changes in body composition as related not only to PCM but also to morbidity and mortality.

**Total body electrical conductivity.** Measurement of total body electrical conductivity is the newest and perhaps the most promising method for future use in nutritional assessment (122, 123). The method draws upon the principle that, because of its much greater electrolyte content, the electrical conductivity of lean tissue is much higher than that of fat. Presta et al. (123) have demonstrated correlation between total body electrical conductivity and both the total body water and total body potassium of 19 adults who varied greatly in degree of fatness.

The procedure, which is similar to that of a metal detector, is simple, causes no discomfort or stress to the patient, and takes less than 1 h. Some of the potential limitations of the method include variability related to any electrolyte imbalances, high degree of fatness (more than 60% fat), variability in bone mass, and need for adjustment for variations in individual body sizes. Recently, Mazess (124) has questioned the accuracy of the total body electrical conductivity method. However, Presta et al. (125) provide convincing arguments to refute the criticism.

**Immunocompetence in PCM**

There is considerable evidence to support the view that malnutrition has a deleterious effect on immunocompetence. PCM has long been known to be marked by increased frequency and severity of infection (9), which accounts for much of the morbidity and mortality associated with it (126). Indeed, malnutrition is recognized to be the most common cause of secondary immune deficiency (127–129). Many studies investigating the effects of nutritional deficiency on the host immune system reveal that moderate to severe PCM is invariably associated with subnormal immunocompetence (130, 131); even for marginal PCM, immunocompetence as evaluated by a panel of responses may serve as a sensitive and useful index of nutritional status (132). The exact nature of interaction between nutrition and host defense mechanisms remains unclear, despite the extensive data available (133, 134). However, the field has only recently begun to be fully explored, and sophisticated immunological tests show promise of serving as reliable standards of nutritional assessment in the future.

The immune system can be considered to consist of mobile, systemic host defenses, which are capable of going to sites of invasion, and local defenses. Each of these consists of specific and nonspecific components. The nature of the immune response is highly complex and involves interaction of three major inter-related systems: (a) B-cell immunity, which represents the humoral component and consists of antibody response by an antigen-stimulated B-lymphocyte and is apparently dependent on bone marrow; (b) T-cell-mediated immunity, which is the thymus-dependent system, comprising antigen-specific responses such as cell-mediated immunity; and (c) nonspecific responses, including phagocytosis, opsonization, complement system, lysozyme, and others. T-lymphocytes do not act separately from B-lymphocytes and may either enhance or suppress the action of B-cells. The manner in which nutritional factors interact with immune status may be either direct, affecting primarily the lymphoid system, or indirect, affecting cellular metabolism or another organ system that is, in turn, involved with the regulation of immunocompetence.

**Cell-mediated immunity.** Cell-mediated immunity, the antigen-specific response of the immune system, is mediated by a subset of lymphocytes called T-cells, dependent upon the thymus, which plays a role in their maturation. The bulk of circulating small lymphocytes (65–80%) consists of T-lymphocytes, which also interact with the B-lymphocytes. Helper T-lymphocytes must cooperate with B-cells for the latter to differentiate into plasma cells, whereas suppressor T-cells may act through helper T-cells to inhibit antibody formation. Suppressor T-cells also regulate effector T-cells, which are responsible for direct cytotoxicity. Thus, a defect in the T-cell system will be reflected not only in the effect on cell-mediated immunity but may also in defective humoral response, even though the B-lymphocytes may be normal in function. PCM affects cell-mediated immunity earlier and much more consistently and profoundly than humoral immunity (135). In studies with malnourished infants (136), as well as in PCM related to complications following surgery, (128), in patients on hemodialysis (137), and in cancer patients (138), cell-mediated immunity has been reported to be altered. However, in these situations a number of factors unrelated to nutritional status may also be operative so that the decrease in immunocompetence may not be directly caused by PCM (139). Thymus and thymic-dependent areas are especially affected in PCM, showing alterations in size and function. Decreased tonsil size can be a useful clinical indicator of malnutrition (132). In adults, PCM leads to decrease in lymphocyte counts, and circulating T-lymphocytes as well as alterations in the delayed hypersensitivity reaction. Cell-mediated immunity is relatively unaffected in adult marasmus.

**Total lymphocyte count.** Total lymphocyte count decreases with progressive malnutrition and correlates with morbidity and mortality in hospitalized patients (129, 140, 141). It can be used as a simple, inexpensive screening parameter for PCM and as a predictor of sepsis (142). Total lymphocyte count indicative of mild malnutrition has usually been taken as less than 1800 cells/mm³, and severe malnutrition as less than 800 cells/mm³ (22); normal range is 2000–3500 cells/mm³.

The use of an absolute value for total lymphocyte count has been criticized as misleading (25); it should always be used in conjunction with the total leukocyte count for proper interpretation of results. Several factors related to patient status and the total hematological profile can affect results and should be carefully evaluated before attributing a lowered total lymphocyte count to PCM (29).

**Rosette forming T-lymphocytes.** One of the indicators of cell-mediated immunity is the enumeration of absolute number and proportion of T-cells that bear receptors for sheep erythrocytes, as recognized by their ability to form rosettes when mixed with neuraminidase-treated sheep blood cells. Malnourished children show a decrease in T-cell

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rosette formation, with return to normal after refeeding (143). More convenient is identifying T-cells by direct immuno-fluorescence staining of whole blood, with monoclonal antibodies specific to T-cells (27). Studies on changes in the number and functions of T-cells subpopulations have resulted from the availability of monoclonal antibodies with specificities for various subsets of lymphocytes and the technique of flow cytometry. Using these techniques, Chandra (144) has shown that in PCM a marked decrease of T4-helper cells and a moderate reduction in the proportion of T3 cytotoxic suppressor cells takes place, which is reversed on repletion. The "null cells," which are devoid of the characteristic surface markers of T and B cells and not detected by the rosette formation assay, were increased in PCM and may represent incompletely differentiated pre-T-lymphocytes (145).

Delayed cutaneous hypersensitivity reaction (DCH). DCH is the simplest and the most widely used of the many tests available to evaluate the status of cell-mediated immunity. It measures the ability of the subject to respond to a challenge with one or more antigens, to which the host has been previously sensitized. The inflammatory reaction, marked by dermal erythema and induration, is the result of complex leukocyte interactions that lead to release of lymphokines and chemotactic factors at the test site. Numerous studies (129, 140, 146) have shown abnormalities in DCH in malnourished hospitalized patients who were resistant to normal reactivity after repletion of body cell mass by vigorous nutritional intervention (140). Abnormalities in DCH in these malnourished patients included decreases both in the diameter of induration and in the percentage of non-responders.

Dionighi's group (147) measured DCH in 177 cancer patients before surgery to assess the relationship between DCH, malnutrition, and post-operative infection and found the incidence of infection to be considerably higher in anergic patients than in patients with normal DCH responses. Meakins et al. (148), studying blunted trauma patients and patients in a surgical ward, found a significant correlation between abnormal DCH and subsequent development of sepsis and mortality; they considered malnutrition to be the main cause of such anergy. However, in a later paper (149), these workers showed that the anergy was reversed by simply draining the site of infection. Several studies confirm that impaired DCH can identify patients with increased risk for sepsis and mortality in various clinical conditions such as burns, trauma, malignancies, and surgery (29). However, a number of factors—recent anesthesia, fever, trauma, surgery, and drugs—affect DCH, and it is not clear that an abnormal reaction is indicative specifically of nutritional depletion. For example, in one study anergy was present in 21% of patients with normal body composition and at low risk for infection (150).

There is no standardized, uniformly accepted protocol for the selection of antigens to be used in testing for DCH in hospitalized patients, nor are the criteria for a positive reaction well defined. Streptokinase–streptodornase and mumps and candida antigen have been used by some workers, whereas others have used these four plus purified protein derivative or trichophyton (29). Various studies have shown that no single antigen elicits a positive response in more than 90% of patients who respond to at least one antigen, which underscores the need for a battery of antigens to determine anergy. The combination of streptokinase–streptodornase, mumps, candida, and trichophyton detected 97% of all the responders in one study (146). For those subjects who do not respond to any of these antigens, sensitization with dinitrochlorobenzene or keyhole limpet hemocyanin is usually attempted. Dinitrochlorobenzene usually produces a strong reaction, giving a significant induration and often leaving a thin scar in most healthy persons (132).

An induration at least 5 mm in diameter 48 h after testing with an antigen is generally considered to constitute a positive response. However, the interpretation of a positive test is controversial and consensus is lacking on this point. A recent study (146) indicates that induration after injection of recall antigens should be measured at both 24 and 48 h and the results should be interpreted as positive if induration is greater than 5 mm at either time. When the induration measures 1 to 4 mm at the time of reading, the term "relative anergy" distinguishes the reaction from a negative response.

In vitro response to T-lymphocyte mitogens. Exposure of sensitized lymphocytes to an antigen that acts as a specific stimulator transforms them into large blast cells, characterized by rapid growth and proliferation with greatly increased DNA synthesis (specific blast transformation). On the other hand, nonspecific blast transformation results after exposure of unsensitized lymphocytes to mitogens such as phytohemagglutinin, pokeweed mitogen, and concanavalin A. In vitro blastogenic transformation in short-term culture with mitogens is impaired in PCM (140, 151, 152), but the alteration is less consistent than changes in DCH with PCM, perhaps because so many factors (the dose of mitogen used, the number of mature T-cells in culture, and the duration of incubation) affect the results (132). Furthermore, serum of malnourished children may lack certain essential factors required for maximal response or may contain inhibitory factors. Few data are available on the production of soluble mediators by sensitized lymphocytes in PCM.

B-cell-mediated (humoral) immunity. T-lymphocytes play a role in the humoral antibody response as well, in that production of antibody by B-cells usually needs adequately functioning "helper T-cells." Thus, some of the abnormalities in B-cell function seen in PCM may be caused by T-lymphocyte defects (28), although direct effects on B-lymphocyte differentiation also occur (139). Measurement of serum immunoglobulins in PCM patients has produced conflicting results, because severe undernutrition is generally complicated by infection, which often has the opposite effect of malnutrition on concentrations of immunoglobulins. The most definitive evaluation of humoral immunity responsiveness is the measurement of antibody response after in vitro immunization. Several workers using this approach (140, 153) have shown that in patients with PCM, antibody synthesis is impaired after challenge with various antigens. Nutritional repletion, however, corrects the subnormal humoral immune response (140).

Besides its primary effect on cell-mediated immunity, malnutrition may impair components of nonspecific immunity such as phagocyte function, opsonic activity of plasma, and complement activation. Chandra (154) advocates the use of some of these tests, along with indicators of cell-mediated immunity, as useful parameters of PCM.

Nonspecific immunity, also referred to as nonadaptive immunity (155), involves cells that take part in the initial defense against infection—neutrophils and macrophages assisted by complement system and acute-phase reactants. In response to chemotactic stimuli, neutrophils migrate to the site of inflammation and, with the help of opsonins, the organisms encountered by neutrophils are phagocytosed (156) and eventually lysed. Defective chemotaxis by leukocytes is seen frequently in patients with various degrees of PCM (157, 158), and several studies have shown that the
bactericidal activity of neutrophils, vital to host resistance, is clearly impaired in children with severe PCM (157, 159), although the number of circulating neutrophils is not changed. In these conditions, phagocyte uptake remains unaltered, and the functional defects primarily involve subnormal intracellular killing and decreased chemotactic responses. Both functions are impaired in patients with infections or in hypermetabolic patients, and may be restored to normal by nutritional intervention (158).

Monocytes and macrophages participate in an inflammatory response to an acute bacterial challenge. The intactness of this response can be measured by the Reckeb Skin Window, which shows abnormalities in under- and malnourished patients and in patients with burns and trauma (160). The concentrations of interferon and lysozyme, which are produced by macrophages, are also lowered in PCM (146).

Complement C3. The complement system consists of multiple components that serve as mediators of reactions involved in the immunologic defense system as well as in the inflammatory responses unrelated to immunity. Several investigators (167, 168) have demonstrated that all serum complement components except C4 and sometimes C5 are decreased in PCM. Palmblad et al. (163) demonstrated that decreases in C3 could be seen fairly early in subjects deprived of energy. In patients who are nonstressed and not hypermetabolic, complement C3 may be a sensitive index of malnutrition, but in infection or in hypermetabolic states in previously well-nourished individuals, C3 serves as acute-phase reactant and may increase in concentration (161). However, infection in an already malnourished patient further decreases C3, partly because of its consumption in an antibody–antigen reaction (154).

Secretory IgA and leukocyte terminal deoxynucleotidyl transferase (DNA nucleotidylexotransferase, EC 2.7.7.31) are two other tests of immunocompetence proposed as potentially useful in assessment of PCM (154). Individuals with PCM are marked by increased occurrence of respiratory and gastrointestinal-tract infections, suggesting impaired mucosal immunity. Concentrations of secretory IgA were decreased in various body fluids in PCM, and the mucosal IgA response to viral vaccines was also reduced (145).

Terminal deoxynucleotidyl transferase is present in large amounts in undifferentiated T-lymphocytes and in very low concentration in fully differentiated T-cells. It is therefore an indirect measure of impaired T-cell differentiation in several nutritionally impaired conditions.

Several monocyte functional assays are available and may be of use in assessment of PCM. Malnutrition-related changes in acute-phase reactants are another potentially valuable and presently unexplored area (164). The review by Cunningham-Rundles (139) provides excellent information on the various parameters of immune deficiency in PCM and available tests for assessing immune status.

Nutritional Assessment Profiles

An “ideal” test for nutritional assessment should be highly sensitive and specific, be unaffected by factors unrelated to nutrition, and correlate with response to nutritional repletion (28). Unfortunately, no such test is available at present, and a panel of tests must be chosen instead from the many available tests discussed so far. Although the exact makeup of the battery of tests used in assessment varies from one center to the other, most commonly used methods include anthropometry (body weight, triceps skinfold, arm muscle circumference), creatinine/height index, serum concentrations of albumin and transferrin, total lymphocyte count and DCH, and nitrogen balance. Data from these measurements can be used to develop an anergetic metabolic profile (165) that may help in defining the nature and type of malnutrition involved.

Nutritional risk indices: prognostic nutritional index and hospital prognostic index. The use of a battery of tests as referred to above has provided statistically valid results for identifying patient populations at high risk of exhibiting morbidity and mortality. However, when used with individual patients, such a battery can be difficult and confusing, since results of some of the tests may be normal and others may be abnormal. Furthermore, these results do not quantify the magnitude of risk associated with malnutrition, which is essential in weighing the need for nutritional support or the risks of consequent delay in surgery.

Mullen’s group (14) at the University of Pennsylvania examined 64 elective-surgery patients in a pilot study, measuring 16 immunological and nutritional assessment indicators on each patient before surgery. For only 9% of these patients were all the tests results within normal limits; the rest had an abnormal result for at least one marker. Serum albumin (<30 g/L), serum transferrin (<2.2 g/L), and skin test anergy were the most reliable predictors of morbidity. A more comprehensive study comprising 161 surgery patients (87) confirmed the findings of the pilot study regarding the usefulness of these markers and also supported the use of measuring the triceps skinfold. Using discriminant analysis and a computer-based stepwise regression, these workers developed a predictive model, the Prognostic Nutritional Index, that correlated baseline nutritional status with the risk of morbidity and mortality after surgery, in measurable terms:

Prognostic Nutritional Index (%) = 158 – 1.66(Alb) – 0.78(TSF) – 0.02(TFN) – 5.8(DH)

where Alb. is serum albumin (g/L), TSF is triceps skinfold (mm), TFN is serum transferrin (mg/L), and DH is maximal skin test reactivity (graded 0 for nonreactive, 1 for <5 mm reactivity, and 2 for >5 mm reactivity). Using this model, they accurately identified 87% of the patients who developed significant complications and 96% of the post-operative deaths. High-risk patients were defined as those with a Prognostic Nutritional Index greater than 50%.

The predictive model has been validated in prospective studies of different patient groups by comparing the risk of morbidity and mortality predicted by the model with the actual outcome (166–168). On the basis of their overall experience, Mullen’s group (168) has concluded that the Prognostic Nutritional Index is highly sensitive, correctly predicting the clinical outcome 80% of the time, with the remaining 20% of the patients being those who do not show a poor outcome although predicted to by the model. Furthermore, it has been shown that seriously ill patients who were identified as high-risk by the Index benefited from the pre-operative nutritional support.

Another prognostic index, the “hospital prognostic index,” has been developed by Blackburn’s group (169). This index is a discriminant function that relates ultimate outcome of surgery to pre-operative baseline nutritional status, as measured by albumin concentrations and DCH as well as clinical status.

Recently, Rainey-Macdonald et al. (81) reported, in confirmation of the results of several other earlier studies, that a serum albumin concentration of less than 30 g/L had the best predictive accuracy for outcome, but also concluded that DCH was not useful in identifying patients at high risk. A four-variable discriminant function with serum albumin,
serum transferrin, triceps skinfold, and DCH gave no better prediction of outcome than a two-variable function with only serum albumin and transferrin. On the basis of these results, they concluded that "only serum albumin and serum transferrin, used in the context of the weighted index, have sufficient discriminating ability to justify their use in nutritional evaluation" (81).

Functional assessment of nutritional status. The markers of malnutrition discussed above, except tests related to immune competence, are static indices of malnutrition and can be affected by several biological and technical factors. The homeostatic mechanisms of the body enable the circulating concentrations of an indicator of malnutrition to remain unchanged at the expense of depletion of body stores. Thus, for example, the static assessment of blood concentrations of a circulating protein may grossly underestimate the extent of malnutrition, because the depletion of body stores is not taken into account. A more desirable, relatively unexplored, but very promising area is the functional assessment of malnutrition. In malnourished patients, adverse clinical events that eventually lead to death are not the result of abnormal static indices but of the disruption of certain physiological processes and organ failure. Functional indicators of malnutrition aim to determine whether certain biological functions of the cell, tissue, organ, or the whole body (164), dependent upon adequate nutriture, can be performed optimally. This mode of assessment may unravel inadequate subnormal function before changes in any index of static assessment take place. Solomons and Allen (164) discuss various aspects of functional assessment in a thorough review.

Functional assessments consist mainly of methods involving in vitro duplication of in vivo function and those involving evaluations of physiological responses. Tests related to immunocompetence discussed earlier in this article fall in the first category. Interesting new work is being done in the use of organ and tissue function as measures of nutritional assessment. Russell et al. (170) studied skeletal function in six obese patients and compared the results with standard measures of body composition. They found clear-cut impairment of muscle function at a time when static indices of body composition were unchanged. The subnormal muscle function was reversible on refeeding. Grant (171) studied muscle function as well as some organ functions in patients and found poor correlation with standard anthropometric determinations and with Mullens Prognostic Nutritional Index.

Other functional tests that have been used to evaluate PCM include nerve conduction studies, changes in electroencephalogram patterns, and measurement of the ability to perform tasks that require expenditure of energy (164). The area of functional assessment of nutritional status is an emerging field, and the potential utility of several physiological processes dependent on adequate nutriture is yet to be explored.

Concluding Remarks

Since the development of intravenous hyperalimentation in 1968 by Dudrick et al. (172), the use of aggressive nutritional intervention for the management of seriously ill patients has substantially increased and its benefits are well recognized. A recent hospital survey (173) reports that hospitals with nutrition-support teams account for 18% of U.S. hospital beds, compared with just a few teaching and research hospitals that offered this service a few years ago. The realization that nutrition support can not only significantly improve the morbidity and mortality of hospitalized patients but also shorten the length of patient stay has great economic relevance as well. Under the diagnostic-related group system of payment, hospitals with nutrition-support teams, if they are able to discharge their patients earlier as a result of active nutrition support where indicated, stand to gain economically. On the basis of these considerations, we can safely predict that the number of hospitals with nutrition-support teams and offering these services will continue to grow. Another area where nutrition-support teams may be utilized and nutritional assessments performed is long-term care facilities, where the residents may be malnourished.

The advantages of nutritional intervention on the one hand, and the need to weigh the risks associated with parenteral nutrition (e.g., metabolic derangements) on the other, have led to great interest in objective means of assessing the nutritional status of patients. Ideally, the clinician should be able to diagnose preclinical or marginal malnutrition with the help of laboratory tests, monitor optimal nutritional support with the least side effects, and recognize harmful drug/nutrient interactions (175). Current tests for nutritional assessment are not specific and sensitive, so that no single test can be considered to be an indicator of PCM. Such tests have wide confidence limits and may be more suited for use in surveys than for application to individual patients. Another problem is that the effects of malnutrition cannot be separated easily from the effects of the underlying disease (24), and the indicators used may actually be marking sepsis or other disease-related conditions. Better indices of PCM are definitely needed. Functional tests and noninvasive and simple tests for body composition analysis hold promise for the future. In the meantime, it is difficult to accept use of clinical evaluation alone for reliable evaluation of nutritional status, considering the wide variability in the clinical expertise of physicians and surgeons involved. The currently available battery of tests will therefore continue to be of benefit until better methods of assessment become available.

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