Due to the improved life-sustaining therapies of modern intensive care, critically ill patients undergo prolonged severe stress, lengthy immobilization accompanied by muscle disuse, and exhibit a severely negative nitrogen balance reflecting reduction of body muscle mass [1]. In addition to the muscle mass reduction, there are major impairments in muscle function, such as changes in the force-frequency curve, relaxation rate and fatiguability [2]. Such symptoms characterize protein calorie malnutrition and are known to alter immune competence and favor infection, which ultimately promotes further catabolism. Finally, a vicious circle begins in which body wasting is progressively more severe. Such a malnourished state is related to prolonged mechanical ventilation, increased morbidity, longer hospitalization stay and rehabilitation duration [3]. Nutritional support has been shown to improve outcome in such patients [4]. Unfortunately, severely ill patients continue to exhibit muscle wasting in spite of nutritional support [5-8]. This observation has strongly stimulated animal and human research on the use of anabolic agents or physical therapies, added to nutritional support, to counteract the debilitating effect of stress and immobilization [9-17]. This short review discusses some of the current knowledge and highlights potential developments for anabolic agent utilization in critical care medicine.

**Promoting anabolism**

Anabolic factors that can be used in the clinical setting to limit stress-related catabolism are insulin, growth hormone, insulin-like growth factor-1, testosterone and its derivatives. Anticatabolic agents, such as β 3-adrenergic agonists or tumor necrosis factor (TNF) antiserum, will not be discussed.

**Insulin**

Insulin acts as a potent anabolic hormone by reducing cellular proteolysis and increasing amino acid intracellular transport and protein synthesis. The anabolic effects of very high doses of insulin and carbohydrate to ICU patients with various levels of stress have been repeatedly reported [18-23]. Nowadays, it is generally admitted that insulin administration in ICU patients is limited to the control of glycemia. Future research into the clinical use of insulin to stimu-
late anabolism should focus on its effects on patient outcome and on the consequences of hyperglycemia on immune status [24].

**Growth hormone**

Physiological growth is associated with endogenous secretion of growth hormone (hGH) with constant plasma levels. During adulthood these levels show considerable variation, depending on sleep pattern, stress, exercise levels, and nutritional status. Acute hypoglycemia or chronic intracellular amino acid deficiencies strongly stimulate hGH secretion. Metabolic stress has a similar but transitory effect during 2-3 days: after that time, hGH secretion is globally diminished, a situation worsened by aging [25]. Recombinant growth hormone (rhGH) is the most powerful anabolic agent, affecting all tissues capable of growth by increasing mitotic index, cell size and protein synthesis, its effect on most body cells being either direct or secondary to the action of insulin-like growth factor-1 (IGF-1). rhGH significantly increases lipolysis and circulating free fatty acid levels, decreases the intracellular transport of carbohydrate and reduces its oxidation, while stimulating glycogenesis [26], and stimulates protein synthesis and deposition in lean tissues [27]. It also positivates nitrogen balance, and reduces phosphorus and potassium losses [28]. On this basis, rhGH administration in critically ill patients has been investigated with the goal of decreasing muscle wasting by shifting substrate oxidation from carbohydrate and protein to lipid, while promoting protein anabolism. The rationale for this approach is supported by clinical trials demonstrating that severely ill patients have low levels of circulating plasma IGF-1 and IGF-1 binding proteins [29], along with an altered regulation of hGH plasma levels [30]. Many clinical reports have shown beneficial effects on metabolic parameters as well as on healing processes and immune competence during prolonged stress [28,31-47]. Conversely, an absence of nitrogen sparing effect during rhGH therapy in septic patients has also been reported [48], as well as in other categories of highly stressed patients such as post-burn adults and children [45]. These discrepant results in cases of extreme metabolic stress suggest that rhGH might have substrate-mobilizing effects dissociated from its nitrogen-sparing effect.

These contradictory results raised the important question of the efficiency of rhGH on improving muscle function in stressed patients [28, 36]. Peripheral muscle dynamometry and respiratory function tests must be performed to address this issue. Increased muscle mass and force have been demonstrated in adult patients with hGH deficiency, healthy volunteers and athletes [49]. Improved respiratory muscle function assessed by maximal inspiratory pressure has been reported in eight stable chronic obstructive pulmonary disease outpatients [50], but no improvement of maximal inspiratory pressure and exercise capacity was found in such patients during a controlled rehabilitation program [51]. Conversely, these beneficial effects were observed in a pre-lung transplantation female patient who received two subsequent 3-week courses of rhGH [52]. In a randomized controlled trial on the effects of rhGH on peripheral and respiratory muscle function in 20 patients requiring prolonged mecha-