When Does Malnutrition Become a Risk?

L. Genton\textsuperscript{a}, W.G. van Gemert\textsuperscript{a}, C.H. Dejong\textsuperscript{a}, P.L. Cox-Reijven\textsuperscript{b} and P.B. Soeters\textsuperscript{a}

\textsuperscript{a}Department of Surgery, University Hospital, and \textsuperscript{b}NUTRIM Institute, Maastricht University, Maastricht, The Netherlands

Introduction

Malnutrition has been defined as a deficiency of energy, protein or other types of nutrients, which produces alterations in body function, is associated with worse outcome from illness and is reversible by nutritional support \cite{1}. Global malnutrition generally results from simple starvation or stress starvation and has to be distinguished from deficiency of one micronutrient or vitamin \cite{2}. Starvation results from a pure deficit of all macro- and micro-nutrients and occurs for instance in hunger strikers, persons with anorexia, or patients with intestinal diseases leading to malabsorption. Stress starvation, or cachexia, represents the accelerated loss of muscle mass in response to metabolic stress and generally affects patients with inflammatory or neoplastic diseases. Some authors report a third type of malnutrition, sarcopenia \cite{3}, which reflects loss of skeletal muscle in the elderly as well as in persons who repeatedly try to lose weight by dieting and in people with growth hormone deficiency, immobilization or arthritis. However, it is questionable whether cachexia and sarcopenia are totally different entities because they may share one or more common pathophysiologic causes including metabolic stress.

Whatever the specific etiology is, global malnutrition results in decreased body cell mass (BCM) and fat-free mass (FFM) and leads to diminished body function. FFM can routinely be assessed by several methods, including measurements of skinfold thickness, arm circumference, bioelectrical impedance analysis (BIA) or dual energy X-ray absorptiometry (DXA). In many studies, parallel decreases in BCM and quality of life have been demonstrated \cite{4–7}.
but in only very few studies has a critical size of BCM been determined to sustain health [8–10].

In this chapter, we will review the factors responsible for malnutrition, the prevalence of malnutrition in hospitalized patients, and the methods available to assess malnutrition. We will also try to link the loss of BCM with physical disability, impairment of physical functioning, immune function, quality of life and mortality.

**Physiological Mechanisms of Malnutrition**

The mechanisms and causes of malnutrition are shown in figure 1. The calorie deficit occurring during chronic starvation forces the human body to rely on its own energy stores for survival. The priority of the organism is to maintain euglycemia in order to ensure proper function of vital organs such as the brain, heart, kidney and muscles. At the beginning of starvation, the human body reduces insulin secretion and stimulates glucagon and
catecholamine secretion to maintain euglycemia. 75% of glucose is produced by liver glycogenolysis and 25% by gluconeogenesis. In the fasted state, hepatic glycogen stores are depleted within 24 h and gluconeogenesis remains the only glucose source thereafter. The substrates used for gluconeogenesis are amino acids (especially alanine and glutamine) resulting mainly from protein breakdown in skeletal muscle and glycerol produced by lipolysis. After a few days (or weeks) of starvation, gluconeogenesis decreases in response to an unknown mechanism. The brain adapts by using ketone bodies derived from non-esterified fatty acids as metabolic fuel. The metabolic alterations occurring with fasting have been linked, in rodents, to decreased levels of leptin, an adipocyte-derived cytokine [11].

In contrast to pure starvation, muscle wasting occurring in cachexia (stress starvation) can appear despite adequate energy and protein intake. It is the complex result of neuronal, inflammatory and hormonal interactions occurring during metabolic stress. Its pathogenesis has been related to increased levels of proinflammatory cytokines (IL-1, IL-6, TNF-α, IFN-γ), reduced secretions of insulin-like growth factor-1 (IGF-1) and gonadotrophic hormones, and increased secretions of glucocorticoids [12]. Cachexia is often associated with physical inactivity, leading to muscle atrophy and anorexia, an abnormal loss of appetite for food, which complicates the interpretation of physiological findings in humans. The major characteristic of cachexia is a stimulation of skeletal muscle degradation and an increased synthesis of the hepatic proteins implicated in the acute phase response. This re-prioritization of nitrogen utilization accelerates weight loss in cachectic fasting subjects. This results from a mismatch between the amino acid composition of muscle and that of acute phase proteins. Indeed, it has been calculated that 2.6 g of muscle protein has to be catabolized to synthesize 1 g of fibrinogen [13]. Another reason for weight loss during metabolic stress is that a major part of the branched chain amino acids derived from protein degradation are irreversibly degraded to yield glutamine and alanine, so that these branched chain amino acids cannot be utilized for protein synthesis. Changes in fat metabolism also occur and include hyperlipidemia, increased lipolysis, increased de novo triglyceride synthesis, increased free fatty acid turnover and decreased lipoprotein lipase activity. Peripheral insulin resistance, hyperinsulinemia and glucose intolerance form an integral part of the inflammatory response. Recent studies suggest that the loss of skeletal muscle mass occurring with aging also arises from an inflammatory catabolic signal, which could either increase catabolism directly or through the inhibition of anabolic stimuli like diet and physical exercise. This signal may be regulated by IL-6, whose production has been shown to increase with aging [14]. However, sarcopenia may also result from physical inactivity or comorbid factors like arthrosis, heart and lung failure, which also induce an inflammatory response.
Clinical Consequences of Malnutrition

The human body responds to malnutrition with changes in body composition eventually affecting muscle function. These changes are usually reflected in abnormal laboratory values. At the tissue level, body composition can be altered with regard to fat mass (FM) or FFM, which is body mass devoid of all extractable fat and regroups bone mineral mass, non-bone mineral lean body mass, and total body water. At the cellular level, BCM (the active, energy-consuming, protein-rich and potassium-rich intracellular tissue) may be distinguished from extracellular fluids and extracellular solids. BCM is viewed by many as the most relevant body compartment to assess malnutrition. In table 1, the changes occurring in the different types of malnutrition are summarized.

Starvation translates into decreased resting energy expenditure, body weight, and a predominant reduction of FM over FFM [3]. The loss of FFM, which presents as muscle atrophy, is inversely correlated with initial adiposity. A closer examination of the composition of the FFM loss shows a reduced bone mass and density and a decreased BCM [3]. The reduction in BCM reflects atrophy and hypoplasia of muscle, intestinal, liver, splenic and immune cells. Total body water as a percentage of body weight is increased with an expansion of extracellular water. Blood values may remain within the normal range, at least during the first 6 weeks of starvation [15]. Refeeding is possible and the resulting gain in body weight is half FM and half FFM.

Cachexia differs from starvation by an increased resting energy expenditure corrected for FFM or BCM but reduced total energy expenditure, resulting probably from limited physical activity [16]. Weight loss is common but not universal. There is a decrease in cellular mass, like in starvation, but which occurs much faster and is generally accompanied by hepatomegaly. It is unclear whether hepatomegaly results solely from steatosis or also reflects an increase in cell size or number. In rats, liver size and protein content have been shown to increase after endotoxin injection [17]. In addition, the liver produces increased amounts of plasma proteins, including C-reactive protein.
fibrinogen, complement factors and others. Although plasma albumin levels are decreased, its fractional synthesis rate increases. The amount of extracellular water remains stable or is expanded [16]. The increased protein degradation in muscle cannot be overcome by the anabolic stimulus of feeding, precluding the reversal of the BCM loss. A decrease in BCM and an expansion of extracellular fluid has also been reported in sarcopenia. Histological data report a myocyte hypoplasia and atrophy [18]. Weight and FM loss are not especially associated with sarcopenia. Indeed, in healthy Swiss subjects, FFM decreases but FM and weight increase on average until the age of 74 years [19]. Plasma levels of albumin have been reported to decrease with aging independently of other factors affecting FFM and albumin levels [20]. However, in that study, inflammatory parameters have not been assessed.

To summarize, all types of malnutrition show decreased BCM, but the quantitative and qualitative alterations differ. It is of interest that patients may be malnourished despite an increase in body weight (sarcopenia, edema). FFM does not reflect BCM and is therefore, especially in the depleted state and in severe illness, an invalid measure of BCM.

**Assessment of Malnutrition**

Malnutrition is not yet well recognized by many health care professionals. This may be due to a lack of training or interest. In addition, the situation is complicated by the fact that the diagnosis of malnutrition does not rely on one single parameter but requires the integration of nutritional markers and the clinical history and physical examination of the patient. Presently, the most often used clinical tools to detect malnutrition are anthropometric parameters, body composition, laboratory values (plasma albumin, pre-albumin, transferrin, C-reactive protein, IGF-1, total lymphocyte count) and nutritional indices (e.g. Subjective Global Assessment, Mini Nutritional Assessment, Nutritional Risk Index). Functional assessment includes testing of muscle function, either by dynamometry for handgrip strength or electrical stimulation, or simply by observation of the physical capacities of the patient [21]. In this context, it must be realized that some of these assumed markers of nutritional status, such as serum albumin, are not nutritional markers, but are predominantly determined by the inflammatory status of the accompanying disease, leading to increased capillary permeability and transcapillary leakage of protein, fluid and electrolytes and to a change in the kinetics of albumin.

The identification of malnutrition requires thorough assessment of body compartments. Methods presently available in clinical routine measure two, three or four compartments, as indicated in figure 2. Skinfold thickness (e.g. triceps skinfold thickness) allows estimation of total body fat using previously published empirical equations. Mid-arm circumference is used to
calculate lean tissue and muscle mass. Both methods are inexpensive and relatively easy to perform but are limited by inter-observer variability, variations in skin compressibility, abnormalities of fat and water distribution in disease (e.g. lipodystrophy, ascites, edema), and inaccessibility of sites (e.g. intensive care patients in a supine position). Their precision is 5% maximum when performed by trained researchers.

BIA is easy, fast, noninvasive and inexpensive. Self-adhesive electrodes are put on the right hand, wrist, ankle and foot. A generator applies an alternating current (0.8 mA, 50 kHz). Resistance and reactance are measured and converted to total body water, FFM and skeletal muscle mass by validated equations. The results are influenced by posture, hydration and ion status, body temperature and body geometry. Its reproducibility is 0.8–4.2% for measures of FFM. Multi-frequency bioimpedance analysis has been used to differentiate between total body water and its extra- and intracellular sub-compartments. The theory is that impedance at low frequencies is correlated with extracellular water and impedance at high frequencies with total body water. However, its use to assess BCM in patients is still not accepted because present equations yield variable results when validated against dilution methods [22]. Disease changes the total protein content and composition as well as the membrane capacitance which affect the resistance. As a consequence, equations to determine FFM are invalid [22]. DXA is a scanning technique measuring FM, FFM and bone mass. Although not yet considered the ‘gold’ standard, it is one of the reference methods for measuring body composition. It uses X-rays of two different energy levels. The attenuation of these X-rays

| Fat mass  
<table>
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<th>(skinfold thicknesses, BIA, DXA)</th>
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| Fat free mass  
| (arm circumference, BIA) |
| Non mineral fat free mass  
| (DXA) |
| Body cell mass  
| (BIA) |
| Bone mineral content  
| (DXA) |
| Extracellular fluids  
| (BIA?) |
| Extracellular solids  
| (BIA?) |

**Fig. 2.** The body has been separated into compartments which can be measured routinely by the methods shown in italics.
as they pass through the body allow differentiation of bone, FM and FFM. For measuring FFM, the accuracy of DXA is 2–3% and its reproducibility 1.5–3%, for bone mass, its accuracy is 30 g and the reproducibility for bone density is 0.8% [23]. Other methods are available for measuring body composition, such as total body potassium, isotope dilution of deuterate-, titrate- or 18-oxygen-enriched H2O, CT scans, magnetic resonance and ultrasonography, but they are not practical for use in clinical routine. The distinction between starvation and cachexia can be made according to the changes in body composition (table 1), plasma albumin and the clinical history of the patient.

In summary, BCM is the crucial determinant of depletion. However, at present, there are no reliable methods to measure BCM in clinical routine. Therefore, in the literature, several surrogates of BCM are used.

### Prevalence of Malnutrition

The prevalence of malnutrition among hospitalized patients varies between 20 and 50%, depending on the methods used to assess malnutrition, the age and the primary disease of the subjects (table 2). The occurrence of malnutrition in the future will probably even rise because of aging of the population, increased frequency of chronic diseases, and the ability to perform more and more invasive and prolonged medico-surgical interventions.

<table>
<thead>
<tr>
<th>References</th>
<th>Year</th>
<th>Total patients</th>
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<tr>
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<tr>
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<td>52</td>
</tr>
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<td>45</td>
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<tr>
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<td>1993</td>
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<td>1990</td>
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NA = Not available.
When Does Malnutrition Become a Risk?

In practice, malnutrition is often only detected upon hospital admission when complications necessitating hospitalization have occurred. However, the WHO defines malnutrition as a risk to health, or in other terms, as a ‘factor that raises the probability of an adverse health outcome’. This definition implies that malnutrition should be diagnosed without the presence of malnutrition-related complications. While cachexia can be expected in many subjects who will undergo major surgery, the detection of malnutrition in outpatients with chronic diseases remains problematic. Therefore, the prevalence of malnutrition mentioned above may in fact only indicate the prevalence of malnutrition-related complications.

Health Risks Related with Malnutrition

Most of the studies regarding malnutrition-related risks have been performed in hospital settings and thus do relate to cachexia. Malnutrition leads to muscle atrophy and weakness. It mainly decreases peripheral skeletal muscle mass, which induces loss of mobility, an increased risk of falling, and probably also plays a role in equilibrium disorders. In addition, it also affects respiratory muscle mass. This translates clinically into impaired exercise tolerance [24], forms an impediment to weaning patients from ventilatory support and an impossibility to adequately mobilize patients postoperatively. This may also constitute an increased risk of community-acquired and nosocomial pneumonia [25]. In the cardiovascular system, malnutrition may lead to abnormalities of mitral valve motion, reduction in left ventricular mass and filling, and increased peripheral resistance [4]. Besides the effects on muscle, malnutrition delays wound healing and leads to immune dysfunction, which both favor infection and promote further catabolism [5]. It has been hypothesized that diminished muscle mass and immune dysfunction are directly linked because muscle is an important supplier of substrate serving to fuel the immune response. Examples of these substrates are glutamine, alanine and possibly arginine.

As a consequence of these complications, malnutrition reduces quality of life. It thereby contributes to an increase in the length of hospital stay and rehabilitation, which raises health-related costs, as well as mortality.

Cutoff Points for Health-Related Risks

It is difficult to determine at what point malnutrition becomes a risk for health because malnutrition is diagnosed by parameters which are in turn influenced directly by other factors such as primary diseases, drugs and physical activity.

Muscle atrophy decreases quality of life and increases mortality. Death results from a loss of 30–50% of BCM. A loss of BCM has been associated with
fatigue, global distress, depressive symptoms and reduced life satisfaction in, e.g., HIV patients [6]. A parallel decrease in muscle mass, physical performance and quality of life has been described in patients with renal transplantation [7], post-poliomyelitis syndrome [26], and elderly subjects [27]. In contrast, treatments which increase FFM and weight, as for example anabolic agents, cytokine inhibitors, and resistance training, have been shown to increase quality of life in diseased subjects.

The question arises whether a subject with decreased BCM due to cachexia (depletion due to inflammation) responds similarly to a metabolic challenge than a subject with simple starvation. This does not appear to be the case. Indeed, inflammation impairs the formation of healthy granulation tissue, healthy re-epithelialization, the growth of hair, nails and skin, the healing of anastomosis and the production of fibrin. Furthermore, preoperative albumin, which is always low in cachexia but not in simple starvation, has been shown to correlate inversely with complications, length of stay, postoperative stay, intensive care unit stay, mortality, and resumption of oral intake [28]. A low subjective global assessment, indicating depletion, has also been related to a higher risk of infectious complications, respiratory failure and cardiac failure, as well as wound dehiscence [29].

Only very few studies have related changes in anthropometrics or body composition to mortality, physical disability or impairment of physical functioning defined as limitations in mobility performance. Engeland et al. [30] showed a U-shaped or J-shaped relationship between body mass index (BMI) and mortality. Mortality was lowest with a BMI of 22–25 kg/m² and appeared to rise sharply with a BMI below 18 kg/m² in men and women. The optimal BMI increased between the ages of 20–29 and 70–74 years from 21.6 to 24.0 kg/m² in men and from 22.2 to 25.7 kg/m² in women [30]. Rosenbaum et al. [31] determined the 95% confidence intervals for normal changes in body weight and found that a normal rate of weight loss would be ±2% in 1 month, ±3.5% in 3 months, ±5% in 6 months and ±10% in 1 year. Many consider weight loss beyond these limits as malnutrition. However, small to moderate weight losses are not always related to changes in function and fatigue and quality of life. Minor weight changes are not a good indicator of malnutrition but large changes should be considered seriously. In 1936, Studley [32] observed a mortality rate of 33% in patients who underwent elective surgery for peptic ulcer disease and lost 20% of their body weight postoperatively. In contrast, a loss of 10% of body weight was not associated with a higher mortality [32]. Nevertheless, modifications in body composition and function assessed by quality of life may better reflect the consequences of malnutrition. This is also apparent if one realizes that sick patients may show an increase in weight, which is merely caused by an accumulation of body water (edema).

Janssen et al. [8] recently published skeletal muscle cutoff points for physical disability in the elderly. Physical disability was defined as an impairment
or health problem requiring help for eating, bathing, dressing or moving around at home or for household tasks, necessary business or shopping. They measured skeletal muscle mass with BIA and normalized it for height (skeletal muscle mass index = SMI). They demonstrated moderate and high risk of physical disability with an SMI <6.75 kg/m² in women and <10.75 kg/m² in men. Other studies have reported physical disability [9] or decreased physical functioning [10] but they used an arbitrary cutoff point to define sarcopenia (SMI <2 standard deviations below the mean of young adults).

**Detection of Malnutrition in Outpatients**

Malnutrition is difficult to diagnose in outpatients, especially in patients with short bowel syndrome. They may report loss of body weight and function which can reflect acute metabolic stress or simply a metabolic adaptation of the organism to a shorter small bowel. Indeed, after small bowel resection, body weight and cell mass decrease in response to reduced intestinal energy absorption and stabilize when energy uptake balances basal and exercise-induced energy expenditure. It would be reasonable to assume that the body weight which is then reached determines the quality of life and the subsequent indication for nutritional support.

However, in patients with a small bowel length between 48 and 60 cm who were followed for a mean of 418 days, the lower weights after surgery (47.6 ± 7.8 kg) than at admission (53.5 ± 2.1 kg) did not seem to affect quality of life [33]. Wilmore et al. [34] treated 45 patients with a jejunum-ileum length of <50 cm and a portion of colon in continuity, with growth hormone, glutamine and a diet high in complex carbohydrates and low in fat for 4 weeks. They showed that independency of nutritional support was predicted by lower body weight, greater small bowel, and greater bowel length–body weight ratio [34]. The presence of terminal ileum or colon in continuity also increases the chance of independence from parenteral nutrition [35]. According to these studies, minor weight loss does not seem to determine quality of life or necessity of nutritional support. However, they did not report BMI or body composition or evaluated weight loss in function of BMI. We suggest that a given weight loss does not have the same consequences on quality of life in persons with low BMI and BCM than in those with high BMI and high BCM. Since no studies have yet addressed this issue in short bowel patients, we presently rely on our clinical experience to determine when a patient needs nutritional support. A low original BMI associated with weight loss, as defined by Rosenbaum et al. [31], and the appearance of physical disabilities (like impossibility to stand, walk or perform domestic tasks) are elements indicating the need for nutritional support. The cutoff points that are used to install artificial nutrition are variable because they are based on the subjective well-being of the patient and on his desire to benefit from nutritional support or not.
Conclusion

Malnutrition leads to changes in body composition, especially in FFM, and body function. A decrease in FFM, which can be assessed by bioelectrical impedance, DXA, isotope dilution or measurement of intracellular potassium, affects muscle strength, decreases quality of life and physical functioning, and increases physical disability. Although it is generally accepted that severe malnutrition presents a health risk and is accompanied by a diminished quality of life, at present very few studies have tried to determine the level of malnutrition at which this risk is increased and quality of life decreases. Further studies are necessary to confirm such cutoff points in terms of body function, quality of life, complications and mortality rates. At present, decision regarding institution of artificial nutritional support in weight-losing patients are predominantly made intuitively on the basis of body weight and quality of life.

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Discussion

Dr. Steinhagen-Thiessen: If, at this stage now, you had to give us a good definition of malnutrition to make a huge register, what would you say? What parameters are absolutely necessary?

Dr. Soeters: I think anthropometrics, weight loss. I would include hemoglobin, and I would certainly include albumin.

Dr. Steinhagen-Thiessen: Not prealbumin?

Dr. Soeters: No, it is a short-term risk. Prealbumin can change over night. Albumin gives a much better reflection of what has been going on over time.

Dr. Steinhagen-Thiessen: These are also clinical parameters so they are not difficult to get. It is easy.

Dr. Soeters: I am just mentioning those because they are easy to do.

Dr. Buchman: You don’t think that the albumin status can change over night, especially postoperatively because of intravascular fluid shifts? Extracellular albumin
can decrease by 30% in patients who come in with a variceal bleed. At baseline their albumin is 2.8 g/l, and with gastrointestinal bleeding it is 1.9 g/l. The liver doesn’t just stop producing albumin, and there are tremendous intra- and extravascular fluid shifts. I think in the acute setting the serum albumin concentration is close to useless as a measure of nutritional status. It is a better indicator of inpatient mortality than anything else [1, 2]. Would you agree?

**Dr. Soeters:** I am not saying that I use albumin as a nutritional indicator; I am saying that to calculate risk you need first of all to know what the body cell mass is. But if that is not possible you have to use weight loss and body weight or body mass index. But then in addition you need to know about albumin, and then if the body cell mass is low or anthropometrics are low and albumin is decreased, then the patient is in a bad shape. You should then try in some way to decrease the inflammatory state. I agree with you about let’s say 48-hour shifts, but in the intensive care patients I mentioned these changes took place over weeks, and then I think it is a very reliable measure. In the acute situation, just after an operation, after a really septic episode, then albumin by itself only says that there is an inflammation.

**Dr. Morley:** I would like to suggest that for undernutrition the only useful parameters are anthropometrics, and that would be weight loss, perhaps skin-fold thickness and/or mid-arm circumference. All the other parameters that we have used classically, whether cholesterol, prealbumin, or albumin, have a cytokine component involved in their production.

**Dr. Soeters:** You are saying the same thing as I am.

**Dr. Morley:** So I would say if we were going to have a definition, the definition for undernutrition should exclude those factors, unless you measure something like C-reactive protein or serum albumin protein, to say that they are not elevated, in which case they suddenly all become very good parameters. I think where we get ourselves into trouble, particularly in acute hospitals, is that we tend to use things like the serum albumin as something that says now we should feed this person aggressively because it is low and clearly often that is not the major thing that that person needs at that time.

**Dr. Soeters:** I tried to say that. You really want to know what the body composition is, and that is very difficult. You still have to guess in some way or use the easy parameters that are there. I was asked to talk about risk, and then the factors like albumin have to be added to give you an idea about increased risk. It doesn’t tell you much about body composition, it will only tell you if albumin drops, then it is very likely that body cell mass is also decreasing and you still have to deal with a catabolic patient. So I think we are saying the same thing.

**Dr. Ockenga:** If you have already identified a patient as malnourished, as depleted, and he is coming to you for elective surgery, maybe a pancreas head resection, what would your concept be for this patient? Do you do any perioperative support or something else?

**Dr. Soeters:** If I am dealing with a pancreatic patient or an esophageal patient, these are the patients who rapidly lose weight, not the colonic cancer patients in general, we would certainly use the preoperative time to replete them because they cannot be admitted immediately. They are generally in negative energy balance anyway, so we will try to replete them using a tube, a nasal tube if it is esophageal cancer for instance. We replenish the pancreatic enzymes in patients with pancreatic cancer, which already generally takes away part of their anorexia. We try to insert tube, intubate the tumor so that their bile will flow again, or we collect it and ask them to drink it or add it to the nasal tube so that bile and nutrition goes in. So those things we certainly do in this kind of patient, not in patients with non-obstructive pancreatic cancer without weight loss obviously.
Dr. Buchman: Do you ever use the delayed skin hypersensitivity response or even a total lymphocyte count as a measure of nutrition status? Although of course they have a number of things that can affect these besides nutrition.

Dr. Soeters: No, we don't use it but it is a pity that it has not been developed further. We have tried to do some of it by vaccination giving several types of antigens to assess the immune system via several pathways, but delayed cutaneous hypersensitivity had the same character and that is why I said, it is a functional measure. I don't know why we left it and why we did not try to improve it. There is so much difficulty in assessing the immune status and immune competence. It is a relatively easy measure and it is the only measure that truly has at least some functional character. Lymphocytes are interesting because they are also always low in depleted patients, they are always low in patients with inflammation, so it is also a relatively reliable sign. It scored high in our study and in others as well.

Dr. Bozzetti: As you know many surgical trials on perioperative nutritional support had some eligibility criteria as body weight loss, 10 or 15%. The level of serum albumin and total lymphocyte count are the most common parameters which have been used. In some of these trials the results of nutritional support were positive, in others negative. Quite recently Kudsk et al. [3] published their experience in Annals of Surgery and they were able to show that the same risk factor, i.e. weight loss and serum albumin, had a different impact in different patient populations. For instance in pancreatic cancer they predicted a higher rate of complications than in colonic cancer patients. So do you think that for any type of surgical operation we should have a set of markers which defines the risk and the potential benefit of nutritional support, because this would be the message of Kudsk et al. [3]?

Dr. Soeters: We are becoming very clinical now. In pancreatic cancer, the obstructed pancreas and the lack of bile in the digestive tract cause an inflammatory state all by themselves. But if you replete the patients and re-infuse bile or allow bile to be added to the normal route, you are certainly doing something good. In colonic cancer, the low albumin in the inflammatory state generally has to do with the fact that you are dealing with a growing gangrenous carcinoma or with necrotic areas in the carcinoma, which is a different situation. So I think that you may have to separate these different cancers from each other.

Dr. Labadarios: My point really continues on what Dr. Bozzetti just said. It is really reassuring to hear a surgeon not considering albumin as an index of nutritional status. At least in my experience, one can define the inflammatory response on clinical grounds reasonably well from serum albumin and at the same time serum cholesterol. The minute those two turn upwards you know the patient is improving. But in the acute situation as you were showing in your slide, and that relates to Dr. Bozzetti's question, although you can have a measure of the intensity of the inflammatory response, can you really have a measure of undernutrition in that type of patient on the basis of weight loss? I don't know how you determine weight loss in that type of patient with the likely huge third space that you showed us. I don't know how you do anthropometrics in an edematous patient.

Dr. Soeters: But that is the message of my talk that in acute disease there is such an enormous increase in the extracellular water compartment that total body water is not a valid measure for lean body mass, especially because the ratio between intracellular water and extracellular water is different, it is not a normal ratio. So you need to look at something different and then you come up with more sophisticated techniques.

Dr. Labadarios: What I am trying to say is that we need to be careful when trying to apply the same parameters in different clinical settings?
Dr. Soeters: I showed a patient not because I applied those parameters in her, but to show that the truly nutritional state parameters cannot be applied to her.

Dr. Cynober: I have several comments. First, I don't think that it is a problem of clinical setting; it is a problem of the goal. In many cases simple diagnosis of malnutrition does not require anything, even body composition. Now if you are looking at patients at risk it is excellent because it takes into consideration, as mentioned by Dr. Soeters, all the components of risk. For me what is most important in terms of follow-up of patients is to follow the parameters such as prealbumin. When it is repeated with time, taking into consideration the inflammation component, and has been measured in parallel, C-reactive protein is absolutely excellent even in burned patients. Now if we are discussing the follow-up of patients, especially critically ill patients, since the key is protein depletion, there is nitrogen balance which is a very good parameter provided that you are really measuring total nitrogen in most cases; of course there are some limitations. Now that we have entered the third millennium, there are specific criteria to look at in patients at risk. Since we know now that perhaps 20% of the population in Western countries has a gene polymorphism, especially for proinflammatory cytokines and also for nitric oxide synthesis, it becomes feasible, not easy but feasible, to determine the gene polymorphism for instance for tumor necrosis factor or IL-6 in patients admitted to the intensive care unit. I am certain that really determining patients at risk, healthy and unhealthy patients, will be the key for the future.

Dr. Soeters: My talk was meant to try to be practical and to really address the issues that we have in daily practice. The polymorphism of tumor necrosis factor and IL-6 is very well taken and that is the future. But regarding nitrogen balance it has become somewhat fashionable to say that nitrogen balance doesn't tell you anything. Regarding protein turnover measurements, I think it depends very much on whether it is done with phenylalanine or leucine. Different measures occur and they are not practical either. I agree with you that nitrogen balance is perhaps laborious and is not so easy for the nurses in intensive care. It may be easier especially in patients who do not have wounds, who do not have great losses outside their urine, stools, and in whom you can adequately measure how much they eat or how much parenteral nutrition is given. Then you can calculate a relatively reliable nitrogen balance, but it takes work. I agree with you that it would be a very good measure to see if the patient is improving or not, but as long as it is so laborious I think it will not be very popular in the intensive care units and certainly under budget restraints. That is why we use albumin, again not as a nutritional parameter but rather as a sign of becoming better, and if the patients get better I am convinced that they are receiving adequate nutrition either enteraly, parenterally, or both. Then I am sure that these patients are becoming anabolic. But again, it is well taken. I think nitrogen balance would still be a good measure.

Dr. Cynober: What do you mean laborious for the nurse? Do you mean urinary collection or the determination of nitrogen balance?

Dr. Soeters: Very rigid discipline must be installed in the intensive care unit. Urine, excretions and wound fluid should be sampled; everything flowing in should be calculated. You should preferably refrain from infusing albumin or plasma or erythrocytes because you don't know how much that is going to influence nitrogen balance. It is laborious in the sense that it is work and it needs discipline, but it can be done.

Dr. Fürst: All stress situations are associated with a decrease in membrane potential. In the late 1970s and early 1980s we measured muscle biopsies, the actual membrane potential, and it was decreased from 87 to 70.

Dr. Soeters: Columbia and Sweden.
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Dr. Fürst: Columbia and Sweden, yes. Now even in a moderate stress situation like immobilization, we could measure significantly decreased intracellular water. The water distribution is highly affected by changes in membrane potential together with a redistribution of electrolytes like potassium and magnesium. Today we might have the possibility of measuring intracellular water with the multi-frequency bioimpedance. What do you think about measuring intracellular water as a marker of stress?

Dr. Soeters: I would like to look at the sick cell. In fact the organs, the parts of the body that are ill are cells. They get leaky, they open up channels, they pump harder, they try to maintain their membrane potential and they leak, and that leads to a different distribution of ions outside and inside the cell. So if we were better able to measure for instance membrane potential in an easy way, it is not easy to do, certainly not in patients, then you might have a disease indicator which is much more reliable than anything else.

Dr. Fürst: A membrane potential can be measured very easily. For instance in Texas, there is a quite easy routinely manageable method. You were looking for a very routine method and bioimpedance is such a method. We measured intracellular metabolites, we measured the energy status of the muscle, there are significant changes but they are difficult, they are not routinely manageable, but today bioimpedance is indeed available.

Dr. Soeters: But you have to validate it.

References