ABSTRACT
Protein-energy malnutrition is present in a large proportion of maintenance hemodialysis (HD) patients, and it is associated with increased morbidity and mortality. The protein requirements are increased because of the presence of endocrine and metabolic factors related to loss of renal function, the HD procedure, and comorbidity factors, which all stimulate net protein catabolism. The intake protein and energy are frequently reduced because of the underlying disease, psychosocial factors, and uremic anorexia. However, the extent to which underdialysis contributes to anorexia and malnutrition is still not well defined. Malnutrition is generally not recognized as a common direct cause of death as reflected in health statistics, except in the highest age groups. Anthropometric and biochemical signs of malnutrition are associated with increased mortality. A low serum albumin level is a strong predictive risk factor that may reflect not only or mainly protein malnutrition but also the influence of several other morbidity factors (overhydration, infection, chronic disease and others) that may entail an increased risk of death. Low levels of serum creatinine (low muscle mass), serum cholesterol (energy depletion), and BUN and low urea appearance rate (low protein intake) are also correlated to increased mortality. For the prevention and treatment of HD-associated malnutrition, measures should be taken to correct factors that may suppress appetite and increase net protein catabolism (underdialysis, acidosis, low energy intake, comorbid conditions, psychosocial and economic factors). Dietary advice should be given with the aim of ensuring an adequate intake of protein- and energy-giving products. Intradialytic parenteral nutrition may have positive effects on nutritional status when other measures fail. However, the indications for such treatment have not yet been well defined, and the effects on survival, morbidity, and quality of life are not sufficiently well proved. More and better data, generated in prospective, well-controlled studies, are obviously needed before intradialytic parenteral nutrition can be generally recommended as therapy for malnourished HD patients.

Key Words: Albumin, anorexia, cachexia, catabolism, malnutrition

In 1960, Scribner et al. (1), in their first report on hemodialysis (HD) treatment of patients with chronic renal failure, pointed out that malnutrition may be a serious problem. Numerous studies published thereafter have demonstrated a high prevalence of malnutrition in HD patients. In more recent years, several reports have focused on the association between nutritional intake and nutritional status, on the one hand, and morbidity and mortality on the other, lending support to the supposition that nutritional inadequacies may be causally related to a fatal outcome. However, the role of nutrition in this regard has not been clearly determined. Several morbidity factors that per se increase the risks of a poor outcome may also cause malnutrition, which may not be the direct cause of death, but rather a marker of illness. There are many causes of malnutrition in renal failure patients who are treated with HD, some being related to endocrine and metabolic disturbances of uremia and some being related to the dialytic procedure. A controversial issue is the extent to which the adequacy of dialysis may affect the nutritional intake of protein (and energy), especially if there exists a link between underdialysis, malnutrition, and increased morbidity/mortality.

GENERAL ASPECTS OF NUTRITION AND MORTALITY
In order for an individual to survive and thrive, nutrients must be ingested in sufficient amounts to serve as metabolic fuel and a substitute for tissue growth and maintenance and to regulate the cellular and metabolic processes. If an essential nutrient (e.g., a specific amino acid or a vitamin) or a macronutrient (protein, energy) is provided in insufficient amounts in relation to the requirements, this will sooner or later have serious consequences for the individual. However, a nutritional deficiency may be clinically unrecognizable for some time and may be detected only by biochemical and physiologic studies or by metabolic experiments. As the deficiency becomes more severe, the altered biologic and physiologic functions in the body and clinical signs and symptoms occur, leading to morbidity and, finally, the death of the subject (2). Only then is the consequence of malnutrition reflected in vital statistics. It should be emphasized that even less severe deficiencies may (indirectly) have a nega-
tive effect by sensitizing the individual to other morbid factors. For instance, protein malnutrition may result in an impaired immune response, carrying an increased risk of severe or even fatal infections (3). The regeneration of cell number and function, e.g., after an acute illness, and wound healing may also be impaired in states of malnutrition (4).

**ASSESSMENT OF PROTEIN-ENERGY MALNUTRITION**

To diagnose malnutrition in maintenance dialysis patients, it is important to assess correctly their nutritional status (see recent review articles [5,6]). The validation of nutritional status may be based on clinical evaluation, diet history, anthropometric measurements, and various biophysical and biochemical methods (Table 1).

The more precise methods for calculating body composition (total water, potassium and nitrogen determinations, protein/DNA determination in muscle biopsy, dual x-ray photon absorptiometry [DEXA], nuclear magnetic resonance, bioelectrical impedance, etc.) require equipment that is not available in most centers, some of which is complicated and expensive. Among the new noninvasive methods, DEXA (7) and multifrequency bioimpedance (which can distinguish between total body water and extracellular water) (8) are now under evaluation for use in patients on maintenance dialysis (9–11). DEXA may be advantageous because it measures both the bone mineral content and the body fat mass, measurements from which the lean body mass is calculated. The lean body mass, as calculated by DEXA or by total body water determination (by monofrequency bioimpedance or isotope dilution or from nomograms) is, by definition, equal to the body weight minus the amount of body fat. Therefore, it is not a reliable index of total cell mass (body protein) in overhydrated dialysis patients, whose lean body mass consists largely of excess water, mainly in the extracellular space (12). Multifrequency bioimpedance may turn out to be more useful by enabling compensation for extracellular overhydration in the calculation of body cell mass. Creatinine is generated largely by the nonenzymatic breakdown of creatine present in the phosphocreatine-creatine pool in skeletal muscle, which is the largest pool of cellular tissue in the body (13). In addition, 10 to 30% of creatinine generation may be derived from the ingestion of creatine and creatinine in meat (14). Potassium, alkali-soluble (cell) protein, and total creatine in the skeletal muscle of normal individuals are strongly correlated (15). The total creatinine output has been shown to correlate well with the total body K in normal and continuous ambulatory peritoneal dialysis (CAPD) patients, and it may be a more reliable index of body cell mass and nutritional status in dialysis patients than the techniques that are based on total water determinations (16). However, the determination of the total creatinine output in HD patients requires the collection of an aliquot of the total spent dialysate during the dialysis session, which is not easily accomplished.

Today, most centers must rely on dietary histories, evaluation of body weight indices, and other simple anthropometric parameters and serum protein determinations to investigate nutritional status and detect signs of protein-energy malnutrition. A simple and reliable method appears to be the Subjective Global Assessment, a technique by which the nutritional status is rated by the clinician in a systematic way based on medical history and physical examination (17). Although originally used to classify surgical patients, this nutritional classification system has proved to be a reliable tool for assessing the nutritional status of dialysis patients (18,19).

**PREVALENCE OF MALNUTRITION IN HD PATIENTS**

Several reports show that malnutrition is frequently present in patients treated with maintenance HD therapy (20–35). The signs of malnutrition in regular dialysis patients include the following: reduced energy stores (subcutaneous fat stores) and muscle mass, as estimated by anthropometric methods, low total body nitrogen determined by in vivo neutron activation analysis (31,33), low concentrations of albumin, transferrin, and other visceral proteins, low alkali-soluble protein in muscle in relation to dry fat-free weight and DNA (22,27), as well as abnormal plasma amino acids and intracellular amino acid profiles.

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**TABLE 1. Methods to assess nutrition used in HD patients**

<table>
<thead>
<tr>
<th>Evaluation of Nutritional Intake</th>
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<tr>
<td>Dietary history and dietary records</td>
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<tr>
<td>Urea appearance (estimation of protein intake)</td>
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</table>

**Simple Anthropometric Methods**

<table>
<thead>
<tr>
<th>Body weight, body mass index, weight loss</th>
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<tr>
<td>Skinfold thickness (triceps and other sites)</td>
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<tr>
<td>Midarm muscle circumference</td>
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<tr>
<td>Muscle strength (handgrip)</td>
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**Body Composition**

<table>
<thead>
<tr>
<th>DEXA</th>
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<tbody>
<tr>
<td>Nuclear magnetic resonance</td>
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<tr>
<td>Computed tomography</td>
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<tr>
<td>Ultrasonography</td>
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<tr>
<td>Bioelectrical impedance</td>
</tr>
<tr>
<td>Total body H2O (isotope dilution), K (10K-count), N</td>
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<tr>
<td>(neutron activation analysis)</td>
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**Biochemical Methods**

<table>
<thead>
<tr>
<th>Plasma proteins (albumin, prealbumin, transferrin, IGF-1, complement C3, others)</th>
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<tbody>
<tr>
<td>Other plasma and blood chemistries (hemoglobin, urea, creatinine, lipids, amino acids)</td>
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<tr>
<td>Urea appearance</td>
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<tr>
<td>Creatinine output</td>
</tr>
<tr>
<td>Muscle alkali-soluble protein/DNA, RNA, amino acids (percutaneous biopsy)</td>
</tr>
</tbody>
</table>

**Immunologic Methods**

| Total lymphocyte count                                                                          |
| Delayed hypersensitivity skin tests                                                            |
(24,26,34). However, other data show that adequately treated HD patients with no complications have an essentially normal nutritional status (36,37).

In various investigations of HD patients (27,30,32,35), a low percent ideal body weight or low body mass index was found in 10 to 30% of the subjects, a low triceps skinfold thickness was found in 20 to 60%, and a low arm muscle circumference was found in 0 to 44%. Low serum albumin was observed (27,30,32,35), a low percent ideal body weight or low triceps skinfold thickness was found in 0 to 60% of HD patients. The anthropometric data may suggest that energy malnutrition is more prevalent than protein malnutrition in HD patients. However, results of a recent study using total body N determination by neutron activation analysis indicate that anthropometric measurements may underestimate the degree of protein malnutrition in HD patients (33).

PROTEIN AND ENERGY REQUIREMENTS IN HEALTHY SUBJECTS AND HEMODIALYSIS PATIENTS

Protein requirements in normal adults are on average about 0.6 g/kg of body weight/day, which after correction for 25% variability to include 97.5% of the population of young adults, raises the safe level of intake (daily allowance) to 0.75 g/kg per day (2). This variability is the result of genetic differences, sex, age, physical activity, environment, chemical form of nutrients, and the effects of other dietary constituents (2).

The protein requirements in HD patients are not well defined. It may be assumed that the variation in requirements is much larger than that in healthy subjects, because there are additional sources of variability, such as physical inactivity, endocrine and biochemical abnormalities, anemia, acute and chronic infections, cardiac disease, diabetes, corticosteroids and other drugs, as well as specific effects of the HD procedure in the form of amino acid losses and the inflammatory response to dialyzer-blood interaction. Each of these factors may to a varying extent stimulate net protein catabolism and increase the requirements for protein. A few nitrogen balance studies in small groups of HD patients and longitudinal studies of nutritional intakes and nutritional status in larger groups of patients suggest that the daily requirements for protein are considerably higher than those in normal individuals (38). On the basis of these results, an intake of 1.2 g of protein/kg body wt per day is generally recommended for HD patients.

Effects of Acidosis

It has become increasingly evident that metabolic acidosis rather than uremia per se is an important stimulus for net protein catabolism (39–42). This effect seems to be mediated by the stimulation of skeletal muscle branched-chain ketoacid decarboxylation, which increases the catabolism of the branched-chain amino acids (valine, leucine, and isoleucine) (43) and stimulates proteolysis in muscle by inducing the transcription of genes encoding for enzymes participating in the ATP-dependent cytosolic ubiquitin-proteasome proteolytic pathway (44). In HD patients, the muscle intracellular concentration of free valine was found to be correlated with the predialysis serum bicarbonate concentration, which varied between 18 and 24 mmol/L, suggesting that branched-chain amino acid catabolism is enhanced even by mild metabolic acidosis (45).

However, the clinical importance of uremic acidosis as a factor for the development of malnutrition and as a death risk factor in HD is far from clear. Retrospective analysis of laboratory data and mortality in more than 12,000 HD patients showed that the risk of death was significantly increased with metabolic acidosis, but only at total CO₂ levels in serum lower than 12.5 to 15 mmol/L (46). In a group of 133 HD patients, no apparent association was noted between CO₂ levels and nutritional status, as evaluated by serum albumin levels (47). Nonvolatile anions (mainly sulfate ions) together with hydrogen ions are generated by protein breakdown and amino acid oxidation, implying that the tendency to metabolic acidosis increases when the protein intake is high, whereas it decreases with a low protein intake. Hence, it is conceivable that a high protein intake may stimulate protein synthesis to the extent that the activation of proteolysis and amino acid oxidation induced by the ensuing metabolic acidosis is counteracted. In support of this position is the observation by Lowrie (48) that the anion gap, which reflects the accumulation of nonvolatile acids, is positively correlated to markers of visceral protein stores (serum albumin), somatic (muscle) protein stores (serum creatinine), and protein intake (BUN); only when adjusted statistically for various nutritional parameters was an increase in the anion gaps associated with an increased death odds ratio.

In nondialyzed chronic uremic patients, the correction of metabolic acidosis improves the nitrogen balance and reduces urea appearance and muscle proteolysis (40,49). However, in a study of HD patients, the correction of acidosis was reported to have had no effect on protein degradation, but it tended to reduce protein synthesis and to increase leucine oxidation (40). The correction of metabolic acidosis in HD patients over a period of 6 months by increasing the bicarbonate concentration in the dialysis fluid was reported to result in a normalization of reduced muscle intracellular branched-chain amino acid concentrations (50); no other effects on nutritional status were recorded in these patients, who had no clinical signs of malnutrition at the start of the study (unpublished observations). Prospective, longitudinal clinical studies of HD patients with documented malnutrition will obviously be needed to determine to what extent the correction of acidosis influences nutritional status and clinical outcome.
HD as a Stimulus of Protein Catabolism

Nitrogen balance studies as well as studies of urea appearance suggest that HD stimulates net protein catabolism (51,52). There is evidence that HD reduces protein synthesis in the musculature, measured as a relative decrease in muscle polyribosomes, and in the whole body, assessed by leucine kinetics (53,54), presumably elicited by the dialytic loss of amino acids induced by the dialytic procedure or by other mechanisms. During HD, the average loss of free amino acids is 6 to 8 g per dialysis (55-57). Protein losses by hemodialysis are generally considered to be minimal. However, there is evidence that dialyzer permeability is altered by dialyzer reuse. Iltizler et al. (57) reported that amino acid losses during high-flux polysulfone dialysis increased by 50% during the 6th reuse and that albumin losses increased substantially (to an average of 9 g/dialysis) after the 15th reuse. Kaplan et al. (58) reported that the reuse of high-flux polysulfone, using bleach in the processing fluid, resulted in significantly increased protein losses in the dialysate, which increased gradually from 1.2 g per dialysis during the first use to 17.5 g during the 23rd to 25th reuse, and that the removal of bleach from the reuse procedure was associated with a substantial and sustained increase in the serum albumin levels.

The biocompatibility of the membrane may be another factor of importance. Blood membrane contact elicits an inflammatory response, the intensity of which depends on the membrane material used and which is more marked with cellulosic than with synthetic membranes (59). Sham dialysis, i.e., the circulation of blood through a dialyzer without circulating dialysis fluid in normal subjects, has been shown to elicit an enhanced release of amino acids from leg tissue (mainly skeletal muscle) when a cuprophane dialyzer was used. With semisynthetic (modified cellulose) and synthetic membranes, which are more biocompatible than cuprophane, the release of amino acids from the musculature was insignificant (60,61). After cuprophane sham dialysis, there was an increase in the leg efflux and also in the plasma concentration of 3-methylhistidine, an amino acid that is released from actinomyosin proteins and cannot be reused for protein synthesis; this indicates that an increase in proteolysis plays an important part in the net catabolic process induced by blood-membrane interaction. It has been speculated but not established that the enhanced proteolysis induced by blood-membrane interaction is mediated by monocyte activation with the release of cytokines (interleukin-1, tumor necrosis factor), which may act in concert and induce the lysosomal catabolism of muscle protein (62). A prospective randomized study, recently presented, comparing patients starting HD with either a biocompatible or a biocompatible (low-flux) membrane showed that the biocompatible group had earlier increases and higher levels of serum insulin-like growth factor-1 (IGF-1), prealbumin, and albumin than did the biocompatible group (63). These results support the conclusion that the biocompatibility of the membrane favorably affects nutritional status, whatever the flux characteristics of the membrane.

Energy requirements depend on the level of physical activity, an intake of 35 to 40 kcal/kg body wt per day being recommended for adult individuals not performing heavy physical exercise. There is no evidence that the energy requirements of maintenance dialysis patients differ from those of normal subjects (64,65). Metabolic studies in healthy individuals and in HD patients indicate that the utilization of protein is greatly dependent on the energy intake, so that a low energy intake reduces utilization, whereas a high energy intake has a protein-saving effect (66,67). Further evidence that an adequate energy supply promotes protein anabolism is the observation that oral energy supplementation increases the growth rate and the serum albumin level in growth-retarded children on HD (68). Dialysis with glucose-free dialysis fluid in fasting HD patients may be expected to enhance gluconeogenesis from amino acids to compensate for the dialytic loss of glucose (about 25 g per dialysis), thus resulting in an increase in protein catabolism. However, we recently reported that there was no difference in amino acid release from the musculature, amino acid loss in the dialysate, and urea appearance during HD after an overnight fast, whether or not glucose (10 mmol/L) was present in the dialysis fluid (56).

LOW NUTRITIONAL INTAKE AND ANOREXIA

Considering all of the evidence that requirements for protein are increased in HD patients and that an adequate energy supply is mandatory for maintaining the energy stores and optimizing the utilization of ingested protein, low protein and energy intakes must be especially harmful in such patients. It may be difficult to fulfill the nutritional requirements, because some dialysis patients tend to lose their appetite and reduce protein and energy intakes spontaneously.

Recent data from the MDRD study in the United States (65) demonstrate that an adaptive reduction in the intake of protein may start early during the progression of renal failure (GFR, 25 mL/min or higher), with a further reduction in protein intake along with progression toward end-stage renal failure and an associated reduction in energy intake and various nutritional parameters (body weight, fat mass, serum albumin, and transferrin). Nutritional surveys indicate that the mean intake of protein is less than 1 g/kg body wt per day in a large proportion of patients on maintenance HD (5-8), suggesting that the requirements for protein are not fulfilled. The energy intake, like the protein intake, is often low in groups of dialysis patients; the mean intake in HD has been reported to be 26 to 29 kcal/kg body wt per day (23,25).
Anorexia, nausea, and vomiting are signs of severe uremic intoxication. It is a common clinical experience that uremic patients who are anorectic regain appetite after the initiation of maintenance dialysis. This suggests that one (or more) uremic toxins causing anorexia has been removed by dialysis. Assuming that a dialyzable uremic toxin accumulates in severe renal failure and causes anorexia, it is conceivable that underdialysis affects the appetite and thus causes malnutrition. In the National Cooperative Dialysis Study (NCDS), a nationwide multicenter study performed in the United States with the aim of defining the adequacy of HD, two groups of patients with low BUN levels and long or short dialysis times, respectively, and two groups of patients with high BUN levels and long or short dialysis times, respectively, were studied for 24 to 52 wk (69). In the high-BUN groups, the dialysis dose of low-molecular-weight solutes (urea) was lower than in the low-BUN groups. In the short-dialysis-time groups, the removal of larger molecular weight solids, so-called middle molecules (MM), was assumed to be less efficient than in the long-dialysis-time groups; plasma levels of MM were not measured. The protein intake was correlated to the length of dialysis, and the two groups on short dialysis had lower mean intakes of protein at the end of 6 months than did the two groups on long dialysis (25). These results suggest that appetite suppression in uremia depends to some extent on the accumulation of toxic MM. This suggestion is supported by our recent finding that an MM fraction in the molecular weight range of 1 to 5 kilodalton isolated from uremic plasma ultrafiltrate and from normal urine induces a dose-dependent suppression of appetite in normal rats after intraperitoneal injection (70).

The dose of dialysis regarding the removal of small molecules may be expressed as $Kt/V_{\text{urea}}$, which is the negative exponential in the equation describing the disappearance by diffusion of urea from the blood during an HD session ($K = \text{urea clearance of the dialyzer [in milliliters per minute]}, t = \text{length of dialysis [in minutes]}, V = \text{distribution volume of urea [in milliliters]})$. $Kt/V_{\text{urea}}$ may be modified to include the effects of ultrafiltration and of residual renal function. A simpler expression of the dose of dialysis for small molecules is the urea reduction rate, i.e., the ratio between predialysis minus postdialysis concentration and the predialysis concentration of urea.

Several recent studies in dialysis patients report a significant correlation between the dose of dialysis for small molecule removal ($Kt/V_{\text{urea}}$) and the protein intake, especially in the lowest dose intervals (38,71,72). Observations in a small group of HD patients with low $Kt/V_{\text{urea}}$ suggest that an increase in the dose of dialysis results in a significant increase in the estimated protein intake (73). Lindsay et al. also reported that the relationship between $Kt/V_{\text{urea}}$ and protein intake seems to depend on the properties of the dialysis membrane used, so that for each unit increase in $Kt/V_{\text{urea}}$, the protein intake increases more when a synthetic, biocompatible, high-flux membrane (AN 69) is used than when a less biocompatible, low-flux, cellulose acetate membrane is used. This observation may further support the hypothesis that uremic toxins that induce anorexia are medium-sized molecules, although it does not exclude that factors related to biocompatibility may be involved in the regulation of appetite. However, there are data that show no relation between $Kt/V_{\text{urea}}$ and protein intake in patients who are adequately dialyzed (74,75). We have reported a significant correlation between $Kt/V_{\text{urea}}$ and the estimated protein intake in a group of 151 HD patients studied in 1990, many of whom had $Kt/V_{\text{urea}}$ levels below 1.0 (38). When we reinvestigated our HD patients in 1992, the correlation was no longer present, presumably because $Kt/V_{\text{urea}}$ had increased to levels where the protein intake became independent of the dose of dialysis (unpublished observations).

In most of the aforementioned studies, the intake of protein was assessed by urea kinetic modeling on the basis of the concept that the amount of urea generated reflects the net protein catabolic rate (PCR), which in patients who are in a metabolic steady state (i.e., not markedly catabolic or anabolic), gives an estimate of the protein intake (51,76). It has been argued that the relationship between $Kt/V_{\text{urea}}$ and protein intake (urea appearance) reflects a mathematical coupling rather than a biologic relationship, because the two variables are to some extent dependent (both are normalized to body size, both are dependent on urea determinations in plasma predialysis and postdialysis) (77). Lowrie (48) reported no significant correlation between the dose of HD estimated as the urea reduction rate and the serum albumin concentration, indicating that the dose of dialysis has little effect on nutrition in HD patients. However, some data show that patients with $Kt/V_{\text{urea}} < 1.0$ have lower BUN, serum creatinine, and serum albumin levels than do more adequately dialyzed patients, suggesting that underdialysis may have resulted in a low protein intake and protein malnutrition (78). In another study (79), HD patients with low serum albumin were monitored longitudinally while being treated with high-flux dialysis ($Kt/V_{\text{urea}}$, about 1.3), which resulted in a significant increase in serum albumin, claimed by the authors to result from adequate dialysis and adequate protein and energy intakes. It was recently reported that an increase in the dose of dialysis from $Kt/V_{\text{urea}} < 0.86$ to $Kt/V_{\text{urea}} > 1.21$ resulted in increases in protein intake and serum albumin along with a reduction in mortality from 23 to 9% (80). In conclusion, the extent to which the adequacy of dialysis affects nutritional intake and nutritional status remains unsettled. It is reasonable to suppose that severe underdialysis results in anorexia, considering that end-stage renal failure patients who are not dialyzed are markedly appetite suppressed. However, it remains to define the dose of dialysis (for small molecules?) required before anorexia becomes impor-
Nutrition and Mortality in HD

important and how much this dose may vary from one patient to another.
Several additional factors may cause or contribute to anorexia in HD patients—factors that in the single patient may be far more important than uremic intoxication (Table 2). They include inadequate diets, gastropathy (in diabetic patients with autonomic neuropathy), medications, and psychosocial and socioeconomic factors, such as loneliness, depression, ignorance, and poverty, especially in elderly patients and those with alcohol and drug problems. Anorexia, nausea, and vomiting during and immediately after HD, which are frequently associated with cardiovascular instability and postdialysis fatigue, may lead to a reduction in food intake on the day of the dialysis.

LOW NUTRITIONAL INTAKE, NUTRITIONAL STATUS, AND MORTALITY

Mortality Statistics

The large registers of patients on renal replacement therapy are not of very great help in determining the role of malnutrition as a cause of death. In the United States Renal Data System (USRDS) Annual Report (81) and in the Register of the European Dialysis and Transplant Association–European Renal Association (EDTA/ERA) (82), cardiovascular and cerebrovascular causes of death predominate (about 50%), followed by death from infections (13 to 16%). In the USRDS report, cachexia and malnutrition are not listed among the causes of death, and in the EDTA/ERA register, cachexia is a relatively rare cause of death—3% in patients aged 16 to 64 yr and 10% in patients ≥65 yr of age. These figures regarding the death rate from malnutrition are low, if mentioned, and may be the result of nonreporting or underreporting; it cannot be excluded that malnutrition may have contributed more than is apparent from these mortality statistics. However, an analysis of a dialysis patient population in northern Italy reveals that malnutrition seems to be a common cause of death in elderly patients, with no less than 32.5% of the patients ≥65 yr and 41% of patients above 75 yr of age dying from cachexia (83).

Nutritional Intakes and Clinical Outcome

The NCDS showed that a PCR below 0.8 g/kg body wt per day was associated with treatment failure (84). It was therefore recommended that the protein intake should be sufficient to obtain a PCR of 0.8 or more (84,85). However, these results hardly lend themselves to general interpretations regarding protein requirements and the effect of protein intake on morbidity and mortality, because it was not demonstrated that low protein intake (PCR) was associated with a significant deterioration of the nutritional status, perhaps because the study periods were too short (24 to 52 wk). Moreover, a nutritional assessment of the NCDS patients revealed that, despite the recommendation for an adequate energy intake, the actual intake was no more than an average of 23 to 26 kcal/kg in the four experimental groups, which is clearly suboptimal and may have impaired the utilization of dietary protein and thus constituted an additional risk factor. Strict inclusion criteria were used, excluding patients over 70 yr of age and those with diabetes, heart disease, uncontrolled hypertension, excessive weight gain, and other pathologic conditions (86). It is questionable whether conclusions regarding nutrition and clinical outcome based on the NCDS results are applicable to such patients, who constitute a large proportion of the dialysis patients today. Most of the causes of death in the NCDS, which occurred after the study period, did not seem to be directly related to events that might have been caused by malnutrition (87).

Other studies have confirmed that a low protein intake may be associated with increased mortality. Among 120 HD patients, Acchiaro et al. (88) found that a subgroup with a mean PCR of 0.63 g/kg per day had a mortality rate of 14% per year, whereas groups of patients with higher intakes—0.93, 1.02, and 1.29 g/kg per day—had mortality rates of only 4, 3, and 0%, respectively. The number of hospitalizations per year was also much higher in the group of patients having the lowest intake of protein, with higher frequencies of heart disease, pericarditis, infections, and gastrointestinal disturbances than in the other patient groups. It was concluded that malnutrition is the main factor in morbidity and mortality in HD patients, as stated in the title of the report. However, these results should be interpreted with caution regarding the role of malnutrition, because the nutritional status of the patients was not reported. Moreover, the results do not exclude that the reduced protein intake in the risk groups was secondary to other morbidity factors that may have caused or contributed to the fatal outcome.

<table>
<thead>
<tr>
<th>TABLE 2. Protein catabolic factors in HD patients</th>
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<tbody>
<tr>
<td>General Effects</td>
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<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Heart failure</td>
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<tr>
<td>Low energy intake</td>
</tr>
<tr>
<td>Endocrine abnormalities</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
</tr>
<tr>
<td>Inflammation, Infection, sepsis</td>
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<tr>
<td>Acidosis</td>
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<tr>
<td>Amino acid abnormalities</td>
</tr>
<tr>
<td>Catabolic Effects of the HD Procedure</td>
</tr>
<tr>
<td>Loss of amino acids 9 to 13 g/dialysis (25 to 40 g/wk)</td>
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<tr>
<td>Loss of glucose 25 g/dialysis (glucose-free dialysate)</td>
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<tr>
<td>Blood-dialyzer contact</td>
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<tr>
<td>Complement activation</td>
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<tr>
<td>Endotoxins</td>
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<tr>
<td>Cytokines</td>
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<td>Inflammation–catabolism</td>
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</table>
In the NCDS, the two groups of patients with high BUN values had a larger number of treatment failures and more deaths in the poststudy phase than did the two groups with a low BUN. In this study, protein intake was normalized to 1.1 ± 0.3 g/kg body wt, and high and low BUN levels were obtained by adjusting the dose of dialysis, implying that the high-BUN groups were underdialyzed compared with the low-BUN groups. However, several other studies where the protein intake was not normalized have shown that a low BUN level is associated with an increased risk of morbidity and mortality (88-90). In those studies, a low BUN may serve as an index of low protein intake and the results have been interpreted to mean that malnutrition due to low protein intake may have been a causative factor in the increased mortality and that BUN is unsuitable as a criterion for the prescription of dialysis.

**Nutritional Status and Clinical Outcome**

There are now several studies suggesting that signs of malnutrition are prognostically unfavorable for the outcome in HD patients. In most of those studies, the evaluation of nutritional status was mainly based on the measurement of serum albumin and other serum proteins, but in some studies, the nutritional status has been evaluated by the use of anthropometric measurements.

Bilbrey and Cohen (35) found a relationship between a protein-calorie malnutrition index, obtained by the addition of eight scores, including anthropometric, biochemical (albumin and transferrin), total lymphocyte counts, and clinical evaluation, and noted a much higher percent mortality over 14 months in patients with moderate (21.4% mortality) and severe (23.8% mortality) malnutrition than in patients with little (10.9% mortality) or no (14.3% mortality) malnutrition. Oksa et al. (34) measured anthropometric parameters, as well as albumin, prealbumin, transferrin, C3, retinol-binding protein, and plasma amino acids, and found that 5 (17%) of 29 patients had evidence of protein malnutrition with lower serum prealbumin and plasma leucine concentrations than the others. All of the malnourished patients died during a follow-up period of 3 yr, whereas only 7 of the other 19 patients died. Marckmann (29) assessed nutritional status, using a scoring system based on relative body weight, midarm muscle circumference, triceps skinfold thickness, and serum transferrin, and found in a small group of dialysis patients that 5 of 32 HD patients who died during a 24-month period had a high score, demonstrating that they were malnourished. Low relative body weight has also been reported to be associated with increased mortality (E.G. Lowrie, personal communication).

The most extensive retrospective analysis of risk factors for mortality in HD patients has been made by Lowrie and Lew (30), who analyzed laboratory data from more than 12,000 HD patients treated at Na-
Serum Albumin as a Marker of Protein Malnutrition

In the discussion of results showing that the serum albumin level is a strong predictor of mortality in HD patients, it is generally assumed that albumin is a key index of nutritional status and reflects visceral protein stores. However, the serum albumin concentration is affected by many non-nutritional factors, such as albumin synthesis inhibition, albumin degradation, albumin losses from the body, exchange between intravascular and extravascular compartments, and the volume in which albumin is distributed. Serum albumin decreases with age in apparently healthy subjects. Infection, trauma, and malignancy may induce an acute-phase response mediated by the release of interleukin-1 and interleukin-6, resulting in an increase in several serum proteins, such as haptoglobin, complement, fibrinogen, amyloid protein A, and C-reactive protein, which participate in host defense. This is accompanied by an increase in catabolism and a decrease in the synthesis of albumin. The host switches from the production of albumin to proteins that have host-immune response functions. Overhydration with pulmonary congestion may also reduce serum albumin by dilution. With tissue injury, e.g., after a major trauma, in cancer, infection, hypertension, diabetes mellitus, and liver cirrhosis, hypoalbuminemia may develop as the result of the capillary extravasation of albumin to the interstitial fluid because of an increase in capillary permeability. An association between hypoalbuminemia and increased morbidity and mortality is not unique in renal failure patients but is also found in the general population of patients admitted to the hospital. Findings in HD patients with 125I-labeled human serum albumin suggest that hypoalbuminemia and reduced albumin synthesis result mainly from non-nutritional factors and partly from a (negative) acute-phase response. In a recent study of CAPD patients, it was observed that low serum albumin mainly reflected the presence of a systemic disease, which was the chief risk factor for reduced patient survival.

Hence, one should be cautious in drawing conclusions regarding the role of malnutrition in dialysis-associated mortality based only on serum albumin data, considering that comorbid conditions, the severity of which are reflected in low serum albumin levels, rather than malnutrition per se, may be instrumental in causing the death of the patients. In other words, hypoalbuminemia in HD patients may be more of a nonspecific marker of illness than a nutritional parameter. When hypoalbuminemia is observed, it is imperative to look not only for other signs of malnutrition but also for comorbid conditions that may reduce the chances of survival.

BY WHICH MECHANISMS IS NUTRITIONAL STATUS ASSOCIATED WITH REDUCED SURVIVAL?

In spite of multiple studies demonstrating that signs of malnutrition (mainly a low serum albumin) are strong predictors of morbidity and mortality in HD patients, malnutrition per se is not recognized as a major direct cause of death, except in the elderly dialysis population. The question has therefore been asked about a possible link between malnutrition and high cardiovascular mortality in dialysis patients. It was recently reported that asymmetric dimethyl-L-arginine (ADMA), an endogenous inhibitor of nitric oxide (NO) synthase, accumulates in renal failure to such an extent that it inhibits the generation of NO in vitro, and it was proposed that high ADMA levels in the plasma of uremic patients could interfere with NO synthesis in vivo, thereby interfering with the regulation of vascular tone and causing hypertension. Ritz et al. have proposed that malnutrition, resulting in low L-arginine levels in plasma, could create an imbalance between the substrate for NO synthesis (L-arginine) and its inhibitor (ADMA), which should further enhance the effect on cardiovascular tone. However, this hypothesis, although elegant, is offset by more recent data using a different analytical method, giving values for ADMA in plasma before HD that are 5 to 10 times lower than those earlier reported and are too low to induce an inhibiting effect on the NO synthase. Moreover, plasma and intracellular L-arginine concentrations are generally not reduced in HD patients.

A link between malnutrition and increased mortality caused by infection and sepsis is more obvious, considering that malnutrition induces immunosuppression with a reduced cellular immune response, impaired antibody production, and inhibition of granulocyte mobility and phagocytic capacity. These abnormalities are very similar to the immunologic changes caused by uremia per se, and it is conceivable that malnutrition and uremic toxicity may act in concert to suppress the immune response. In addition, the NO synthase generates nitric oxide (NO) and it was proposed that high ADMA levels in the plasma of uremic patients could interfere with NO synthesis in vitro, thereby interfering with the regulation of vascular tone and causing hypertension. Ritz et al. have proposed that malnutrition, resulting in low L-arginine levels in plasma, could create an imbalance between the substrate for NO synthesis (L-arginine) and its inhibitor (ADMA), which should further enhance the effect on cardiovascular tone. However, this hypothesis, although elegant, is offset by more recent data using a different analytical method, giving values for ADMA in plasma before HD that are 5 to 10 times lower than those earlier reported and are too low to induce an inhibiting effect on the NO synthase. Moreover, plasma and intracellular L-arginine concentrations are generally not reduced in HD patients.

Hypoalbuminemia per se may also contribute to much longer hospital stay than did patients who were referred early. Concern has been expressed that prolonged treatment with a low-protein diet may cause protein malnutrition. However, the treatment of near-end-stage renal failure patients with a low-protein diet may not only reduce uremic symptoms but may even correct low serum albumin and protein levels, provided that the energy intake is high and the diet is supplemented with adequate amounts of essential amino acids or ketoacids.
morbidty and mortality. Water balance between intravascular and interstitial spaces may be adversely affected by low intravascular oncotic pressure (121). Albumin also has important roles as a scavenger of free radicals, a binding agent for toxic compounds, and a carrier for a wide variety of drugs and hormones (122). Reduced albumin binding of drugs and endogenous ligands is a feature of uremia (123), and it is conceivable that potentially adverse effects of reduced albumin binding are further promoted when serum albumin is low. However, exogenous albumin therapy has generally not been successful in reducing morbidity and mortality in intensive care patients (124) and there is no evidence that such therapy is of any value in hypoalbuminemic HD patients.

Withdrawal from dialysis is among the most common causes of death (13%) in maintenance dialysis patients, as reported in the USRDS annual report (81). It is conceivable that in some of these patients, who are usually elderly, the presence of severe nutritional problems may have been a reason why the decision was made to withhold dialysis.

EFFECT OF INTERVENTIONS ON NUTRITIONAL STATUS AND SURVIVAL

Assuming that malnutrition is a significant risk factor for mortality and morbidity in HD, one might expect that measures taken to improve nutritional status should be beneficial in improving survival and rehabilitation. The elimination of catabolic factors such as acidosis, infectious complications, and other comorbidity factors are obvious goals of treatment. In underdialyzed HD patients, an increase in the dose of dialysis may have salutary effects by improving general well-being and survival and by promoting an increase in food intake (61,73,80,125). However, it should be emphasized that it is not known to what extent the beneficial effects on survival, achieved by increasing the dose of dialysis, are mediated by the correction of malnutrition. Moreover, anorexia in HD patients may be related to various comorbidity factors apart from underdialysis (Table 3) that must be identified and corrected in order to ensure an adequate nutritional intake. Psychosocial and economic support should be provided whenever needed. Dietary advice with the aim of increasing the quantity, quality, and palatability of the food consumed may be helpful. Attention should be paid not only to the protein intake but also to the energy intake, which needs to be adequate for the optimal utilization of protein (67). Oral supplementation with special formula preparations containing high-quality protein, essential amino acids, carbohydrates, and fat may be added to the diet (126).

If severe malnutrition develops despite adequate dialysis and measures to eliminate various anorectic and catabolic factors, enteral or parenteral nutritional supplementation may be necessary to ensure an adequate supply of nutrients. Feeding by a nasogastric tube, a percutaneous gastric catheter, or a gastroscope button is preferable, whenever possible, to parenteral feeding through an indwelling catheter, which is more expensive and carries the risk of catheter-related sepsis (126). The effect of such therapies on mortality in HD has not been assessed.

Intradialytic parenteral nutrition (IDPN), i.e., the intravenous supply of a mixture of amino acids, glucose, and lipids during the HD session, has become increasingly popular in recent years, because it can be given without the need of a central catheter and does not confine the patient to an intravenous line (127–129). Favorable effects on nutritional status, including anthropometric parameters and serum proteins, have been reported in some studies. Most of the studies comprised small numbers of patients over short periods, and they lacked control groups; no beneficial effects on morbidity and mortality were reported. Recently, Capelli et al. (134) reported the results of a prospective, nonrandomized study of malnourished HD patients over an average of 9 months. Fifty patients who received IDPN had a significantly lower mortality rate than did 131 untreated patients (134). Chertow et al. (135) analyzed retrospective survival data in a subgroup of 1,679 HD patients who received IDPN (one or more infusions), comparing them with data from more than 22,000 patients, and monitored the two groups for 1 yr or until death. There was a significant reduction in the odds of death and an increase in the serum albumin and creatinine levels in the IDPN-treated patients with low serum albumin compared with nontreated patients with hypoalbuminemia. Patients with normal serum albumin levels did not benefit from the treatment. Although the two aforementioned studies suggest that mortality is reduced by IDPN in malnourished HD patients, it should be noted that they were both retrospective and potentially subject to selection bias and that the effects noted were modest. Nor can it be excluded that

<table>
<thead>
<tr>
<th>TABLE 3. Causes of anorexia in maintenance dialysis patients</th>
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<tr>
<td>Uremic Toxicity (Underdialysis)</td>
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<tr>
<td>Unpalatable or Inadequate Diets</td>
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<tr>
<td>Gastrointestinal Illness</td>
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<tr>
<td>Other Complicating Illness</td>
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<tr>
<td>Inflammation, Infection, Sepsis</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Dental Status</td>
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<tr>
<td>Psychosocial and Socioeconomic Factors</td>
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<tr>
<td>Loneliness</td>
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<td>Depression</td>
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<td>Ignorance</td>
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<tr>
<td>Poverty</td>
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<tr>
<td>Alcohol and drug abuse</td>
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<tr>
<td>Effects of the HD Procedure</td>
</tr>
<tr>
<td>Cardiovascular instability</td>
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<tr>
<td>Nausea, vomiting</td>
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<tr>
<td>Postdialysis fatigue</td>
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these effects might have been obtained equally well by intensive dietary counseling plus other measures to improve the nutritional status. Hence, the issue of whether or not IDPN is of proven benefit is still controversial (136,137). Nevertheless, it is reasonable to try this form of therapy in severely malnourished HD patients when all other measures fail, and especially during episodes of concurrent illness, with deterioration of nutritional status. Prospective, well-controlled studies are obviously needed to establish whether IDPN should be generally recommended as a therapy for chronically malnourished HD patients, especially because it is a very expensive form of therapy.

Recombinant human growth hormone (rHGH) is now available for the treatment of growth retardation and malnutrition (138); its anabolic effects are partly mediated through the induction of IGF-1. Treatment with rHGH is now an established therapy in growth-retarded uremic and transplanted children (139,140). Short-term studies in adult HD patients with malnutrition have demonstrated that the administration of rHGH in combination with parenteral nutrition results in reduced urea appearance, sustained nitrogen retention, and improvement of nutritional status (141,142). These very promising results suggest that rHGH potentiates the anabolic effects of IDPN. However, the effect of this very expensive form of therapy on morbidity and mortality has not been established.

Recombinant human IGF-1 (rhIGF-1) has also been proposed as a nutritional support in malnourished dialysis patients (143) and has been reported to cause anabolism in a small group of CAPD patients (144). However, there is evidence that HD and CAPD patients are resistant to the metabolic effects of rhIGF-1 (145) and that treatment with rhIGF-1 in uremic patients is associated with a high frequency of side effects (146).

CONCLUSIONS

Anthropometric and biochemical signs of malnutrition in HD patients are associated with increased mortality, but malnutrition per se is generally not recognized as a common cause of death as reflected by health statistics, except in the oldest age groups. A low serum albumin level is an especially strong predictive risk factor; it may, however, not only or mainly reflect protein malnutrition, but also the influence of several other morbidity factors (overhydration, infection, chronic disease and others) that may entail an increased risk of death. The protein requirements are increased and the intake of protein (and energy) is frequently reduced in relation to the requirements, as the result of several factors associated with uremia per se—the HD procedure and various comorbidity factors. Anorexia and malnutrition may be related to underdialysis, but the causative role of uremia, uncorrected by the dialysis treatment, is not well defined. For the prevention and treatment of HD-associated malnutrition, it is important to correct factors that may suppress appetite and increase net protein catabolism. Only when all such measures fail to produce a positive effect, may enteral and parenteral nutrition be tried, although there is still insufficient evidence that these types of therapy have a beneficial effect on patient survival. The same applies to treatment with rHGH in combination with IDPN, which in short-term studies shows very promising results.

REFERENCES


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