Depletion of body proteins is a major feature of critically ill patients [1, 2]. Despite enteral or parenteral feeding and treatment of the underlying disease, protein catabolism often persists and increases the morbidity and mortality of the patients [3-8]. Indeed, it has recently been pointed out that, besides optimized artificial nutrition, a useful addition can be the administration of specific nutrients or substrates at pharmacological doses (pharmacological nutrition) or the administration of specific drugs or active hormones to counteract the metabolic disturbances.

**Mechanisms of protein catabolism in ICU patients**

Net protein breakdown is the result of the balance between the absolute rates of protein synthesis and breakdown. It is evident that loss of lean body mass in severe stress conditions results mainly from a sustained increase of the rate of protein breakdown in skeletal muscle [1, 2, 9]. This metabolic change is a common response in almost every acute illness, including trauma and sepsis [1]. After elective surgery the rate of protein degradation increases proportionally to the degree of surgical stress [10]. Depressed protein synthesis may also contribute to the catabolic response. However, despite the fact that both total muscle RNA and specific myofibrillar protein mRNA levels were drastically reduced in trauma and sepsis [11, 12], studies utilizing stable isotopes have often reported increased rates of whole-body and muscle protein synthesis in patients [1, 9]. Irreversible catabolism of free amino acids derived from proteolysis is also accelerated, both in the liver (increased urea synthesis) and muscle (increased oxidation of the branched chain amino acids, leucine, valine and isoleucine).

**Modulation of protein metabolism by drugs, hormones and nutrients**

An optimal nutritional support has been shown to decrease morbidity in critically ill patients [13, 14]. Unfortunately, current forms of artificial nutrition are usually ineffective to induce anabolism (positive nitrogen balance) in severely catabolic patients. Therefore, a number of therapeutic approaches have been
Substrates

Currently, great interest is being devoted to the concept that some metabolites also present in the diet, such as arginine, glutamine, carnitine, the branched chain amino acids and the ω-3-fatty acids, may regulate protein metabolism when given at pharmacological doses.

Arginine plays a critical role in the urea cycle and in the biosynthesis of creatine phosphate, nitric oxide, and polyamines. Numerous studies have demonstrated that arginine supplementation can improve wound healing, stimulate the immune system, and reduce protein catabolism in trauma and septic patients [15]. Arginine is also a potent secretagogue for several hormones, such as growth hormone, prolactine, insulin, and IGF-1. Thus, at least some of the metabolic effects of arginine could be mediated by hormone secretion. The role of arginine in regulating immune function mainly involves stimulation of T lymphocyte proliferation and functions. The postulated mechanisms of action for the immunomodulating effects of arginine involve synthesis of nitric oxide, polyamines, and cytokines and the stimulation of prolactin and growth hormone secretion. Glutamine is the most abundant free amino acid in the body. In skeletal muscle, the large glutamine pool declines markedly in many catabolic disease states, possibly because of increased glutamine release and/or decreased de novo synthesis [1, 2, 16]. Such decreased intracellular glutamine concentration is potentially one factor which may adversely affect body protein metabolism in stress conditions [17]. It has been shown that glutamine is a major fuel for rapidly growing cells, including enterocytes, reticulocytes and lymphocytes. Thus, glutamine administration in patients may restrain protein catabolism and improve gut function and immune response to infections. Unfortunately, glutamine is only stable for a limited time in solution and cannot be used in parenteral formulas. Thus, dipeptides containing glutamine, which are rapidly hydrolyzed into the bloodstream, have been developed to be used as substitutes for glutamine alone [18]. In several studies, administration of glutamine or its precursors (α-ketoglutarate or ornitine α-ketoglutarate) to hypercatabolic patients resulted in beneficial effects on protein metabolism [19-21]. These patients were affected by severe trauma, short bowel syndrome, and other enteric diseases or had undergone a bone marrow transplantation for hematological malignancies. Recently, Griffiths et al. [22] reported that glutamine supplementation may improve survival in critically ill patients.

Hormones

Insulin is probably the most important regulator of protein metabolism. This hormone stimulates protein synthesis and inhibits protein degradation in selected tissues. Insulin deficiency in type 1 diabetes rapidly results in severe