

International Workshop on Cachexia Cachexia in the Critically Ill

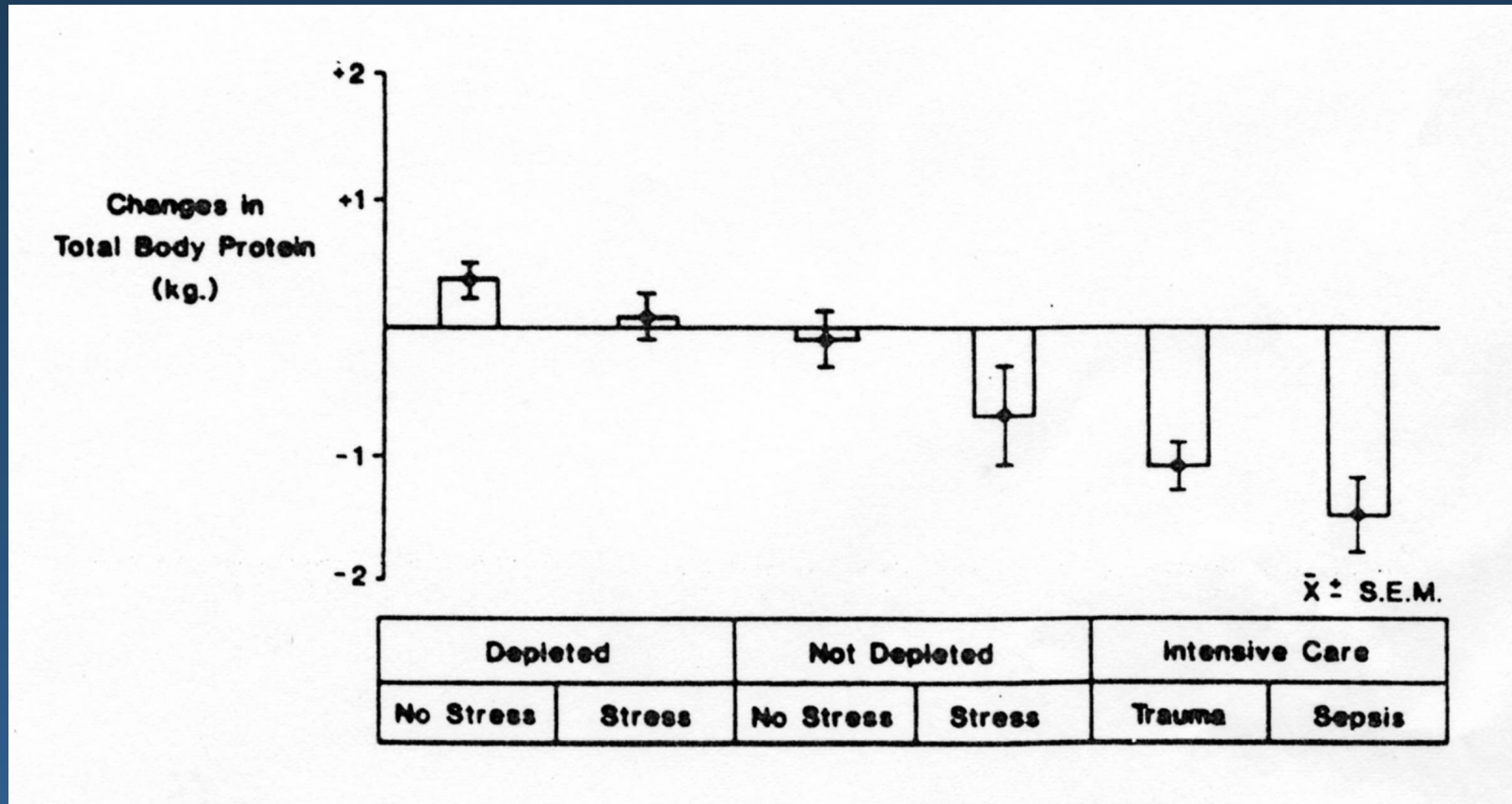


ernährung 2006; Berlin, June 1, 2006

Body Composition in Surgical Practice

Hill GL et al

Aus NZ J Surg 1988; 58: 13-21



Changes in Total Body Protein in various groups of patients

Cachexia in the Critically Ill

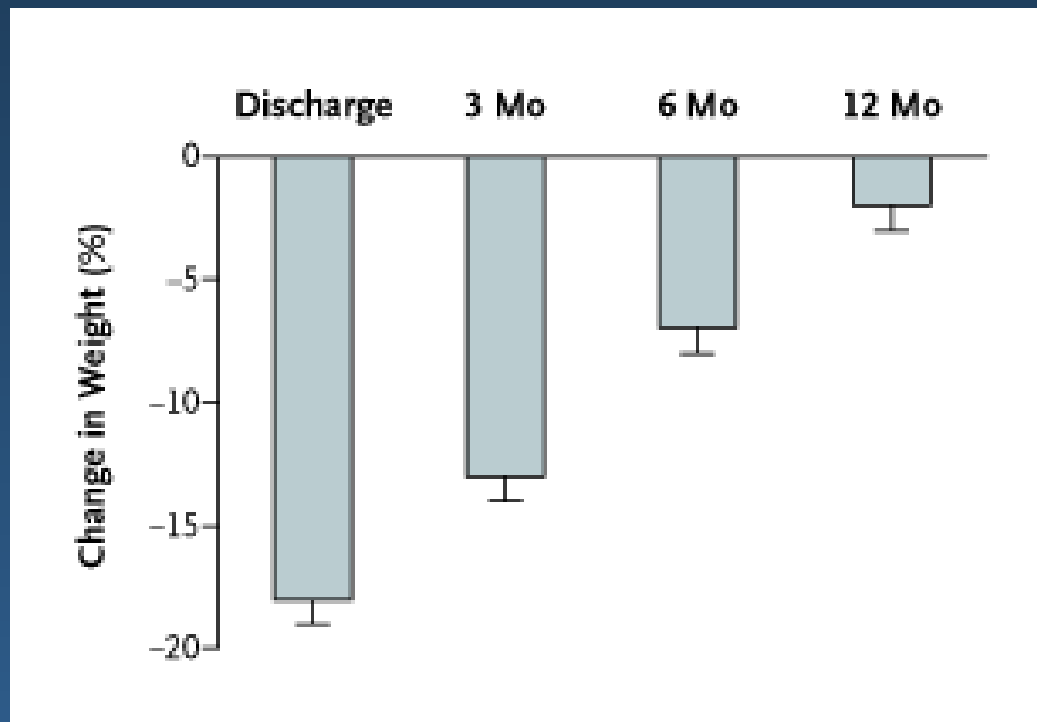
Statement I Critical illness is characterized by activation of protein catabolism

Statement II In critical illness activation of protein catabolism is correlated to severity of disease

Statement III In critical illness severity of disease and activation of protein catabolism is correlated with outcome

One-year outcomes in survivors of the acute respiratory distress syndrome

Herridge MS et al. *N Engl J Med* 2003; 348: 683



Change in Weight from Base Line among Patients with ARDS at the Time of Discharge from the ICU and at 3, 6, and 12 Months

Cachexia in the Critically Ill

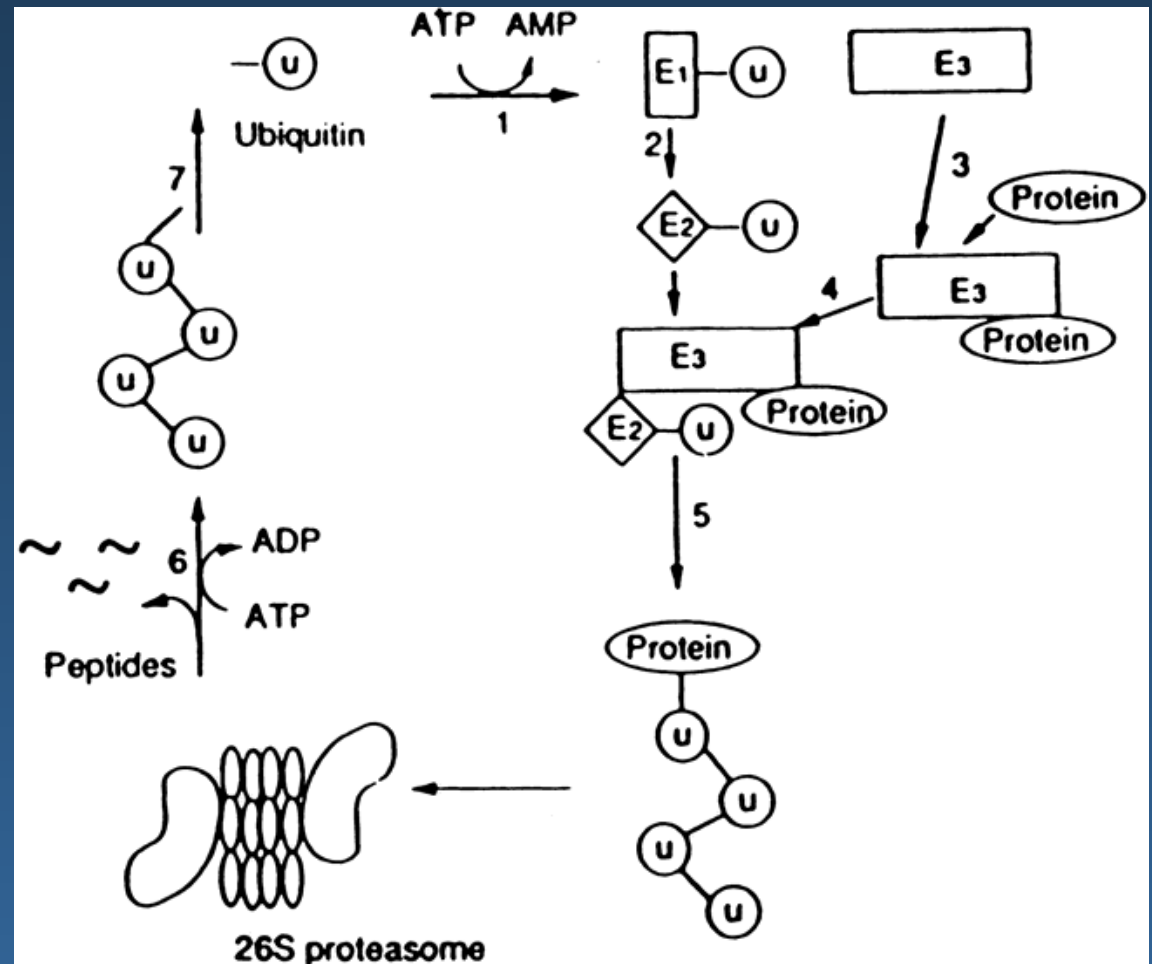
A decade-old dogma in therapy of critical illness

**Suppression of protein catabolism will
improve prognosis of the critically ill patient
(“The search for the magic bullet”)**

Muscle Cachexia: Current Concepts of Intracellular Mechanisms and Molecular Regulation

Hasselgren P-O et al.
Ann Surg 2001;
233: 9-17

Simplified scheme
of the ubiquitin-
proteasome
proteolytic
pathway.



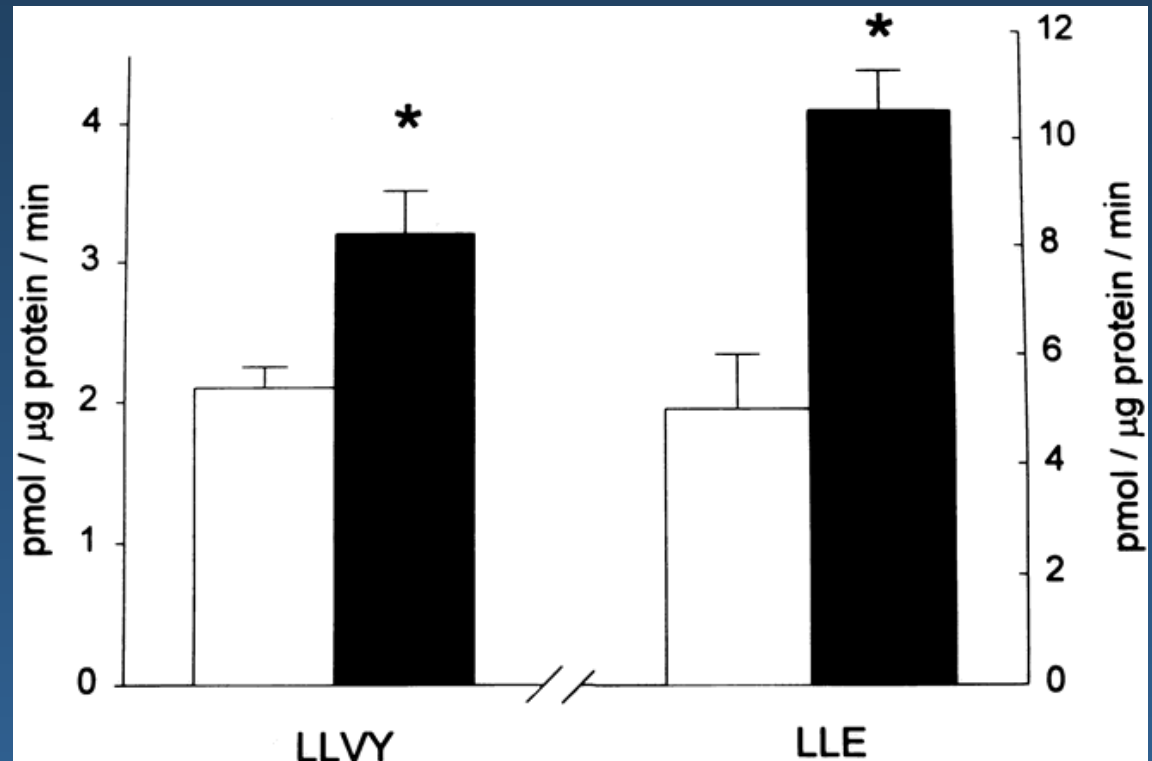
Muscle Cachexia: Current Concepts of Intracellular Mechanisms and Molecular Regulation

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233: 9-17

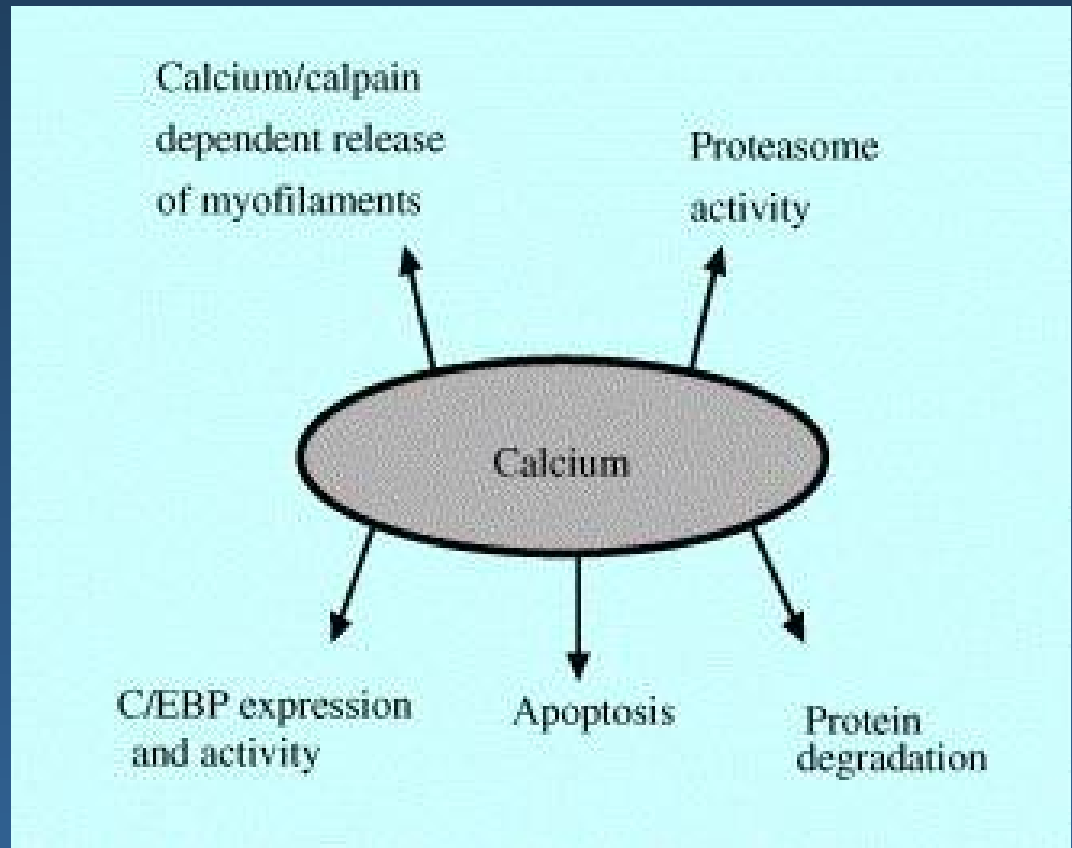
Sepsis results in increased activity of the 20S proteasome in skeletal muscle. 20S proteasomes were isolated from muscles of sham-operated (open bars) or septic rats (filled bars)



Novel aspects on the regulation of muscle wasting in sepsis

Hasselgren P-O et al.
Int J Biochem Cell Biol
2005; 37: 2156-68

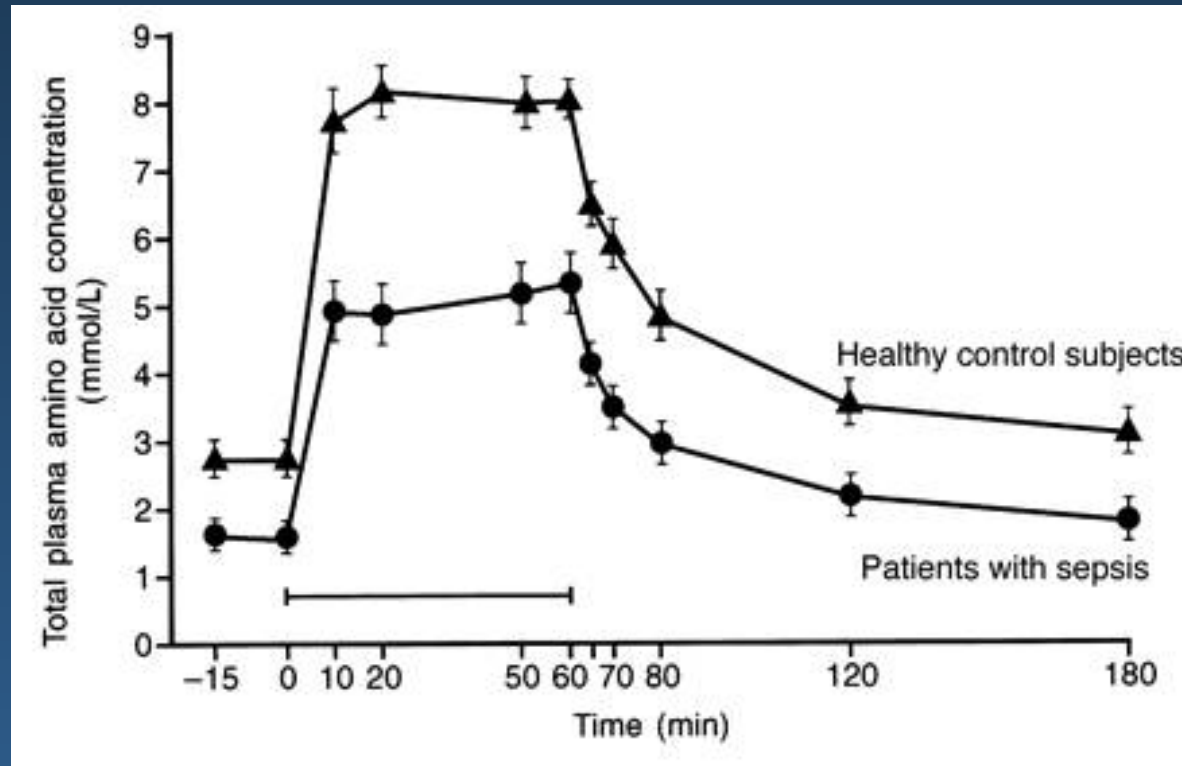
Increased muscle calcium levels may regulate multiple processes that participate in the development of muscle wasting during sepsis.



Amino acid kinetics in patients with sepsis

Druml W et al.

Am J clin Nutr 2001; 73: 908-13

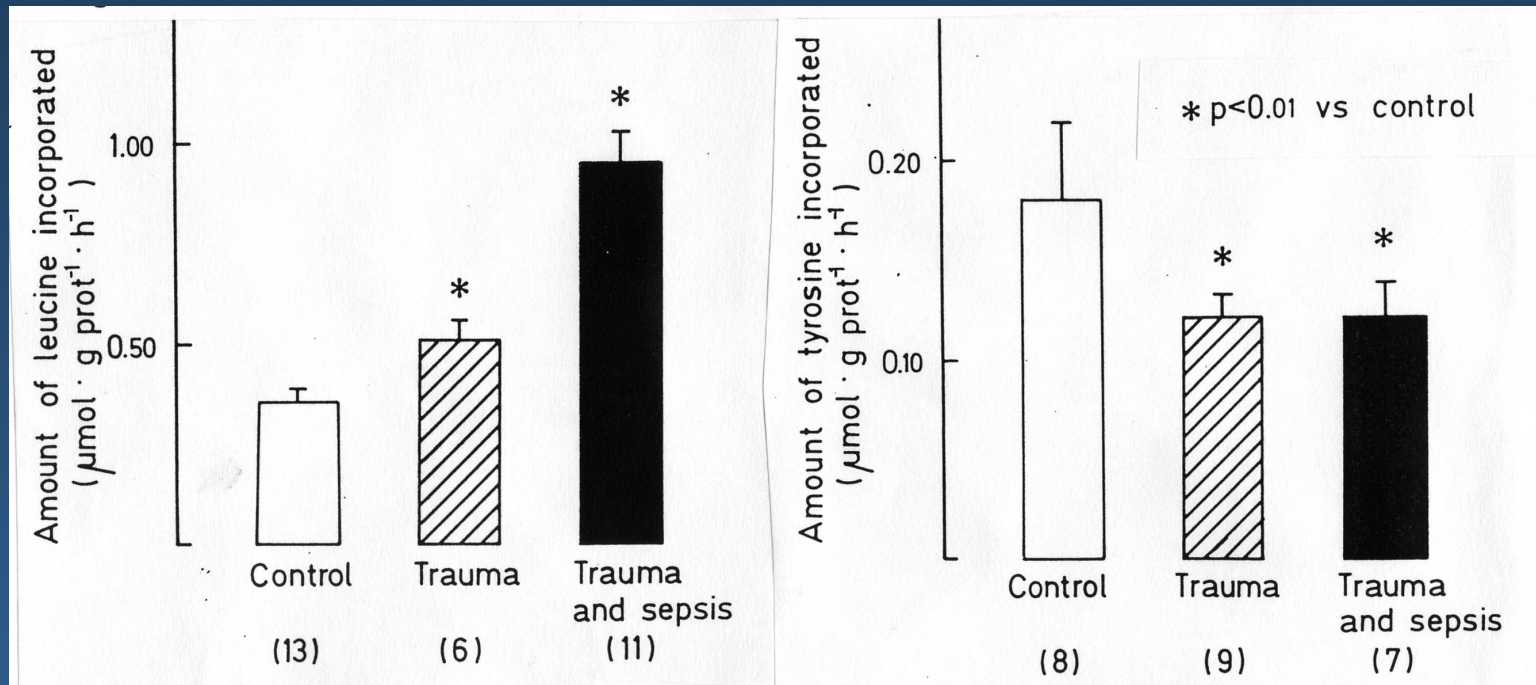


Mean total plasma amino acid concentrations before, during (from time 0 to 60 min), and after infusions of an amino acid solution providing $375 \text{ mg} \cdot \text{kg} \text{ body wt}^{-1} \cdot 60 \text{ min}^{-1}$ in patients with sepsis and in healthy control subjects
The curves are significantly different at all time points, $P < 0.001$

Changes in protein metabolism in liver and skeletal muscle following trauma complicated by sepsis

Hasselgren PO et al

J Trauma 1984; 24: 224-229



Leucine incorporation into hepatic proteins (left) and tyrosine incorporation into muscle proteins (right).

Cachexia in the Critically Ill

Statement V

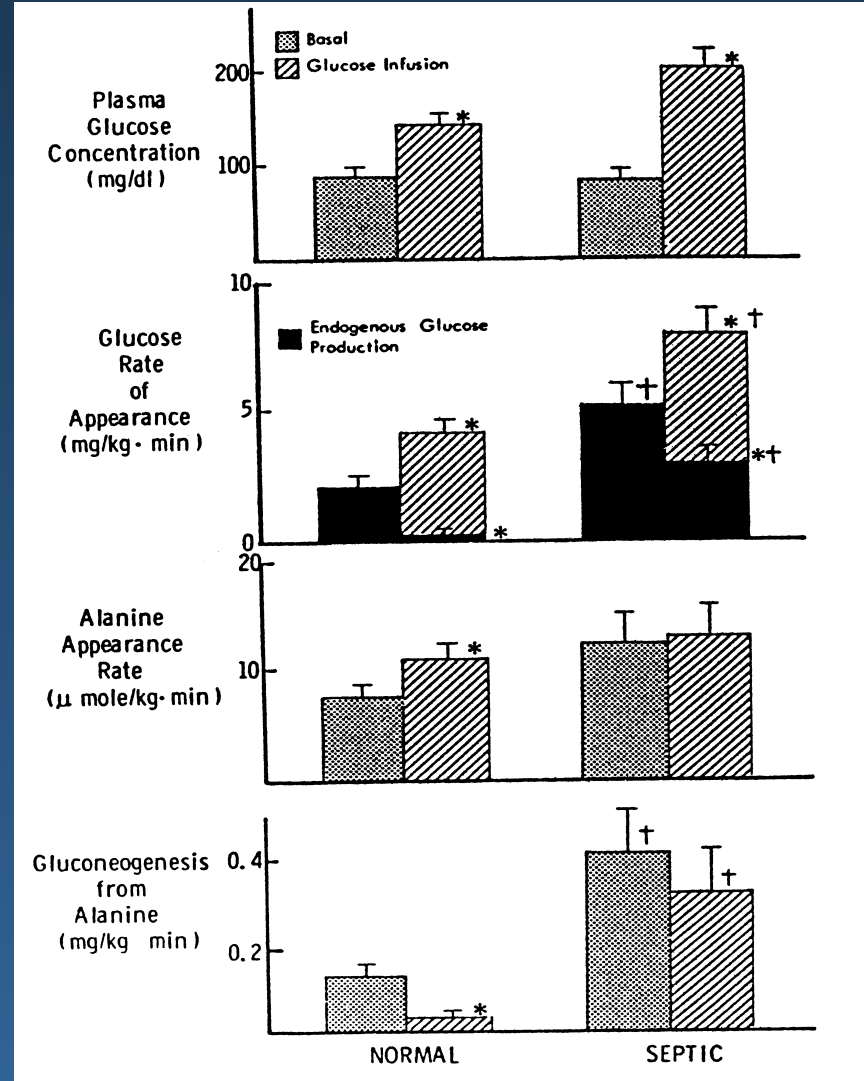
The primary problem in protein catabolism of acutely ill patients is the liver !

Whole Body Protein Kinetics in Severely Septic Patients The Response to Glucose Infusion and TPN

Shaw JHF et al.
Ann Surg 1987; 205:
288-292

Glucose and alanine metabolism in normal volunteers and in patients with sepsis in the basal state and during the infusion of glucose (4mg/kg/min).

*between periods 1 and 2 in the same group ($p < 0.05$).
** from the control value for the corresponding period ($p < 0.05$).



Cachexia in the Critically Ill

Statement IV

Activation of protein catabolism in critical illness can not be (completely) suppressed by exogenous nutritional substrates

Cachexia in the Critically Ill

A dogma in nutrition therapy of critical illness

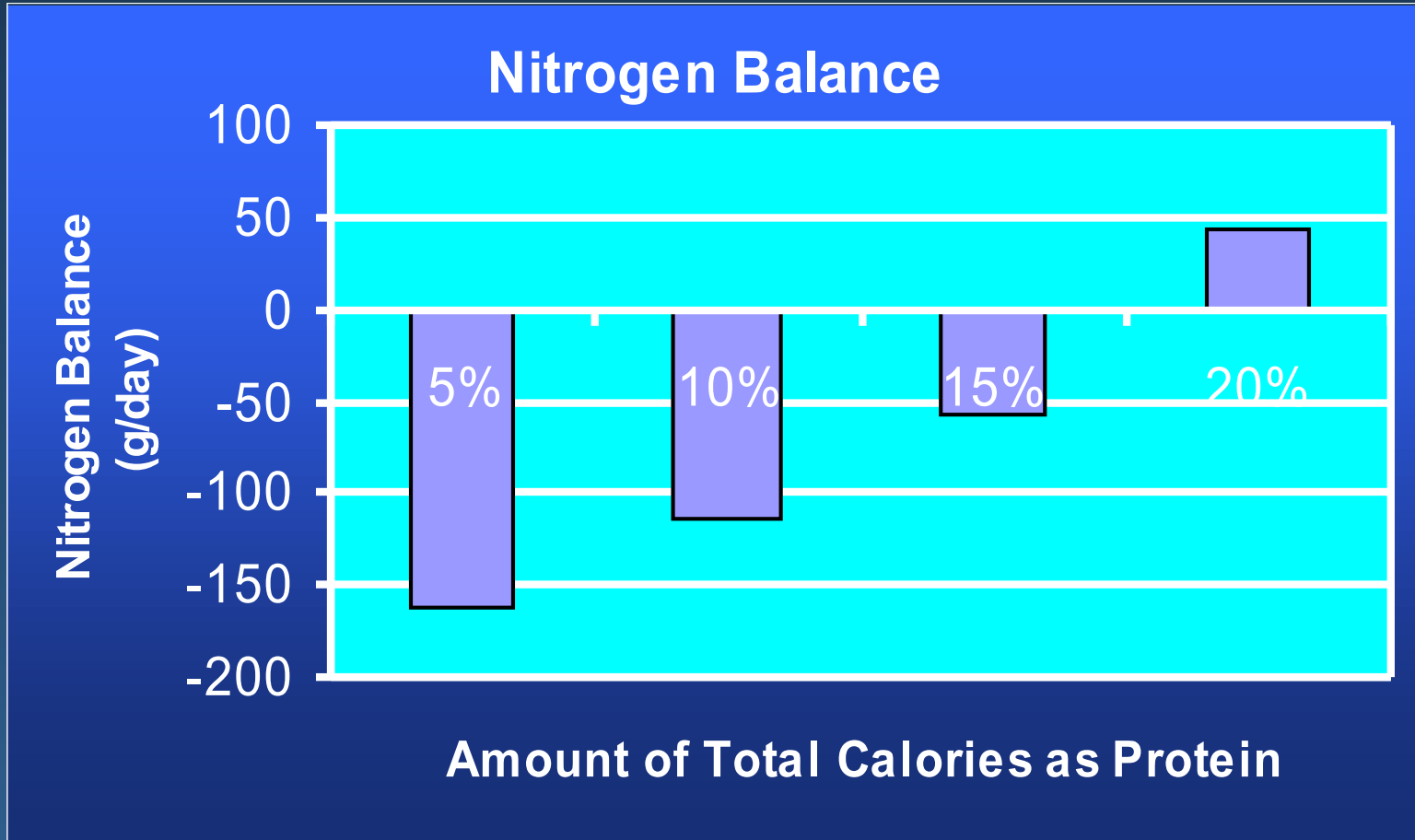
Nutrition in the critically ill is not very important (“wait and see”)

Cachexia in the Critically Ill

A decade-old dogma in therapy of critical illness

**Suppression of protein catabolism will
improve prognosis of the critically ill patient
(“The search for the magic bullet”)**

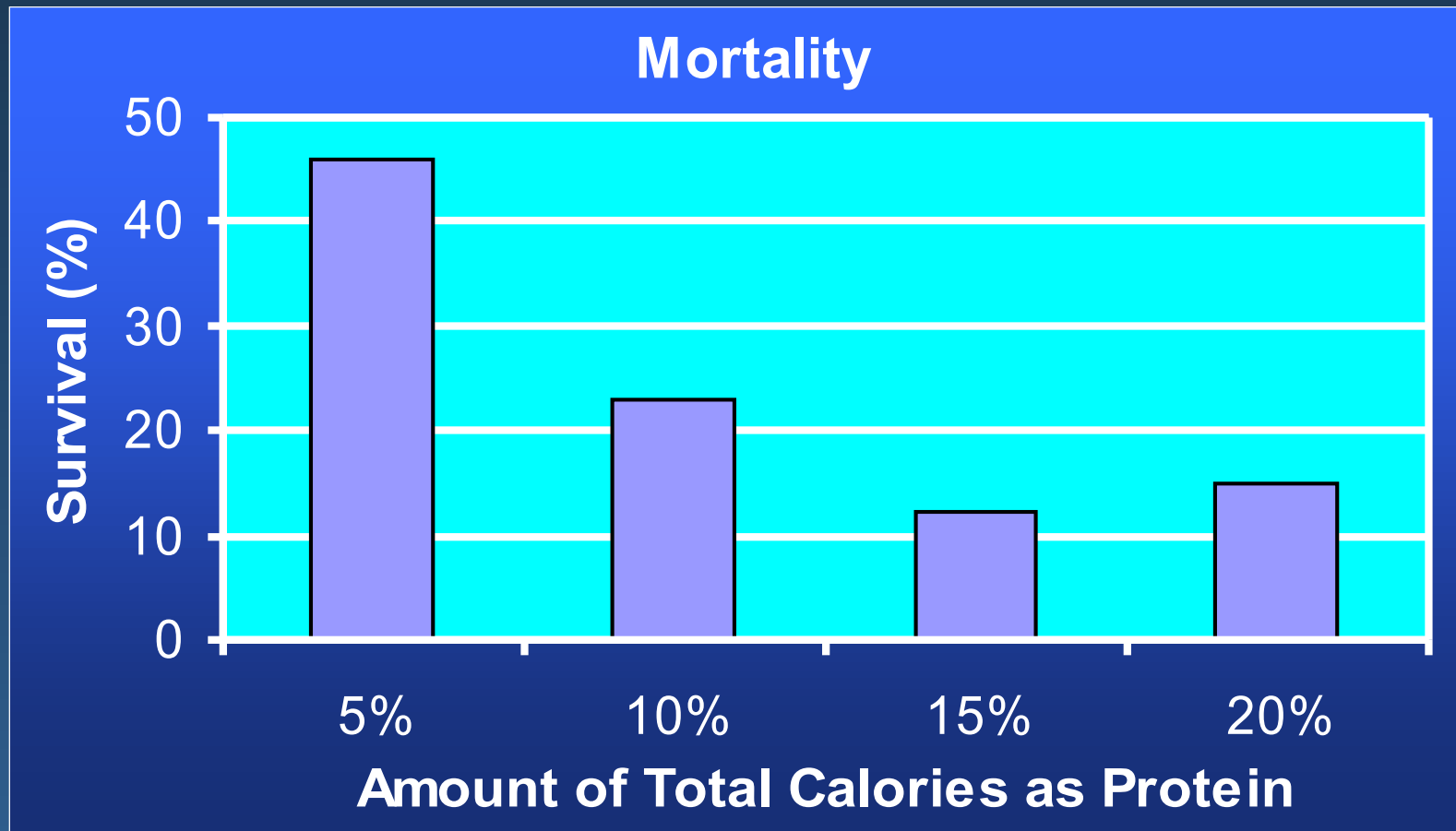
Low Protein Diets Improve Survival from Peritonitis in Guinea Pigs



from Peck MD et al.

Ann Surg 1989; 209: 448 - 454

Low Protein Diets Improve Survival from Peritonitis in Guinea Pigs



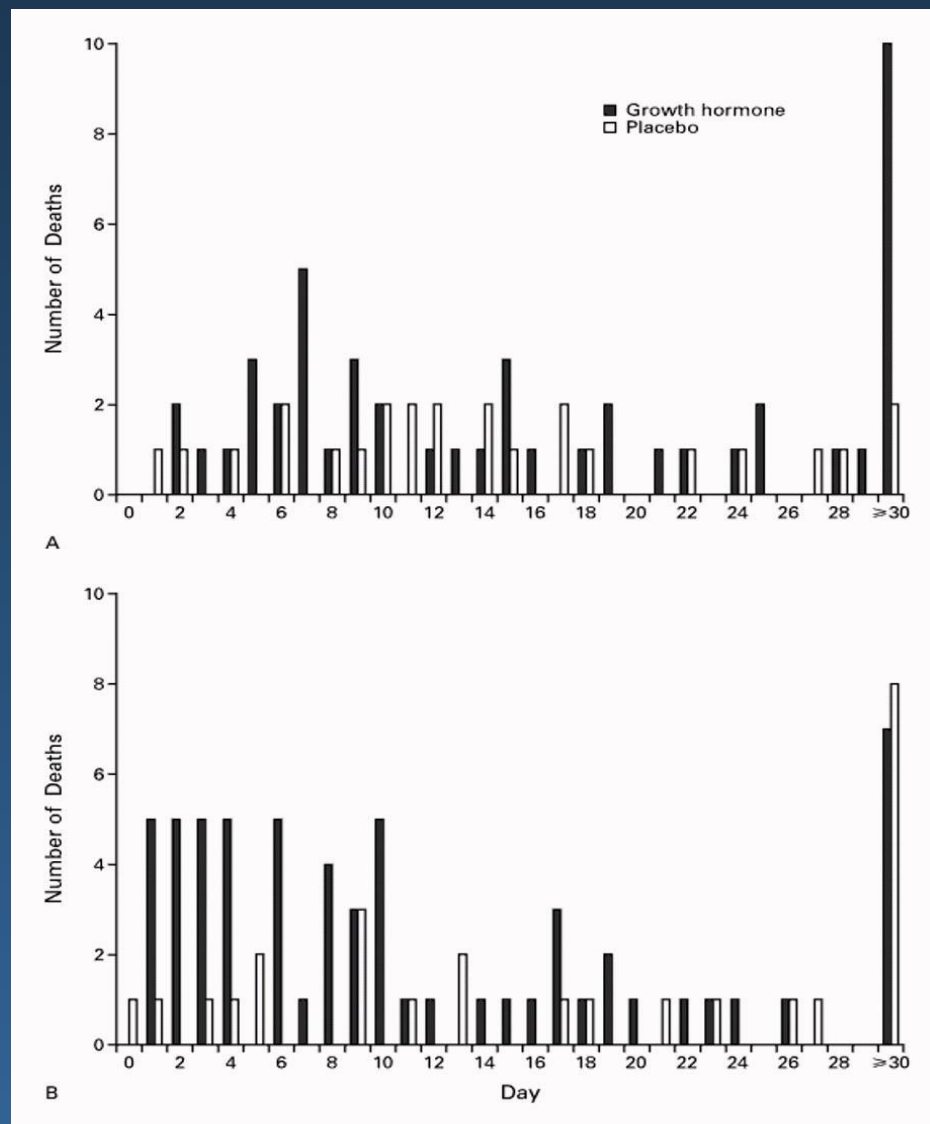
from Peck MD et al.

Ann Surg 1989; 209: 448 - 454

Increased Mortality Associated with Growth Hormone Treatment in Critically Ill Adults

Takala et multi al.
N Engl J Med 1999;
341: 785-792

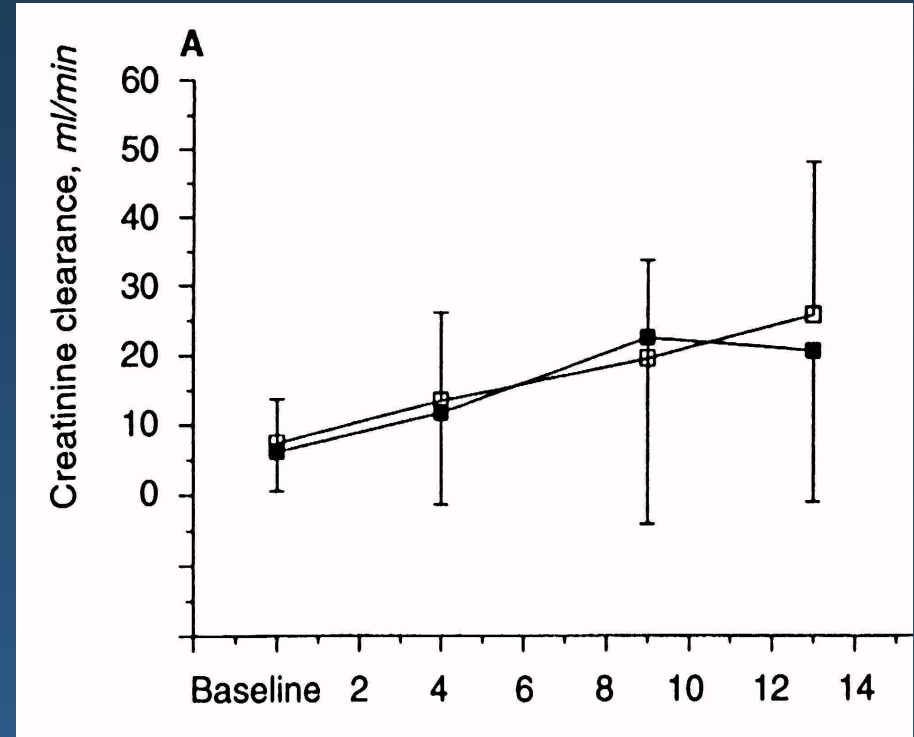
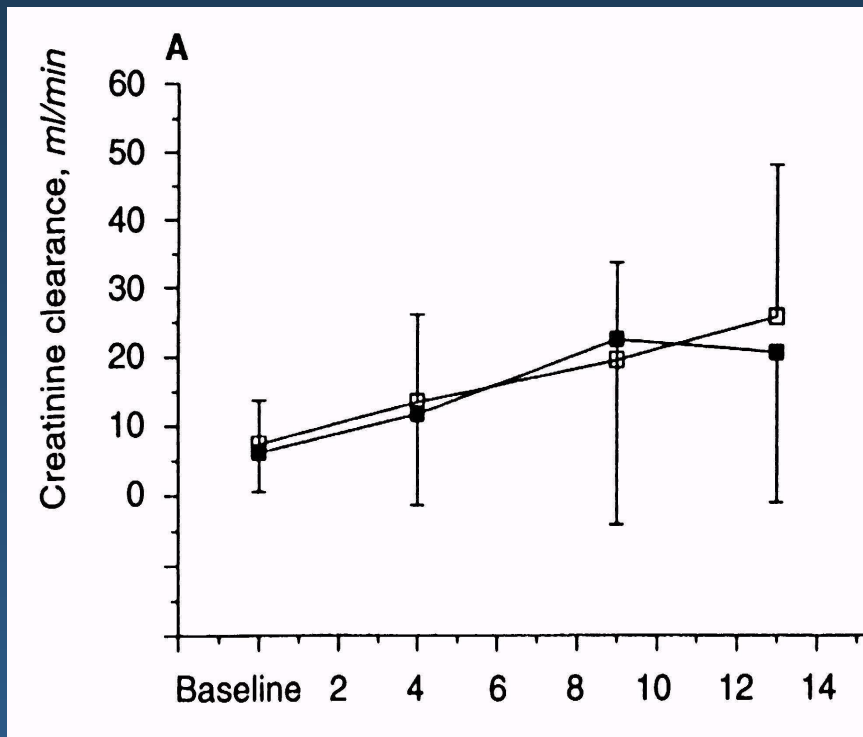
Numbers of Deaths in
the Finnish Study (Panel
A) and the Multinational
Study (Panel B)
According to the
Treatment Assignment
and Day of Treatment



Multicenter Trial of rh-IGF-I in Patients with ARF

Hirschberg R. et multi al.

Kidney int 1999; 55: 2423-32



Creatinine clearances in subjects with sufficient urine flow rates (A) and in subjects who were oliguric, receiving rhIGF-I (filled symbols) or placebo.

Cachexia in the Critically Ill

Statement V

**Catabolism / nitrogen balance not necessarily
an indicator of treatment success or even a
primary goal of therapy !**

Cachexia in the Critically Ill

Statement V

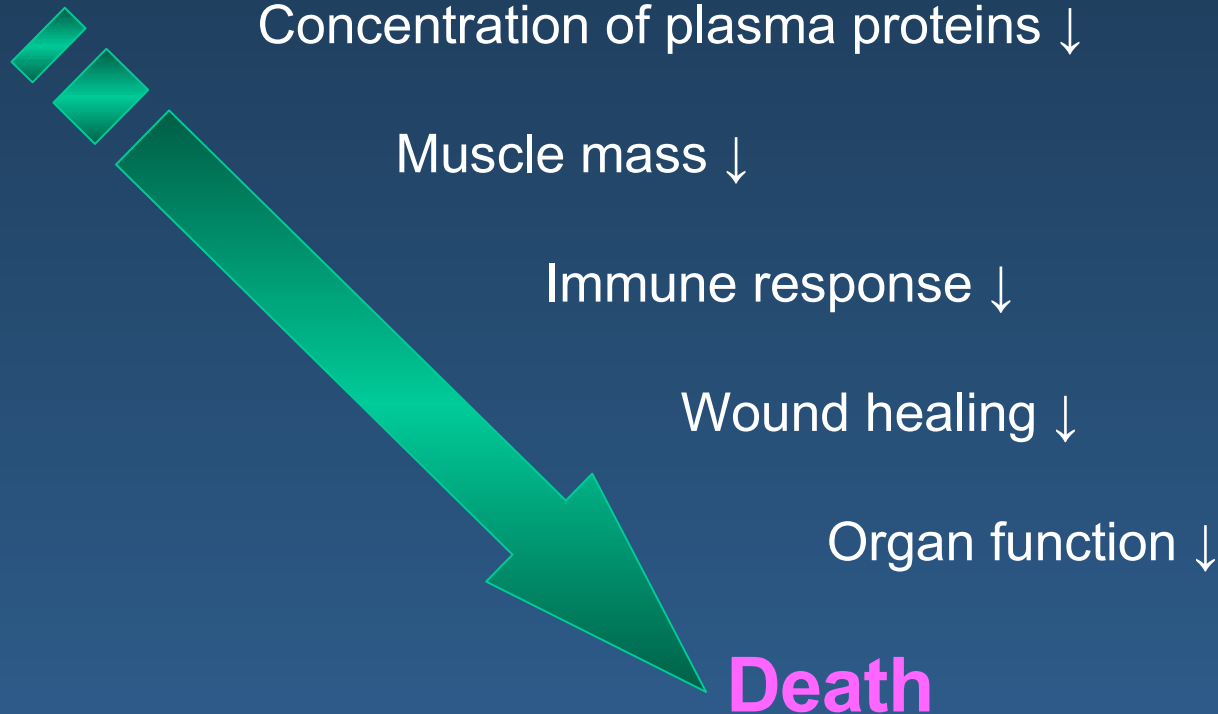
Activation of protein catabolism in critical illness is a physiologic, adaptative response to injury !!

Mere suppression of protein catabolism is ineffective !!

**However : Can also be “maladaptative” in hyperinflammatory / hypercatabolic states
“septic autoaggression”**

Clinical consequences of malnutrition/catabolism

„healthy“ 100%



Malnutrition + inflammation: 25 % protein loss
Malnutrition: 40% protein loss

Cachexia in the Critically Ill

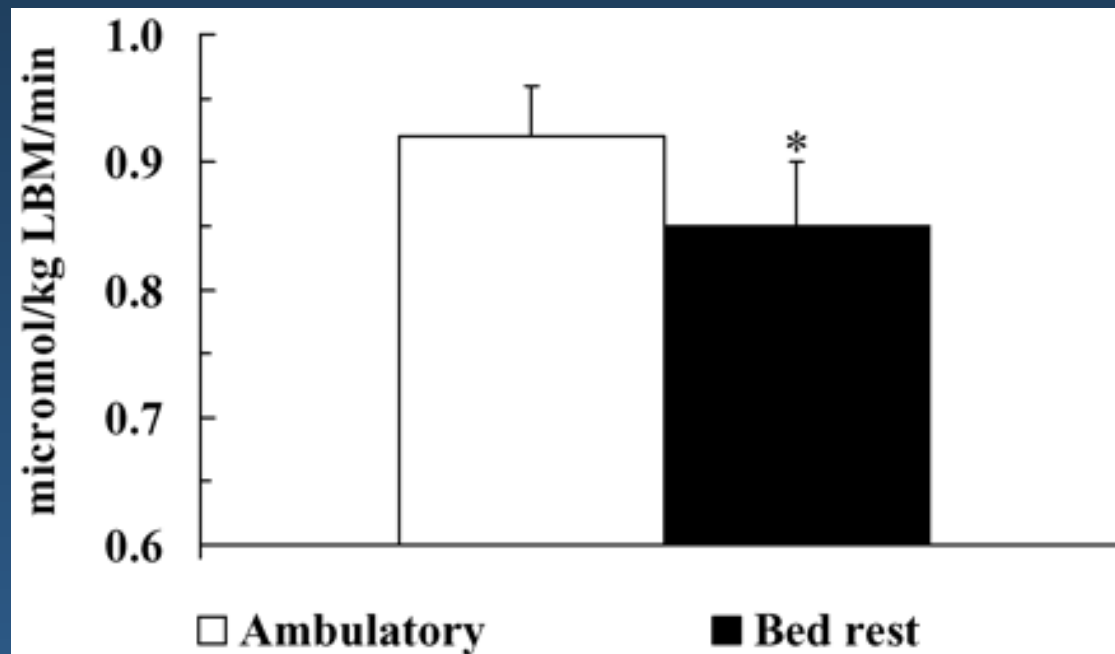
Potential therapeutic approaches

Therapeutic interventions should not be aimed primarily at the reduction of protein catabolism but **MUST** be focused at the underlying problem; i.e. at mitigating the inflammatory state !!

Short-term bed rest impairs amino acid-induced protein anabolism in humans

Biolo Ch. et al

J Physiol 2004; 558: 369-80

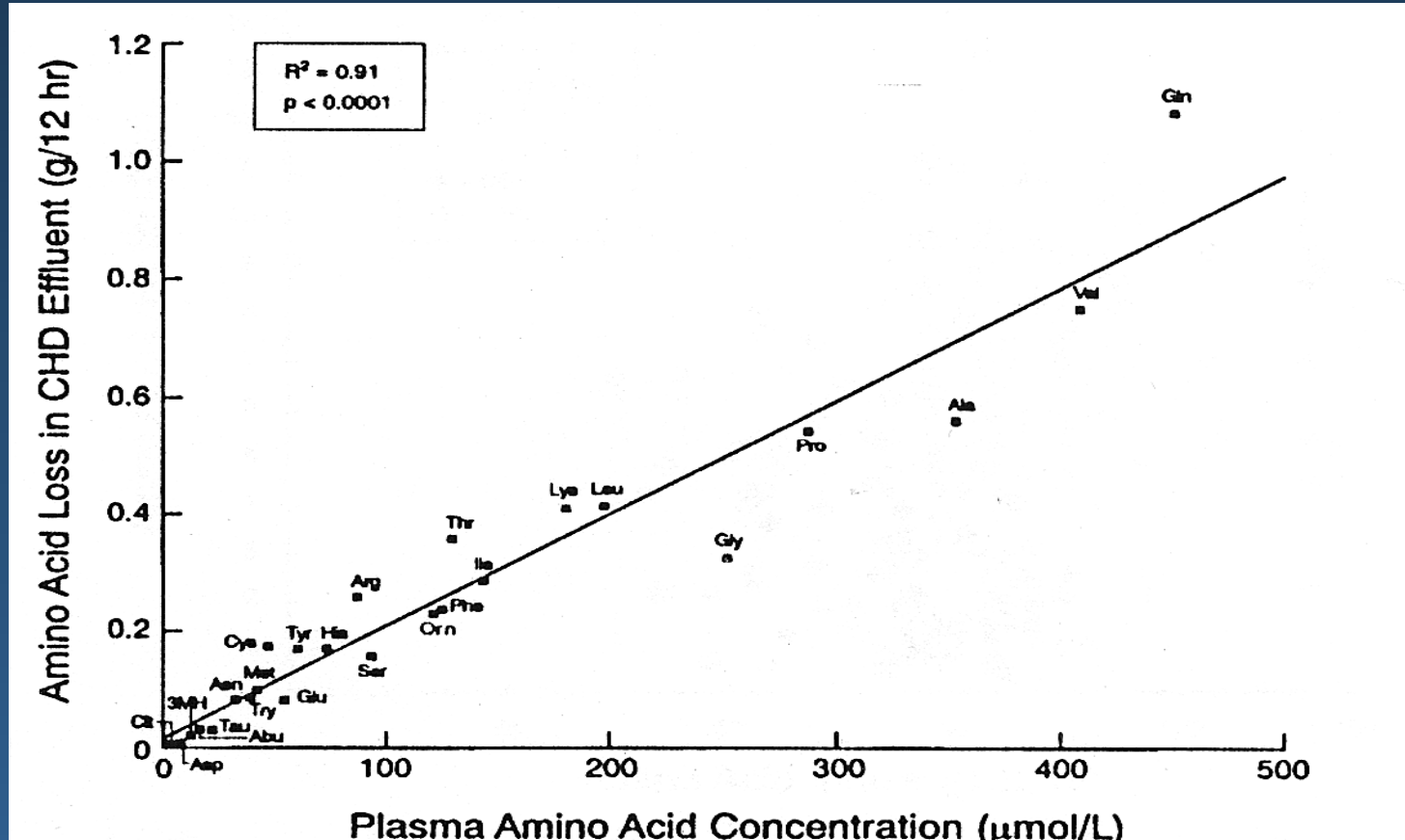


Rates of net leucine deposition (i.e. R_d to protein synthesis minus R_a from proteolysis) into body protein during amino acid infusion in ambulatory and bed rest conditions. * $P < 0.05$

Amino Acid Loss and Plasma Concentrations During Continuous Hemodiafiltration

Frankenfield DC et al.

JPEN 1993; 17: 551 - 61



Mean losses of individual amino acids in CHD effluent as a function of mean plasma concentrations of each amino acid.

Cachexia in the Critically Ill

Potential therapeutic approaches

Nutrition support

- adequate provision of macro- and micronutrients
- specific nutrients (glutamine, arginine, BCAAs, ω -3-FA etc.)
- pharmaconutrients : selenium
- immunonutrition

Hormones and hormone antagonists

- insulin
- HGH, IGF-I, testosterone, anabolic steroids
- anticytokines (TNF- α blockers, etc.)
- anti-glucocorticoids
- β -blockers etc.

Direct catabolism inhibitors

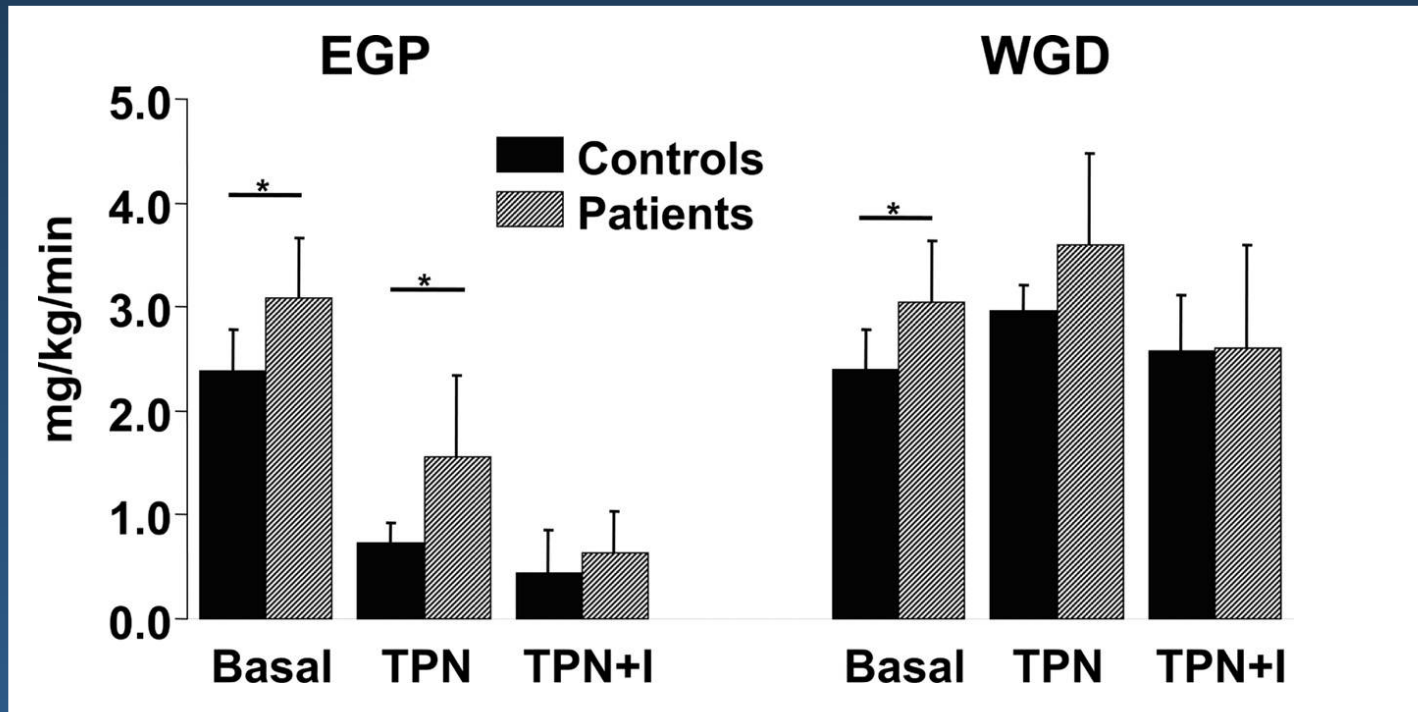
- proteasome blockers, dantrolene, NF- κ B-inhibitors, protease inhibitors etc.

Muscle stimulation etc. etc.

Intensive Insulin Treatment in Critically Ill Trauma Patients Normalizes Glucose by Reducing Endogenous Glucose Production

Thorell A et al

J Endocrinol Metab 2004; 89: 5382-86



Glucose kinetics in traumatized subjects and healthy controls in the postprandial state (basal), during TPN, and during TPN+I. *, $P < 0.05$ vs. control. Endogenous glucose production (EGP) and whole-body glucose disposal (WGD)

Response of glutamine metabolism to glutamine-supplemented parenteral nutrition

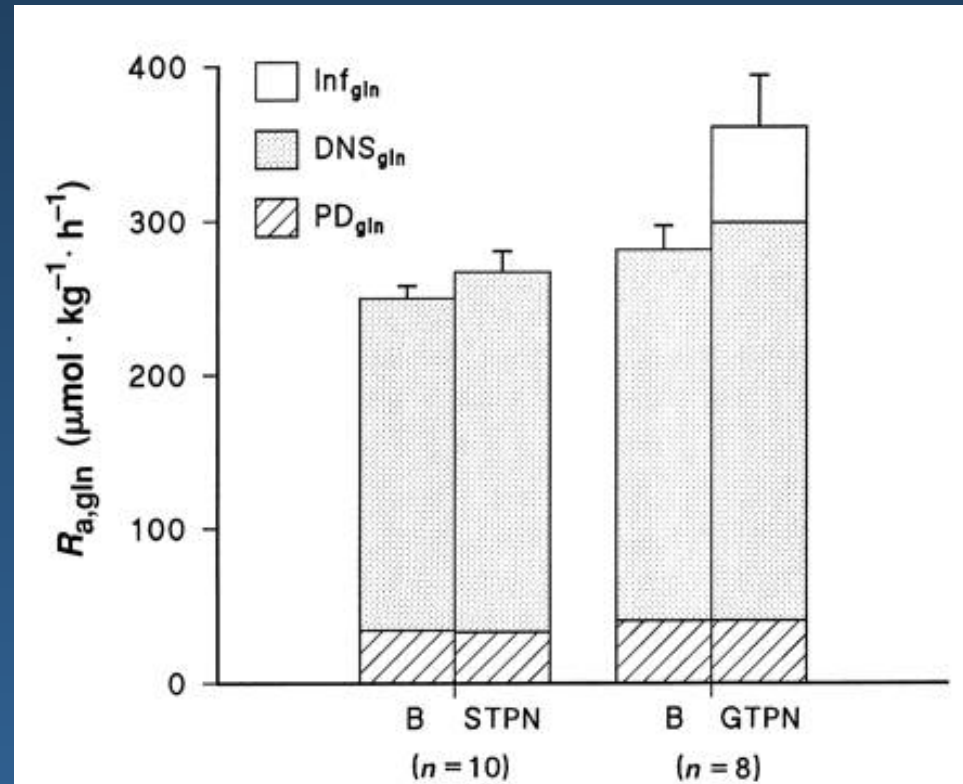
Van Acker et al

Am J Clin Nutr 2000; ; 72:790

Glutamine appearance rate (R_a) at baseline (B) and during standard TPN (STPN) or Gln-enriched TPN (GTPN).

Significant effects (baseline versus 9 d) ($P < 0.001$) and for DNSgln ($P < 0.05$), (GTPN versus STPN; $P < 0.05$)

PDgln, glutamine arising from protein degradation; DNSgln, glutamine arising from de novo synthesis; Infgln, exogenous glutamine.

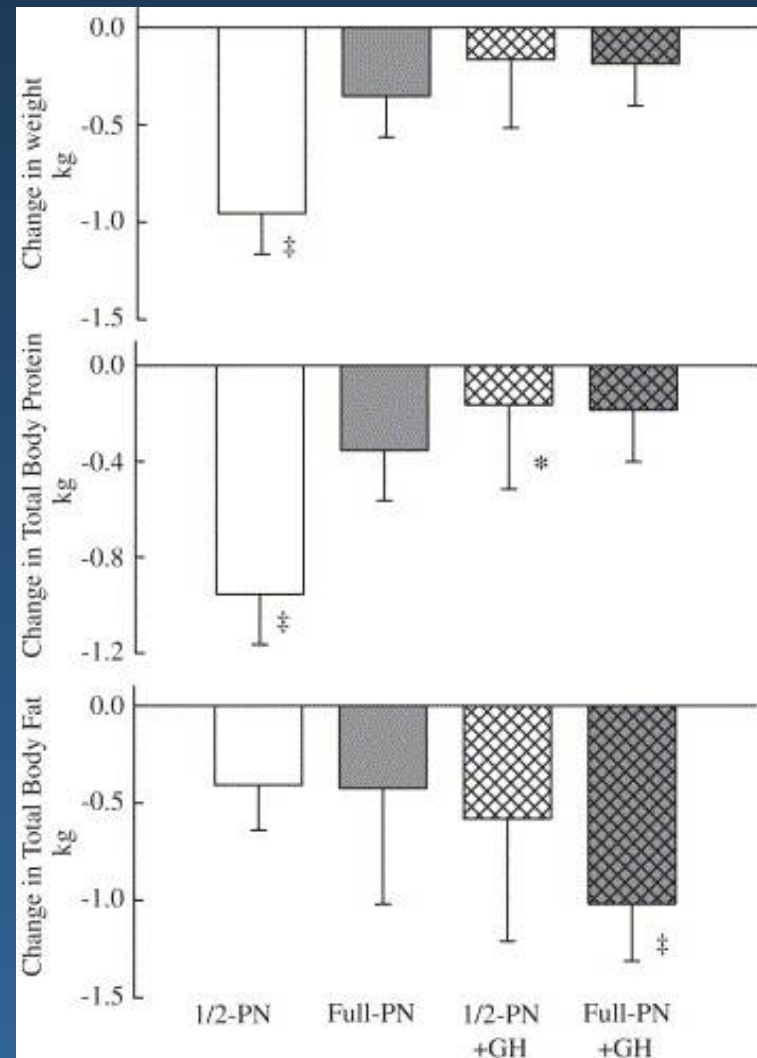


Does growth hormone allow more efficient nitrogen sparing in postoperative patients requiring parenteral nutrition? A RCT

Sevette A et al.

Clin Nutr 2005;
24: 943-955

Body composition.
Values are mean and SEM of the changes in each group on Day 14 compared to the pre-operative values.



Cachexia in the Critically Ill

Potential therapeutic approaches

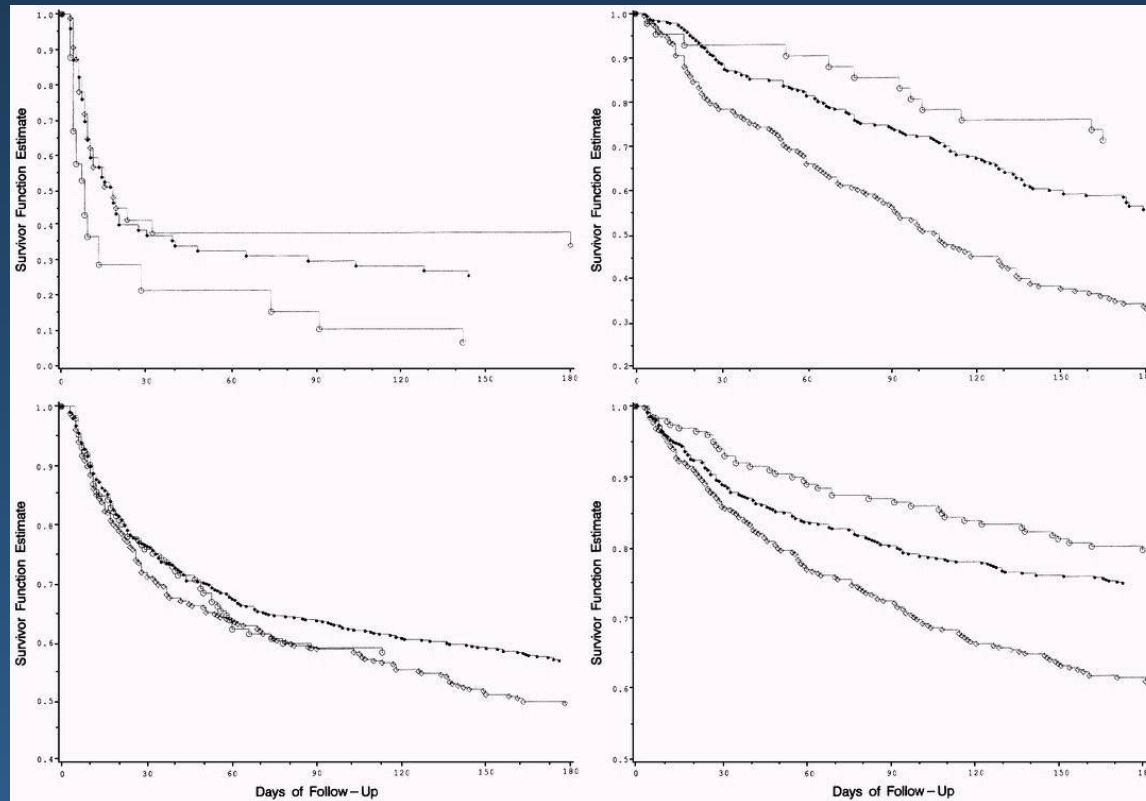
Is it a believe, conviction, a wishful thinking ?

Nutrition is the basis of any adequate therapeutic intervention to minimize protein catabolism (and improve prognosis) in the critically ill

Relationship of BMI to subsequent mortality among seriously ill hospitalized patients

Galanos AN et al.

Crit Care Med 1997; 25: 1962-65



Estimated survival curves by BMI group for four disease classes: coma (top left panel), cancer (top right panel), acute respiratory failure/multiple organ system failure (bottom left panel), and chronic obstructive pulmonary disease/congestive heart failure/cirrhosis (bottom right panel)

Cachexia in the Critically Ill

Back to the roots: Nutrition is the future !



Thank you for your attention !