Overview on Metabolic Adaptation to Stress

Vickie E. Baracos

Department of Agriculture, Food and Nutritional Science, University of Alberta, Edmonton, Alta., Canada

What Do Nutritionists Mean When They Use the Word ‘Stress’?

The patients that we wish to feed properly are stressed in different ways and very often in more than one way. The word ‘stress’ appears in the nutrition and clinical nutrition literature attached to a wide variety of meanings. This usage is a simple reflection of the complexity and diversity of stressors and stress responses, which are often considered by individual investigators in a specific, somewhat narrow context. The primary ‘stress’ may be a surgical procedure [1–3], an inflammation [4] or injury such as a burn. The ‘stress’ is understood to have degrees: surgery is more or less invasive, and inflammation, infection and burn are more or less extensive. ‘Stress’ most often connotes a physiological response (neuro – endocrine – metabolic – immune) to an insult or injury. There are no universally used indicators or benchmarks of stress (table 1). The ‘stress response’ evaluated may be considered to be the activation of the hypothalamic-pituitary-adrenal (HPA) and sympathetic nervous system (SNS) associated with elevated secretion of adrenal hormones, particularly epinephrine and glucocorticoids. The ‘stress response’ may be considered to consist of inflammation and activation of the immune system with emphasis on the postoperative or postinjury ‘cytokine storm’ [5]. Oxidative ‘stress’, including reactive oxygen species and antioxidants, is another manifestation of inflammation and injury of various types [6]. ‘Nutritional stress’ refers to a suboptimal preoperative or predisease nutrient supply, as well as to a depleted state that may evolve secondarily to another stress type. Stress of all of these types includes the concomitant psychological response. Nicolaïdis [7] emphasizes the
importance of the manner in which a stress is perceived by the individual, in the pattern of neuroendocrine activation. ‘Stress’ includes pain [7, 8].

The broad definition of stress that includes all of these stressors and stress-response elements, is disruption of homeostasis. Stress is not a single entity. Stressors can be psychosocial/behavioral, environmental, nutritional, or arise from infectious or neoplastic processes or injury, and are set in a backdrop of genetic makeup and age which may range from varying degrees of prematurity to senescence.

An understanding of the nature of stress is fundamental to the rational design of nutrient mixtures to feed patients whose homeostasis has been altered by one or more stressors. All stresses may be presumed to be associated with characteristic modifications in the metabolism of lipids, carbohydrates, amino acids and micronutrients. A number of alterations may take place. Taking the example of the metabolism of protein and amino acids, multiple modifications of amino acid utilization can occur such that the total and relative amounts of essential amino acids required may change. In some cases, amino acids normally considered nonessential for humans become conditionally essential in the diet. Hepatic or renal insufficiency may limit the tolerance to the total amino acid supply or to imbalanced amino acid mixtures. Similarly, metabolic energy expenditure may increase, but utilization of energy fuels may be substantially limited by factors such as insulin resistance or limited lipoprotein lipase activity. Oxidative stress may place a substantial draw on antioxidant nutrients. A grouping of such changes is associated with stresses, yet we lack a comprehensive formula for the

<table>
<thead>
<tr>
<th>Stress characteristics</th>
<th>Benchmarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathoadrenal</td>
<td>Epinephrine, norepinephrine</td>
</tr>
<tr>
<td>Hypothalamo-pituitary-adrenal</td>
<td>ACTH, cortisol</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Cytokines, cytokine receptor antagonants, soluble cytokine receptors, acute phase proteins, C-reactive protein, immune cell functions, immune cell activation markers, functional tests of immunity</td>
</tr>
<tr>
<td>Infectious</td>
<td>Bacterial, viral and fungal organisms, endotoxin, sepsis</td>
</tr>
<tr>
<td>Oxidative</td>
<td>Reactive oxygen species, NO, enzymes i.e. superoxide dismutase, antioxidant nutrients</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Nutritional markers: anthropometric, biochemical, metabolic, short-lived plasma proteins</td>
</tr>
</tbody>
</table>

Table 1. Commonly used markers of stress responses
identification, clinical management and feeding of patients based on their previously existing state of chronic stress, throughout the course of a new stress of an acute or chronic nature.

Many published clinical trials of nutritional support provide evidence for a large degree of heterogeneity in any typical study group of patients. The patients are admitted based on a certain set of inclusion and exclusion criteria, however a constellation of stresses (fig. 1) and related metabolic differences may be hidden below the surface of a group of ‘intensive care unit patients with multiple organ failure’ or ‘patients with advanced cancer defined as locally recurrent or metastatic’. It is thus perhaps not surprising that such studies sometimes lack statistically significant main treatment effects, at the same time that inspection of the results on an individual basis reveals a marked heterogeneity of apparent response. It is the difference between the responders and nonresponders within these cohorts that we need to identify as the basis for prospective study. On some occasions the reason for a positive response in some patients is evident. As often as not, there is no way to determine the difference between responders and nonresponders in a given trial, as the nature of appropriate observations, analysis or samples to take is unknown. Nutritional and metabolic ramifications of each stress variant are indeed what we need to be able to assess.

**The Concept of a Stress Classification**

A suitable, pathophysiologically based classification of stress responses may aid nutritionists in their efforts to devise diets tailored to deal with
specific stress-related problems. A classification of stresses and responses to stressful stimuli will make it possible to test the overall concept by establishing a correspondence between the suggested hormone/mediator profile and the associated clinical picture. A classification of stress will also enable assessment of the benefit of a nutritional strategy designed to fit the particular category of stress response exhibited by the patient.

Building a clinically meaningful categorization of stress requires a broad conceptual base. There is a logarithmic increase in the order of complexity when one moves from the considerations of a single stress response element, such as a glucocorticoid or tumor necrosis factor-α (TNFα), to the multiple elements of the endocrine response to stress. The highly orchestrated interplay amongst the nervous, endocrine and immune systems must be considered for each stress, and the clinical reality of multiple acute or chronic stresses that may be simultaneously present.

A reductionist’s approach brings out a comprehensive understanding of an individual stress mediator signal. On the response side there is the regulation of gene expression, synthesis, secretion and eventual degradation of a mediator, and on the reception side, its receptor isoforms, signal transduction and effects upon the metabolism of key nutrients on an organ and whole body basis. By contrast, it is exceedingly difficult to conceptualize the overall sum of a stress response, which can be likened to an orchestra or chorus in terms of the number and types of factors at play. The responses to stress are highly complex and can vary widely. Ideally we would like to know the metabolic alterations in utilization of macro- and micronutrients for each player. In spite of a perhaps daunting conceptual task, the concept of a stress-related classification or taxonomy is emerging, and it is useful to consider current thinking in this regard.

**Taxonomy of the Neuroendocrine Aspects of the Response to Stress**

It is proposed by Nicolaïdis [7] that classical endocrine criteria could be employed to characterize stress responses in terms of the associated hormonal secretion ratios and their temporal evolution. While this is considered exclusively in the context of the effects of stresses on the activation, the HPA axis and the SNS, it is an interesting perspective. The work of various authors suggests that ratios of the responses to stressors of the sympathoadrenal system and the HPA axis can be either unity (ratio = 1) or dissociated in varying degrees, with dominance of one or the other system and for more or less prolonged periods. ‘Balanced’ stress types are characterized by a similar level of activation of the HPA and sympathoadrenal systems. Elective surgery is associated with this type of response, and is generally of brief duration. Chronic psychosocial stress, of the type that is
associated with renin-dependent hypertension, is another example, and in
this case the response may be long-term. Chronic, parallel activation of the
HPA and SNS are seen in certain forms of depression.

A second family of stress responses suggested by Nicolaidis [7] are
those where the HPA and SNS responses may be dissociated in varying
degrees and directions. For example, the fight or flight response is dominated
by sympathoadrenal activation. By contrast, the HPA system is activated
preferentially in stressful situations where there is a perception of loss of
control, and when chronic this state is associated with abnormalities of
blood glucose metabolism and insulin resistance. Some unique patterns emerge,
such as in posttraumatic stress syndrome which is usually characterized by
increased sympathoadrenal activity together with suppressed activity within
the HPA axis with below normal levels of glucocorticoids.

These specific families of stress responses as conceived by Nicolaidis [7]
are not yet accompanied in his analysis by a parallel taxonomy of associated
changes in the metabolism of key nutrients. He does, however, point out that
dysregulation of the HPA axis is known to be associated with the deposition
of visceral fat, atherosclerosis, hypertension and insulin-resistant
dyslipidemia. It would seem plausible to be able to eventually assemble a map
of the corresponding stress types and metabolic changes.

**Grading the Severity of Stress**

The degree of stress may be exceedingly difficult to grade. For example,
with regard to stress within the HPA and sympathoadrenal systems, Nicolaidis
[7] has proposed 5 intensities of activation (5 = very high, 4 = high,
3 = moderate, 2 = basal or normal, and 1 = reduced or below normal)
but avoids dealing with specific cutoff values due to the highly variable
values cited in the literature. To express the magnitude and dimensions of
activation of the HPA and SNS, one might elect to use some or all of the
factors that are practical and possible to determine in everyday clinical
practice using blood and urine samples, such as ACTH, cortisol, epinephrine
and norepinephrine. At the same time this sample is under-representative
of the vast array of endocrine, neurochemical, electrophysiological and
behavioral indices that can only be revealed by analyses specific to a research
setting.

A concept of the degree of stress clearly emerges in the clinical nutrition
literature with respect to the severity of injury, infection and inflammation.
The degree of stress is often ranked using a clinical severity score specific to
the insult in question. Direct comparisons of nutritional manipulations have
been conducted in populations or severely versus moderately stressed
individuals with the same illness or injury, within the same study. For
example, Furukawa et al. [1] compared feeding soybean lipid emulsion in
‘severely stressed’ patients undergoing esophagectomy with ‘moderately stressed’ patients who underwent gastric or colorectal surgery. These authors have studied responses to nutritional intervention after an operative procedure for thoracic esophageal cancer (thoracotomy, laparotomy, and three-field lymph node dissection), a particularly invasive surgery, by itself and in comparison with less invasive surgery [1–3].

The panel of stress-response elements associated with injury, infection and inflammation to be considered could be very large and could contain, for example, acute phase proteins, proinflammatory cytokines, reactive oxygen species, and nitric oxide (NO; table 1). Whatever might be measured, it is an important complication that the magnitude of stress responses may not present on a linear scale. It seems likely that at least some stress responses are intended to have a high amplification factor. The metabolic purpose of such an arrangement would be to have the capacity to develop a large response quickly, and this is typical of many elements of inflammatory and immune responses. This type of regulation can be seen at the cellular level, as well as in the whole organism. For example, skeletal muscle cells respond to proinflammatory cytokines with an increase in basal glucose uptake and oxidation, as well as a large decrease in the insulin-sensitive component of glucose metabolism [9]. The effect on glucose metabolism is mediated by inducible NO synthase (iNOS) and the production of NO. In cultured L6 myoblasts, neither TNFα, interferon-γ or bacterial endotoxin alone induce iNOS, NO production or alterations in basal or insulin-stimulated glucose metabolism. TNFα and interferon-γ together produce a 5-fold increase in NO production and this effect is further enhanced 6-fold by the addition of endotoxin to the mixture. Similarly, the effects of these factors on glucose metabolism emerge only in the presence of multiple effectors and also had a characteristic magnitude that was not directly proportional to NO production. In the presence of TNFα, interferon-γ and bacterial endotoxin, basal glucose metabolism was increased by 125% and the insulin-dependent component of glucose metabolism decreased by 47% [9].

A synergy of stresses and proinflammatory effectors can be seen in vivo, and the magnitude of the reaction to multiple stresses may be difficult to predict. Exposure to stress of one type often alters the subsequent responsiveness of many systems. For example, the presence of a tumor, infection or psychological stress appears to alter the magnitude of the metabolic response to endotoxin. A low dose of 10 μg endotoxin/kg body weight in rats with previous exposure to stress (tail shock) was associated with increased secretion of corticosterone and ACTH, as well as a doubling of serum proinflammatory cytokine levels in response to endotoxin compared to control rats [10]. Servatius et al. [11] provide evidence that some of the changes induced by an initial stress of this type may be relatively long-lived (i.e. days or weeks) when one would have expected acute responses to even intense stressors to end within hours after the end of the stressor.
In tumor-bearing rats challenged with a higher dose (1,000 μg endotoxin/kg), the plasma TNFα 3 h after injection was 45-fold higher than in non-tumor-bearing rats that received the same dose of endotoxin [12]. This would explain why a dose of endotoxin that would only normally be associated with transient anorexia and fever might be fatal if administered to animals bearing a tumor [13], even though the tumor burden was small and otherwise not life-threatening at that point. Arsenijevic et al. [14] show that in mice with chronic toxoplasmosis, a second nonspecific challenge (with endotoxin) exacerbates the hypophagic and hypermetabolic states, the latter being associated with hyperresponsiveness in the production of TNFα and interleukin-10. These data suggest that the superimposition of multiple stresses generates the most difficult situations, both clinically and for the nutritionist.

**How Can Advances in Molecular Biology Provide the Tools and New Opportunities for Characterizing the Stress Response and Potential Therapeutic Targets**

These are exciting times, as we are able to begin to appreciate responses to stress and to diet in terms of the vast array of gene expression events that follow a disruption of homeostasis. A few examples of this powerful approach are illustrative of the large potential. Studies on tissue stress responses are beginning to emerge. Of these, a particularly interesting example is that of Chinnaiyan et al. [15] who described a gene expression profile of sepsis, in an animal model employing cecal ligation and puncture. These authors identify an organ-specific pattern for sepsis-related gene expression events. Cole et al. [16] examined the gene expression profile of human skin immediately following injury using cDNA microarrays. Specimens of the epidermis and dermis were obtained at 30 min and 1 h after the initial injury. At 30 min, injury resulted in a consistent increase (>2×) in gene expression of 124 of 4,000 genes (3%). These genes were primarily involved in transcription and signaling. One hour after injury only 46 genes were increased in expression (1.15%), but 264 of 4,000 (6.6%) genes were decreased by greater than 2-fold, indicating a silencing of many structural genes. The identification of several previously known as well as novel genes that are highly expressed after injury suggests a key role for certain proteins in regulating the initial inflammatory response.

Gene expression profiling is also being applied to the physiologic responses to stress, such as muscle protein catabolism. Muscle protein serves as a primary reserve of amino acids that can be mobilized during stresses such as fasting and disease to provide a source of carbon for glucose production as well as amino acids for protein synthesis. An important physiological adaptation is thus an increase in the overall rate of breakdown of muscle proteins.
This stress response is common to starvation, diabetes, cancer, sepsis, injury, hyperthyroidism, and uremia, and while adaptive in the short-term, depletion of muscle protein is eventually associated with metabolic dysfunction, morbidity and mortality. Although many investigations into this phenomenon have been confined to an individual catabolic state, it emerges that when this response occurs, it is accompanied by a common set of biochemical changes, especially activation of proteolytic processes. Gomes et al. [17] have taken advantage of gene expression microarray technology to more broadly answer the question of which gene transcription events are common to muscle protein catabolism of all types, and which are exclusive to one or a few individual catabolic states. These authors compared gene expression patterns in rodent skeletal muscle after 2 days of starvation versus fed animals, and in tumor-bearing, diabetic and uremic animals versus healthy, fed controls. The initial report by these authors focuses on one highly expressed gene common to all of the studied catabolic states, which they have characterized as a novel muscle-specific ubiquitin ligase with an F-box motif [17]. Ubiquitin ligases are a key element of the major degradative system participating in muscle atrophy, the ATP-ubiquitin-proteasome-dependent pathway. This study design allows identification of gene expression patterns that are common to all of the stress states. In taking this approach, these authors have discovered what may be a critical component in the enhanced proteolysis that leads to muscle atrophy in diverse stress states.

Effects of feeding and diet are also being examined using gene expression microarray approaches. For example, Takahashi et al. [18] examined gene expression profile of liver using high-density oligonucleotide arrays after feeding a high-fat diet (safflower oil or tuna oil) to mice. Similarly, some data for adipose tissue gene expression profile are available for high-fat diet-induced obesity in laboratory animals [19]. During fasting and many systemic diseases, muscle undergoes rapid loss of protein and functional capacity. To define the transcriptional changes triggering muscle atrophy and energy conservation in fasting, Jagoe et al. [20] used cDNA microarrays to compare mRNAs from muscles of control and food-deprived mice. The observed transcriptional changes indicate a complex adaptive program that should favor protein degradation and suppress glucose oxidation in muscle.

A systematic analysis of all of the transcriptional changes in these different conditions is a rather large enterprise, and the results of this analysis will emerge over time. The quantity of information generated by these approaches in the short-term creates a logistical log jam for interpretation. It is a large task to integrate the volume of data generated on expression of known genes, and another huge undertaking to seek the identity and function of novel genes discovered. However, an eventual synthesis of reactions to stress and diet may identify further critical elements that will eventually come into use as key markers related to altered nutrient requirements. This knowledge will guide a multimodal approach to overall patient management, including nutritional
support, which may approach the ideals in a manner currently considered to be science fiction.

References


Discussion

Dr. Moore: I have never come across the term ‘nutritional stress’, it sounds like a valid concept. In our studies we have attempted to randomize patients but we get mixed signals. How much of this do you believe is due to underlying nutritional stress, or do these patients have a different inflammatory response?

Dr. Baracos: What I mean by the term ‘nutritional stress’, is that there is some limitation to the availability of essential nutrients, a subclinical deficiency, and I think that can be an underlying factor in a person's response to a major injury. For example we recently completed a study on patients with generalized malignancy: those receiving a fish oil supplementation were compared to controls receiving a placebo containing a different mixture of fatty acids. In this population there was a clear set of responders and a clear set of nonresponders to the fish oil treatment. This study reveals a couple of interesting things. The first one is that there seems to be some abnormality in these patients' ability to assimilate fatty acids, so fatty acids went in the mouth but I don't know where they actually went, maybe they were not absorbed, maybe they were oxidized, but there was a poor correlation between the dietary intake and the appearance of those fatty acids in the plasma phospholipids. If the whole study is re-stratified according to the actually determined increase in eicosapentaenoic acid or docosahexaenoic acid in plasma or tissue phospholipids, then you have a highly conclusive result which was not seen if you consider the results on an intend-to-treat basis. Some people ate fatty acids but did not show any incorporation and therefore did not manifest a response. This was one instance where it was possible for us to go back and see what happened because we had the means to do so. It was possible to retrospectively analyze the data to determine that there was a problem with nutrient assimilation that explained the failure of the treatment or the appearance of a particular response. I think a deficiency in n-3 fatty acids is a good example of a previously existing nutritional stress, at least in my environment. I live as far away from the ocean as it is possible to be and the diet typically does not contain marine fish. The fatty acid intake is dominated by n-6 fatty acids from vegetable oils and red meats. So I am not certain whether the vast majority of the ill, critically ill or elderly people where I live would suffer from, if not a clinical deficiency, an imbalance in essential fatty acids, that may in part dictate the outcome of a serious illness.

Dr. Cynober: I was very impressed with the data you presented about the protein atrogin-1. I would like to know your feelings about the place of this new mediator in the game. In other words, in your opinion is it just a new transient star in the sky or something very important? For example we remember the cachectic factor discovered by Todorov et al. [1] some years ago and we have absolutely no further news about this cachectic factor which was then presented as something very important.

Dr. Baracos: We now understand that proteasomes are degrading muscle protein in the vast majority of states in which muscle atrophy presents as a problem. Todorov et al. [1] extracted a proteolysis-inducing glycoprotein from tumors, and treated animals and muscle cells with this factor. It causes activation of the protein breakdown process and very strong induction of the proteasome-dependent proteolytic system. Activation of the ubiquitin proteasome system is common to many forms of muscle wasting, regardless of which hormone, cytokine or other factor appears to be the circulating signal for the system’s activation.

In the past we had only been aware of the lysosomal and calcium-activated proteolytic systems of muscle, however these systems are of limited importance in the pathogenesis of many forms of muscle atrophy. Now that we have identified the ubiquitin-proteasome system as the major proteolytic system contributing to muscle
wasting, we are beginning to learn what is important in that system. Something has to attach ubiquitin to the protein so it can be identified and degraded by the proteasome. Ubiquitin availability is not limiting and the variation in the amount of ubiquitin does not correspond with the rate of the proteolytic process. Several enzymes are possible sites of control, the ubiquitin-activating enzymes, the ubiquitin-conjugating enzymes and then the ubiquitin ligases that participate in eventually making ubiquitinated protein substrate. It cannot yet be stated definitely but I would bet you a bottle of Margaux that because it is the element which confers substrate recognition to the whole pathway, the ubiquitin ligases, including atrogin-1, are likely to emerge as important.

There is another recent ubiquitin ligase discovery [2], very similar in approach to the work of Gomes et al. [3]. Bodine et al. [2] took three kinds of muscle atrophy associated with inactivity (denervation, immobilization, hind-limb suspension), and looked for the most expressed genes. In that approach they independently discovered atrogin-1 and also at the same time discovered a new previously uncharacterized muscle-specific ubiquitin ligase. So a family of ubiquitin ligases is emerging.

Dr. Moldawer: Do you want to comment briefly about the specificity of using the proteasome as a target for therapy of either cachexia? On the market or in clinical testing there are several proteasome inhibitors of primarily NFκB. Some of them are in development for cancer and there is a great deal of toxicity associated with some of the earlier proteasome inhibitors. Do you see attacking the proteasome as a valid therapeutic target for treating protein-wasting syndromes or is it because it is sub-ubiquitous in terms of its function in cells that it will never be a valid target for cachexia-type research?

Dr. Baracos: I think that is an important question. If protein synthesis is completely blocked, death ensues because of the rapid loss of all proteins with short half-lives. When protein catabolism is blocked, something similar occurs. Good inhibitors of the proteasome are lethal because they generate a metabolic catastrophe. If they are given to an animal in a dose efficient to block the activation of that system ubiquitously, the animals will be dead in the morning. Drug development in this area evolved in the direction of modulating these agents so that they are not as toxic or in a way to make them specific to a certain organ or class of protein.

Dr. Moldawer: I guess that is the question. Can you target the specificity of the ligase so that you can distinguish between the degradation of structural protein versus the degradation of the regulatory proteins which seem to be more what confers the toxicity of these inhibitors?

Dr. Baracos: I guess that is what is pleasing about the discovery that there may be muscle-specific ubiquitin ligases, as it may be possible to inhibit proteolysis locally in muscle without affecting other tissues. I think you need to work upstream of the proteasome, you can’t just knock that out, it is too dangerous.

One of the things I see as problematic is the heterogeneity of upstream factors that turn on protein breakdown by the proteasome, even with a single disease type. For example, proinflammatory cytokines cause activation of the proteasome through the cytokine receptors on the muscle cell. The proteasome is also activated by an unusual proteolysis-inducing factor that acts on muscle directly [1]. Although both factors activate the proteasome, this is through separate receptor-mediated events. So if you are going to approach this problem right up at the humoral mediation end, you have to be able to identify which specific mediators patients are making – cytokines, the proteolysis-inducing glycoprotein or whatever, and intervene specifically in those cases. If one intervenes downstream, within common (rather than divergent) elements in the pathway leading to proteolysis, a single agent may be effective for multiple forms of muscle atrophy.
We are not there yet, but it is encouraging that industry is taking a renewed interest in drug development in the area of muscle protein catabolism, as their investment is very substantial compared to sponsorship from government.

**Dr. Chioléro:** You have nicely shown that you can have a balanced or an unbalanced response to stress with, for example, a different preponderance, the hypothalamic-pituitary-adrenal (HPA) axis or the sympathoadrenal response, and clearly in our intensive care patients we have different clinical pictures sometimes with a preponderance of one or the other or a very complex tableau. Do you think that we should assess our patients more systematically to know who is a more sympathoadrenal responder or has a more inflammatory response or a more HPA axis response since we have the therapeutic possibilities to influence this response?

**Dr. Baracos:** I think so. I think it is necessary to pick the panel of stress response elements to measure which, in that case, would be the adrenal-secreted hormones. We need to examine the nutritional changes, and to measure the prognostic significance of the individual elements of the stress response panel, i.e. to link them to the clinical outcome, including survival.

**Dr. Déchelotte:** To go ahead with this question, what would you suggest for a standard-sized hospital as a reasonable tool for clinical use in direct response of these patients?

**Dr. Baracos:** I don’t think there is a question of looking at this in a standard-sized hospital at this point in time. In Canada with colleagues at the University of Montreal I am presently involved in a study of non-small cell lung cancer patients in advanced stages, so stages IIIB and IV. We are subjecting them to a comprehensive evaluation in a center for nutrition and function. Using a very broad panel of possible stress factors, we are trying to determine those factors which have prognostic significance. But because of the cost, patient burden and the complexity, this can only be accomplished on a limited scale in this patient group, but this should at least give us the opportunity to test these ideas.

**Dr. Zazzo:** You spoke about the sympathetic profile of one category of patients, and in the intensive care unit (ICU) we have many patients receiving therapy with epinephrine, norepinephrine. Do you think this profile of patients in metabolic response is symmetrical, is the same, if we consider the endogenous sympathetic response and therapeutic sympathetic administration?

**Dr. Baracos:** That is a very important question to which I don’t think we presently have an answer but it would be necessary to figure it in some analysis of those concepts.

**Dr. Allison:** I greatly enjoyed your combination of analysis and synthesis which you attempted to integrate and as a clinician I could sort of respond to the difficulties you posed to us. A lot of the animal studies are of course necessarily short-term and become the acute event, whereas the ICU experience or the critical care experience is a rather long one and it evolves into different patterns. Whereas I used to look after people in the acute stage I now look after people who have just left the ICU and I can see the continuing stresses to which they are subjected. I was interested in your combination of the psychological and physical because these people have the most colossal psychological stress, of an order which is almost unimaginable, and if you don’t inquire of it and measure it you are not aware of it, and this continues. So the challenge therapeutically is how we see what you describe as evolving in a longitudinal way and are we looking at different things? In the acute phase are we looking at actual metabolic support? Let’s get away from the term nutrition and nutrition only comes in when you’ve got over that phase. How do we integrate this longitudinally as well as horizontally in the acute phase?

**Dr. Baracos:** Your remarks make me think about something that I have encountered in my current work in a palliative care service and has to do with the psychological consequences. The chaplain in our unit is earning her doctorate studying patients who,
facing a diagnosis of advanced cancer, face a period of anguish so profound that it obliterate everything else from their conception. You are probably familiar with the term somatization in the psychiatric context, but her area is the understanding of how this horrible anguish can manifest this somatization of pain, and she is interested in identifying clinical markers at the entry into that stage, of the duration of that stage and then the passage through it into a stage of acceptance. The acceptance phase is characterized by a completely different perception of the person's own situation and I cannot believe that it does not have physiologic and metabolic correlates. There are researchers trying to measure this and bring together the understanding of somatization from a spiritual context and a psychological metabolic context.

Dr. Déchelotte: Thank you very much Dr. Allison for addressing this important question that we not only have fat stores and proteins but also the whole body reaction to take into account.

References