Mécanismes et conséquences de l'anorexie dans l'agression

Jean Charles Preiser, MD, Ph.D.
Service des soins intensifs
Hôpital universitaire Erasme
Bruxelles, Belgique

Déclaration d'intérêts en rapport avec la présentation

➢ **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

Non *Société(s)*

➢ **Essais cliniques, autres travaux, communications de promotion**

Non *Société(s)*

➢ **Intérêts financiers (actions, obligations)**

Non *Société(s) : ……*

➢ **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

Non *Société(s) : ……*

➢ **Réception de dons sur une association dont je suis responsable**

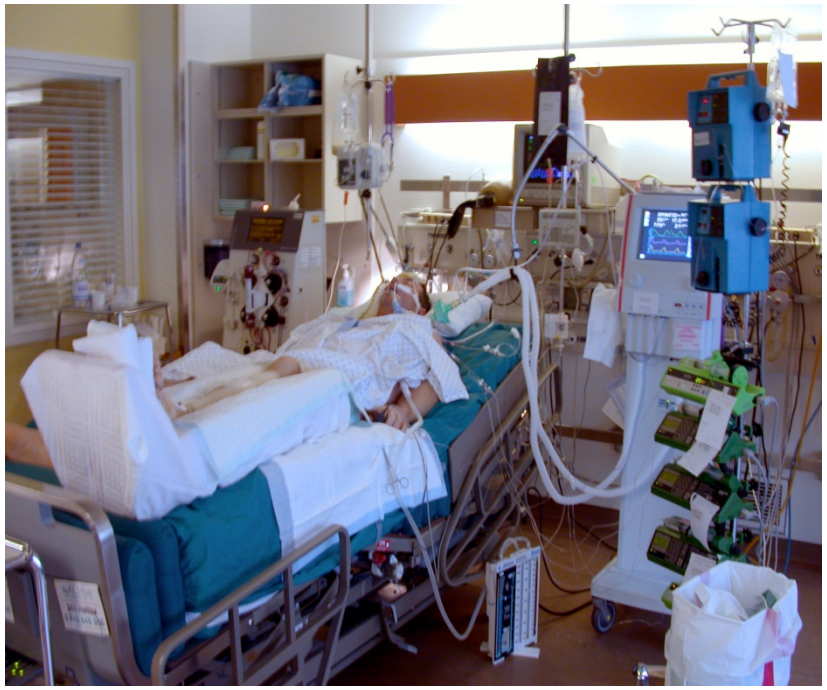
Non *Société(s) : ……*

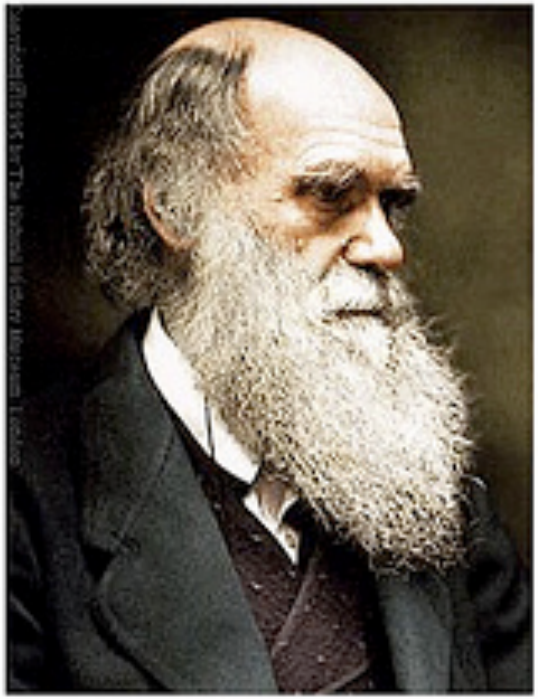
➢ **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

Non *Société(s) : ……*

Le malade agressé

- Un défi constant à la physiologie.. Très révélateur des mécanismes adaptatifs…





It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change.

- Charles Darwin

Clinical Nutrition 31 (2012) 1002–1007

Contents lists available at SciVerse ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Opinion paper

The evolutionary benefit of insulin resistance

Maarten R. Soeters [a,*], Peter B. Soeters [b,**]

[a] Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands
[b] Department of Surgery, Maastricht University Medical Center, Maastricht University, The Netherlands

Here we hypothesize that insulin resistance promotes glucose availability for the inflammatory response in the defense against starvation, disease and trauma and to promote growth during lactation, pregnancy, puberty and cancer, and in situations where the organism prepares itself for migration or hibernation. This mechanism is evolutionarily well preserved in multiple species, including the human organism. It is also likely that in other insulin resistance states like chronic inflammatory illnesses (chronic obstructive pulmonary disease, rheumatoid arthritis etc.), insulin resistance is initially beneficial in promoting the inflammatory response and healing and not the result of mitochondrial dysfunction.[55,56]

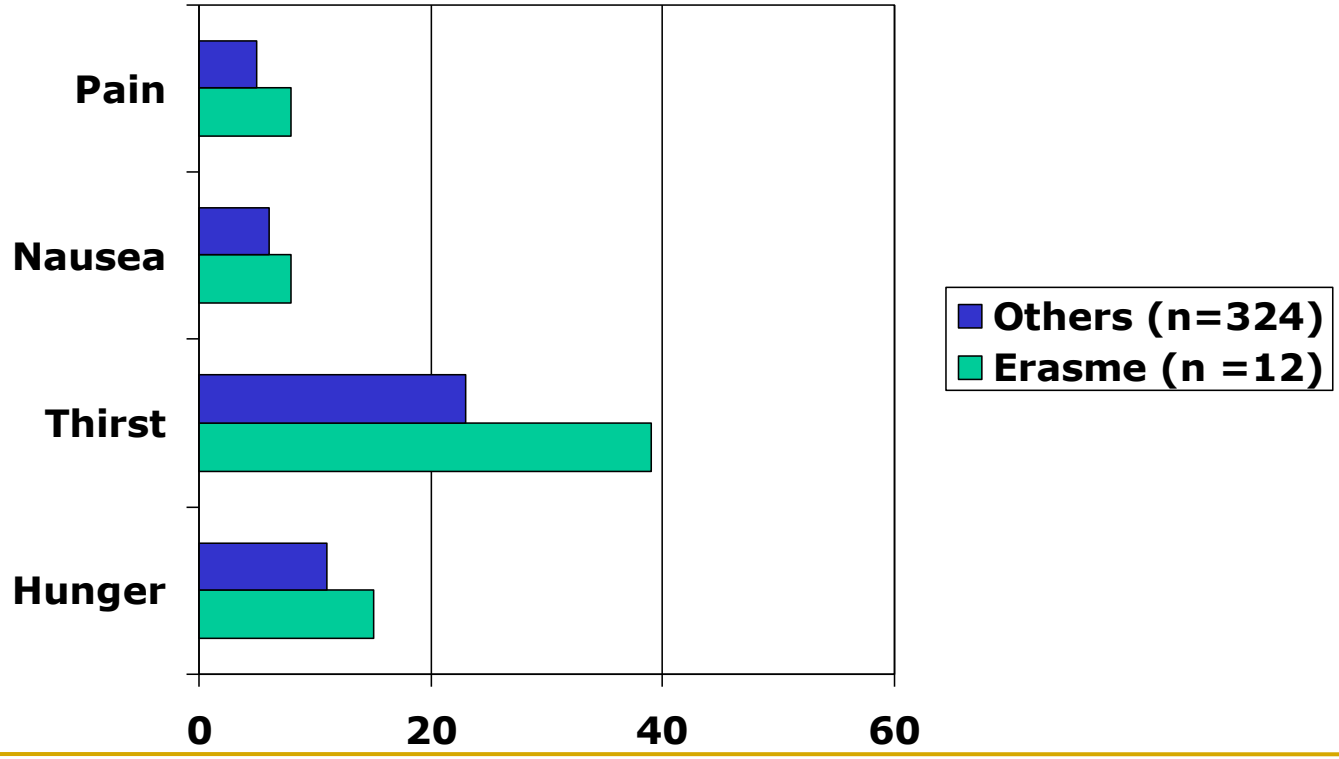
Prise alimentaire chez l'agressé?

- Inappétence lors d'états inflammatoires aigus (grippe..)

NutritionDay in ICU

November 2011

Patients' feelings



NutritionDay in ICU

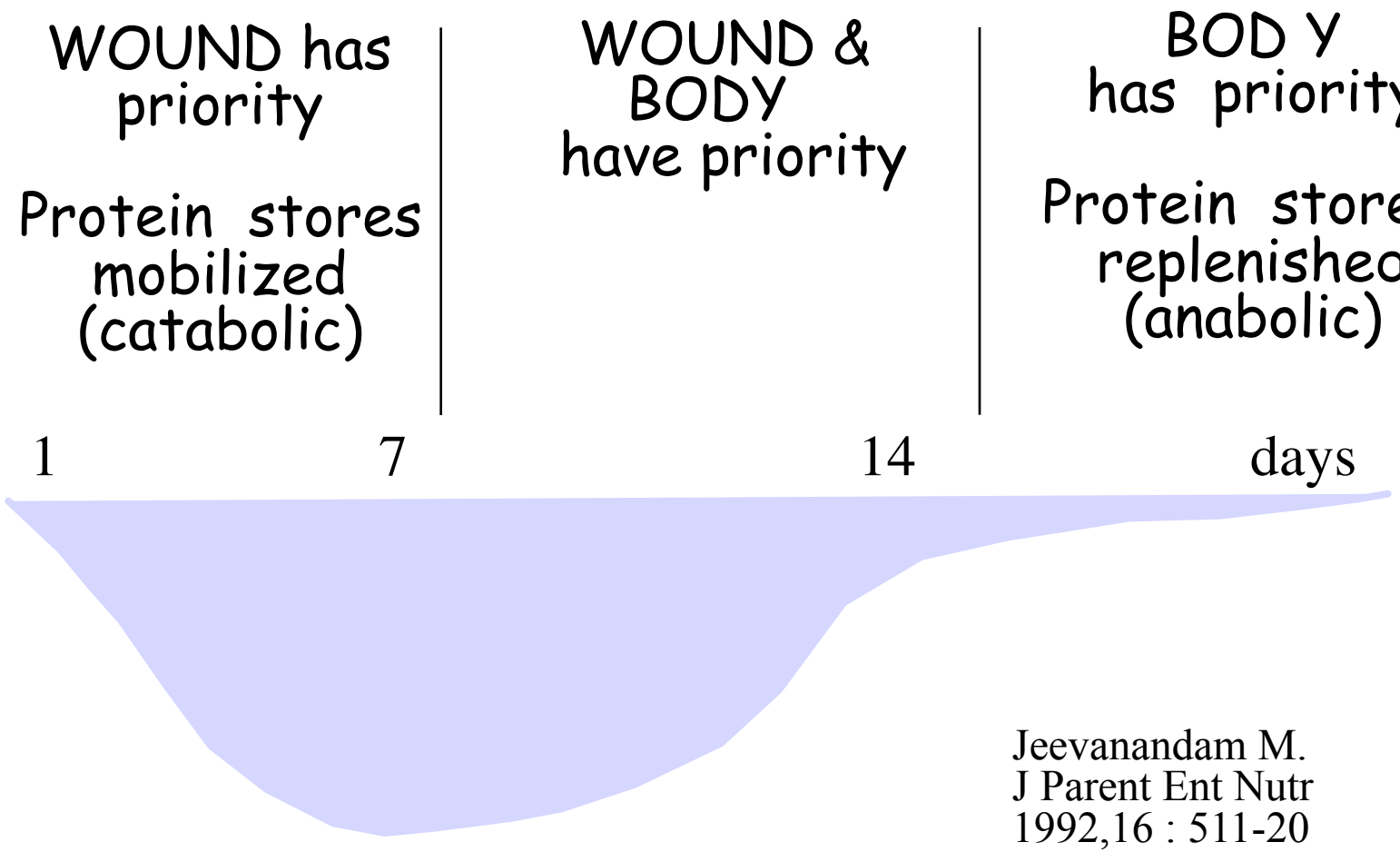
November 2011

Nutrition intake at lunch or dinner (n):	Erasme	Others
 All	2 (7.69%)	89 (8.88%)
 ½	3 (11.5%)	70 (6.99%)
 ¼	5 (19.2%)	55 (5.49%)
 Nothing	9 (34.6%)	83 (8.28%)
? Missing	7 (26.9%)	705 (70.4%)

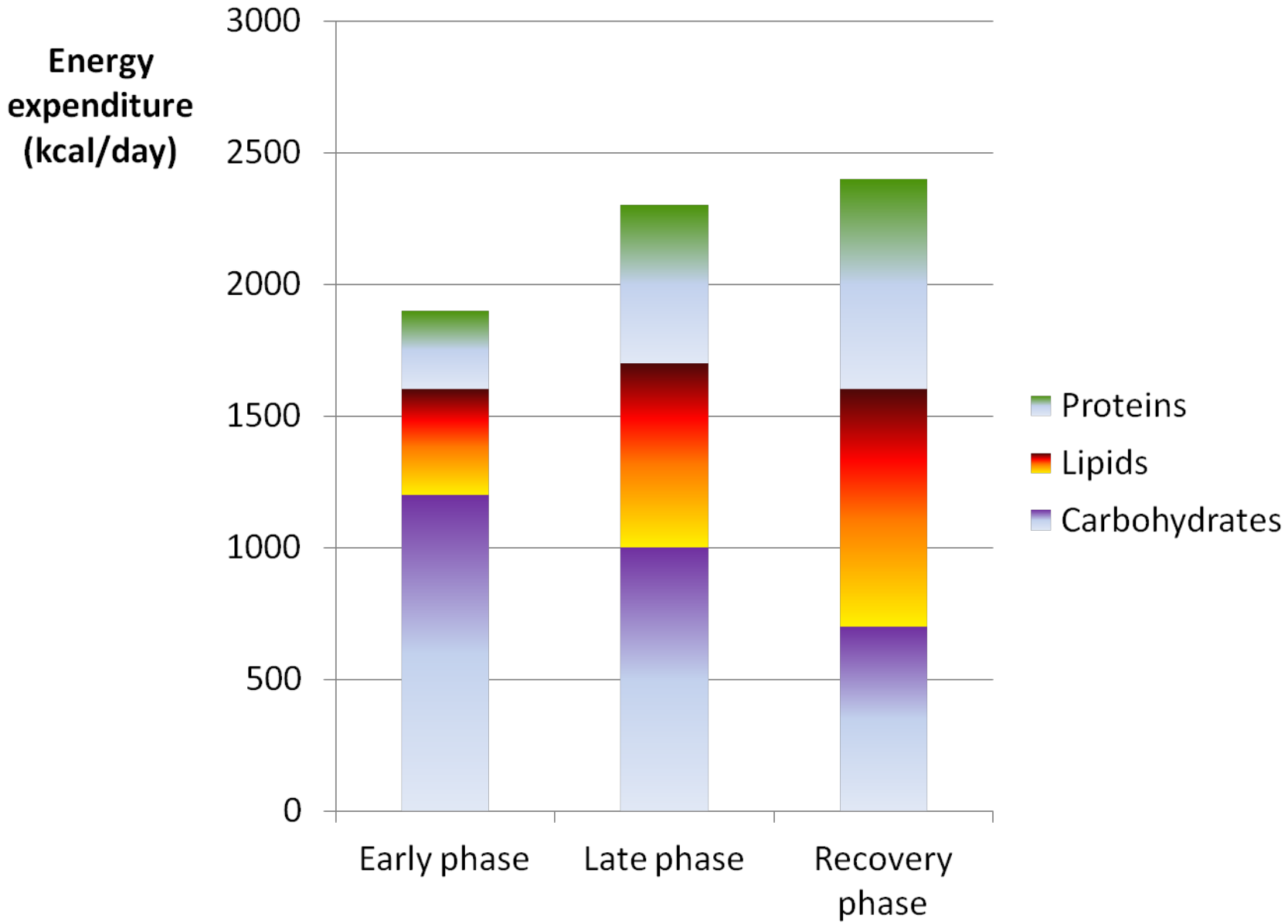
Prise alimentaire chez l'agressé?

- Inappétence lors d'états inflammatoires aigus (grippe..)
- La réponse métabolique à l'agression est triphasique

Réponse métabolique à l'agression



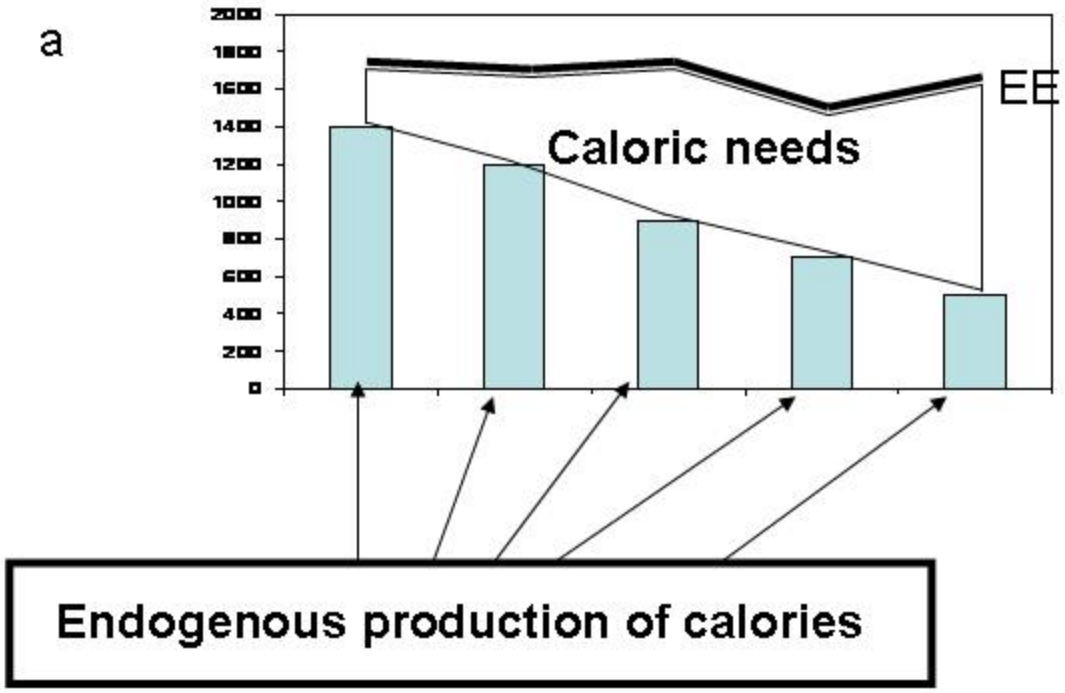
Jeevanandam M.
J Parent Ent Nutr
1992,16 : 511-20


Energy expenditure (kcal/day)
3000
2500
2000
1500
1000
500
0
Early phase
Late phase
Recovery phase
Proteins
Lipids
Carbohydrates

Prise alimentaire chez l'agressé?

- Inappétence lors d'états inflammatoires aigus (grippe..)
- La réponse métabolique à l'agression est triphasique
- A la phase aigüe, un excès de calories peut être nocif

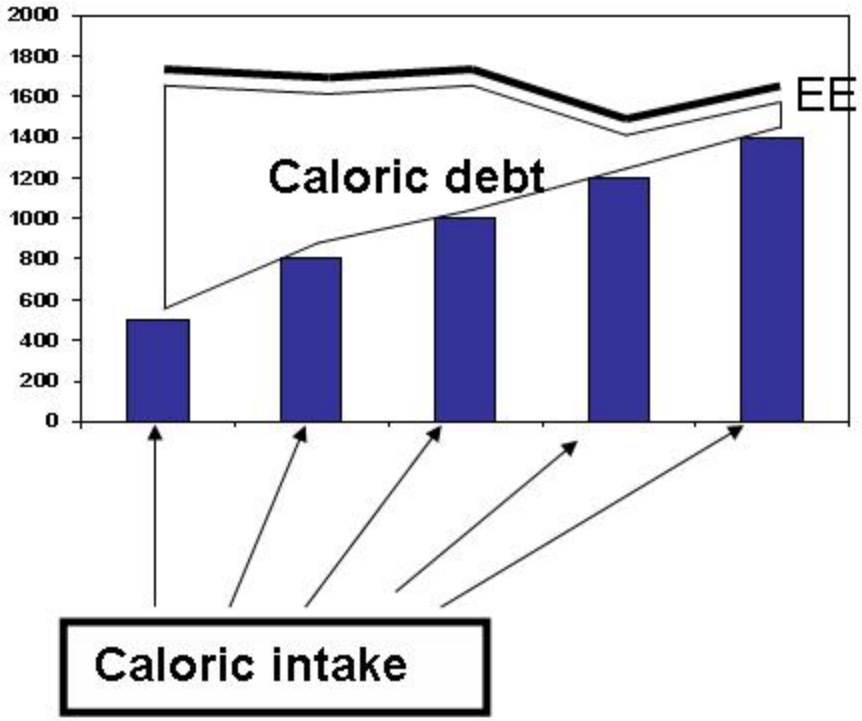
a



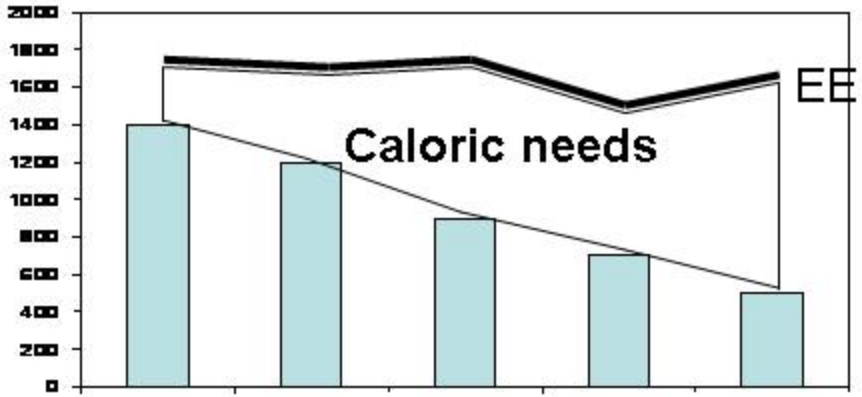
Energy estimation and measurement in critically ill patients.
Fraipont V, Preiser JC. JPEN J Parenter Enteral Nutr. 2013 Nov-Dec;37(6):705-13

Energy estimation and measurement in critically ill patients.
Fraipont V, Preiser JC.
JPEN J Parenter Enteral Nutr. 2013 Nov-Dec;37(6):705-13

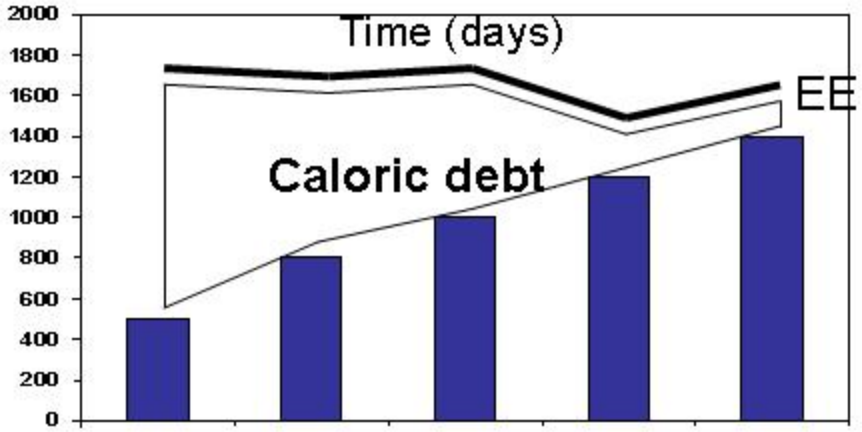
b



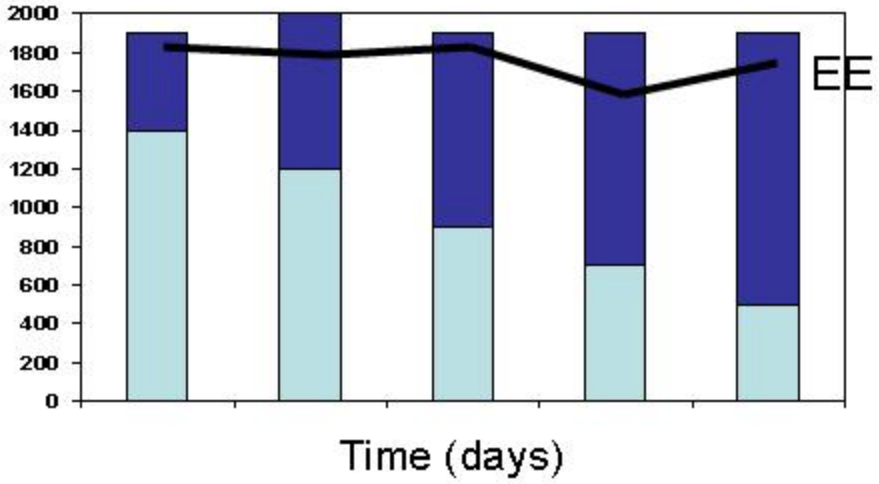
a



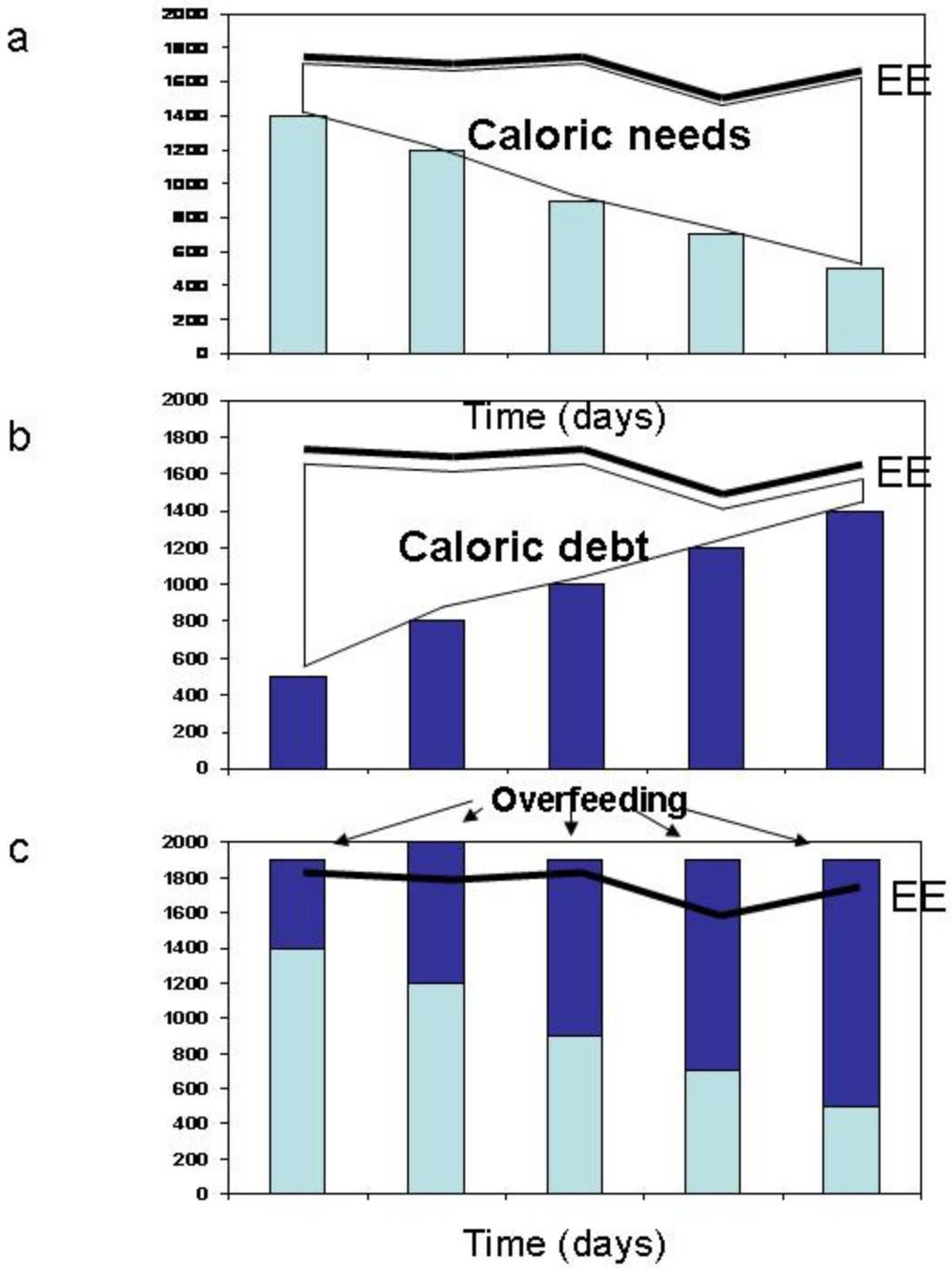
b



c



Energy estimation and measurement in critically ill patients.
Fraipont V, Preiser JC. JPEN J Parenter Enteral Nutr. 2013 Nov-Dec;37(6):705-13



Energy estimation and measurement in critically ill patients.
Fraipont V, Preiser JC. JPEN J Parenter Enteral Nutr. 2013 Nov-Dec;37(6):705-13

Ziegler et al N Engl J Med. 2009;361:1088

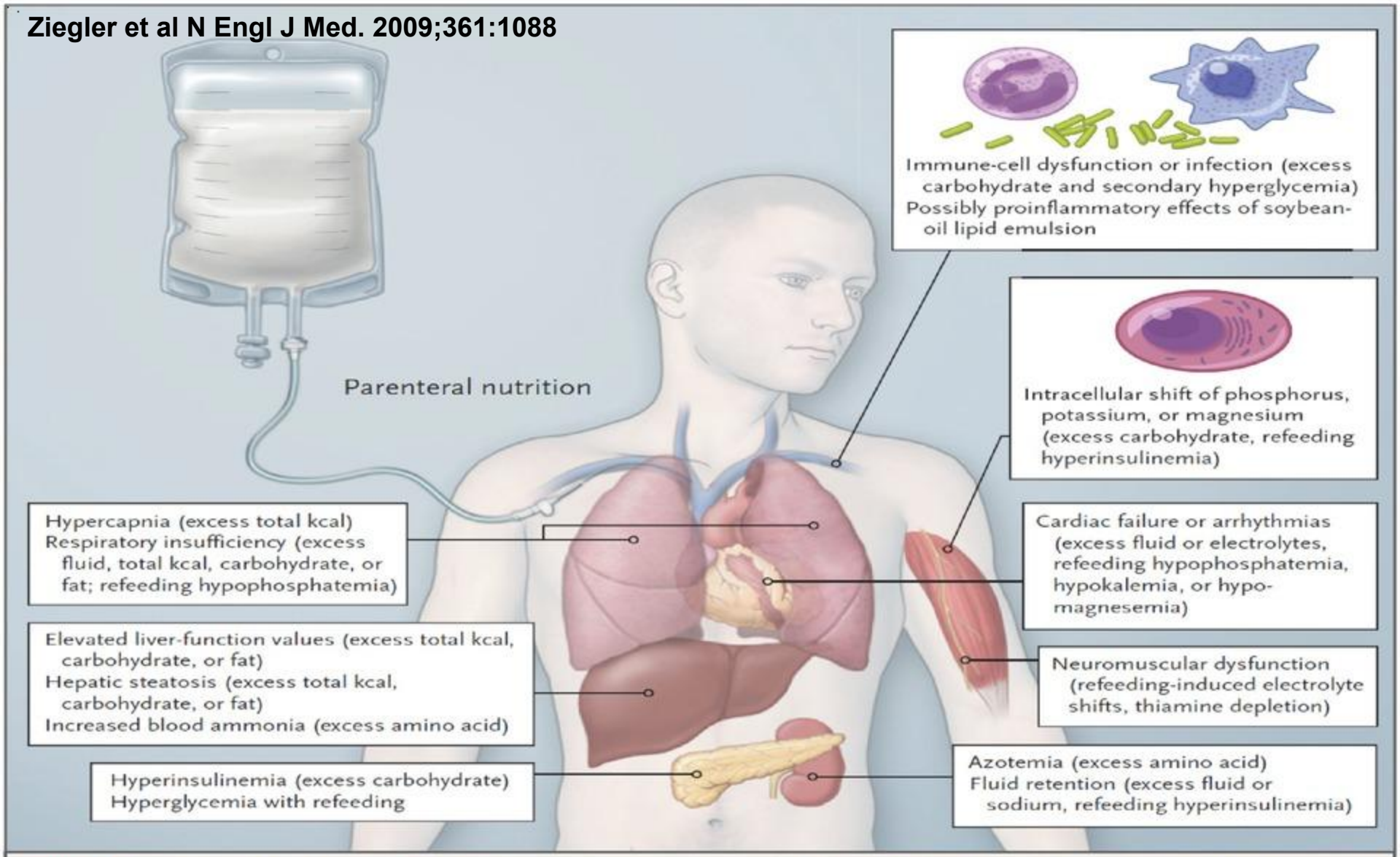
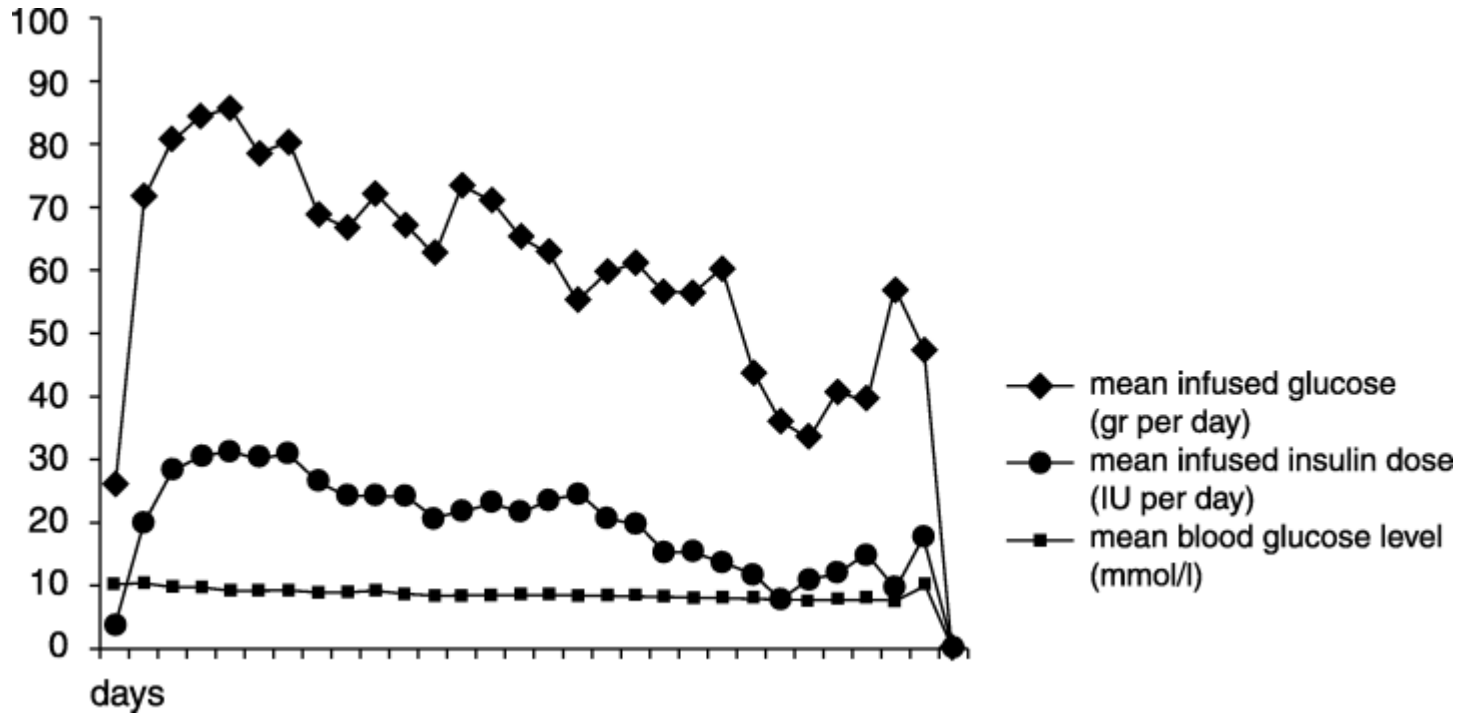


Figure 1. Potential Metabolic and Clinical Consequences of Overfeeding and the Refeeding Syndrome during Administration of Central Venous Parenteral Nutrition in Patients with Critical Illness.

Hypertriglyceridemia can occur with excess administration of carbohydrates or fat emulsion; excess administration of specific electrolytes in a variety of clinical conditions (e.g., acute kidney injury) can lead to elevated blood levels, whereas inadequate administration, especially during refeeding, can lead to decreased blood levels. Inadequate energy provision in relation to the dose of amino acids can contribute to azotemia.

Intravenous glucose and hospital mortality

Van der voort Clin Endocrinol 2006;64:141



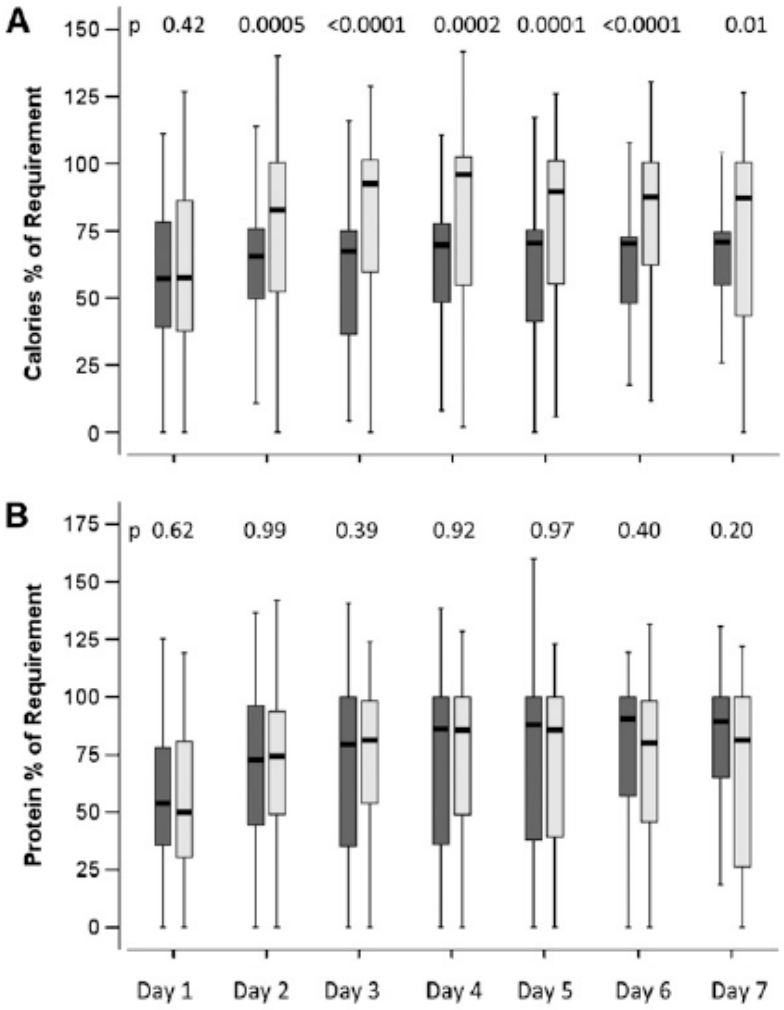
Retrospective cohort study on ICU long-stayers (7-30 d)
N = 273 (/ 2042)
Hospital mortality lower when mean BG < 8 mmol/L

Logistic multivariate regression analysis : APACHE II and mean daily amount of IV Glucose associated with lower survival (OR 0.94 (0.9-0.98) and 0.65 (0.47-0.89))

Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial[1–3]

Yaseen M Arabi, Hani M Tamim, Gousia S Dhar, Abdulaziz Al-Dawood, Muhammad Al-Sultan, Maram H Sakkijha, Salim H Kahoul, and Riette Brits

Am J Clin Nutr 2011



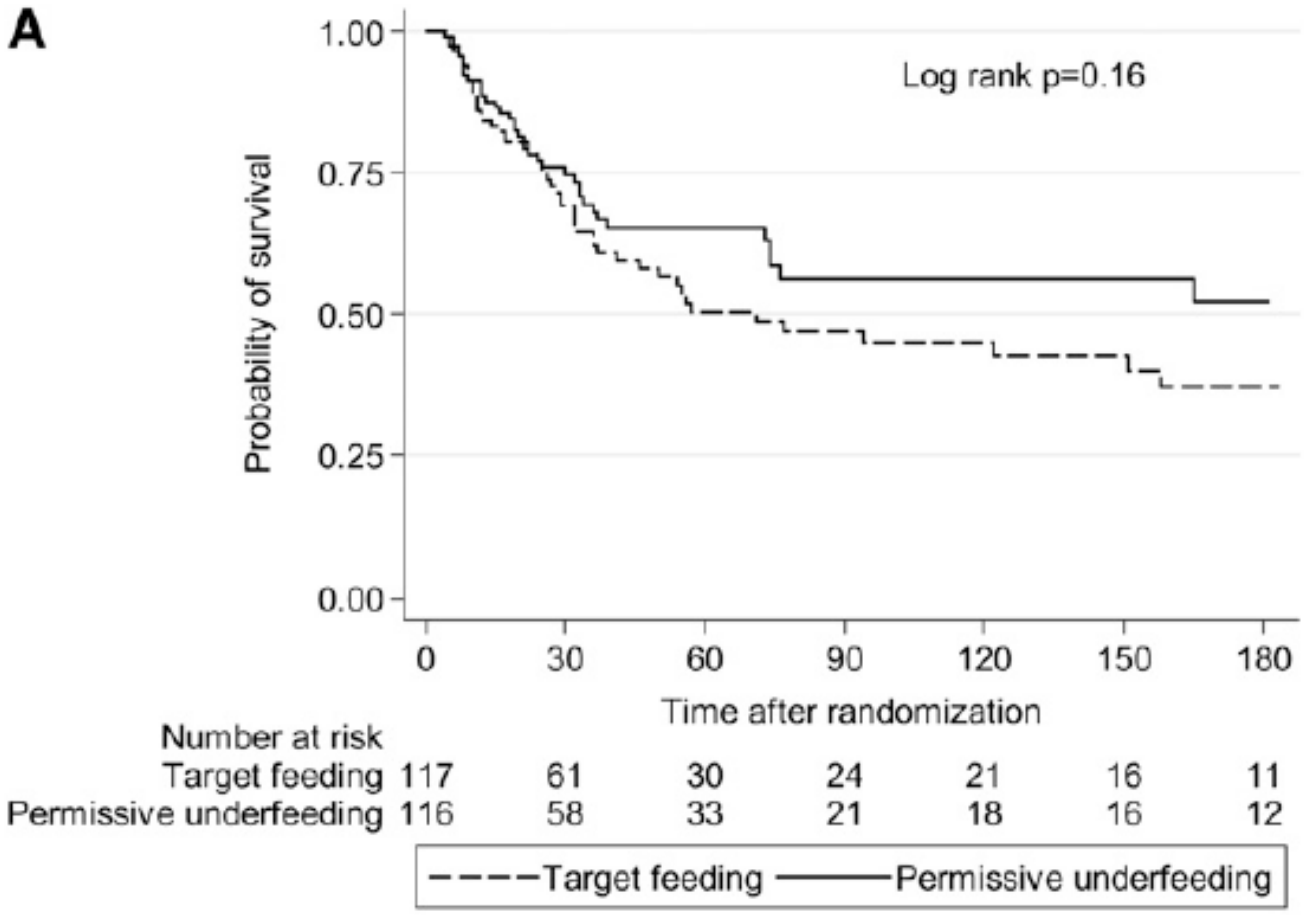
Design: This study had a 2 × 2 factorial, randomized, controlled design. Eligible patients were randomly assigned to permissive underfeeding or target feeding groups (caloric goal: 60–70% compared with 90–100% of calculated requirement, respectively) with either IIT or CIT (target blood glucose: 4.4–6.1 compared with 10–11.1 mmol/L, respectively).

Results: Twenty-eight-day all-cause mortality was 18.3% in the permissive underfeeding group compared with 23.3% in the target feeding group (relative risk: 0.79; 95% CI: 0.48, 1.29; $P = 0.34$). Hospital mortality was lower in the permissive underfeeding group than in the target group (30.0% compared with 42.5%, respectively; relative risk: 0.71; 95% CI: 0.50, 0.99; $P = 0.04$). No significant differences in outcomes were observed between the IIT and CIT groups.

Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial[1–3]

Yaseen M Arabi, Hani M Tamim, Gousia S Dhar, Abdulaziz Al-Dawood, Muhammad Al-Sultan, Maram H Sakkijha, Salim H Kahoul, and Riette Brits

Am J Clin Nutr 2011



3 major PRCTs on supplemental PN

- EPaNIC (Casaer NEJM 2011)
- SPN (Heidegger Lancet 2013)
- Early PN (Doig JAMA 2013)

Can these results be aggregated?

Yes

- Same intervention :
  - Supplemental PN started early during the ICU course

Can these results be aggregated?

Yes

- Same intervention :
  - Supplemental PN started early during the ICU course

No

- Different study populations
- Different interventions
- Different primary outcomes

Can these results be aggregated?

Yes

- Same intervention :
  - Supplemental PN started early during the ICU course

No

- Different study populations
- Different interventions
- Different primary outcomes
- *Differences is secondary outcomes : increased rate of complications / LOS in one study – difference in late infection rate – duration MV*

Can these results be aggregated?

Yes

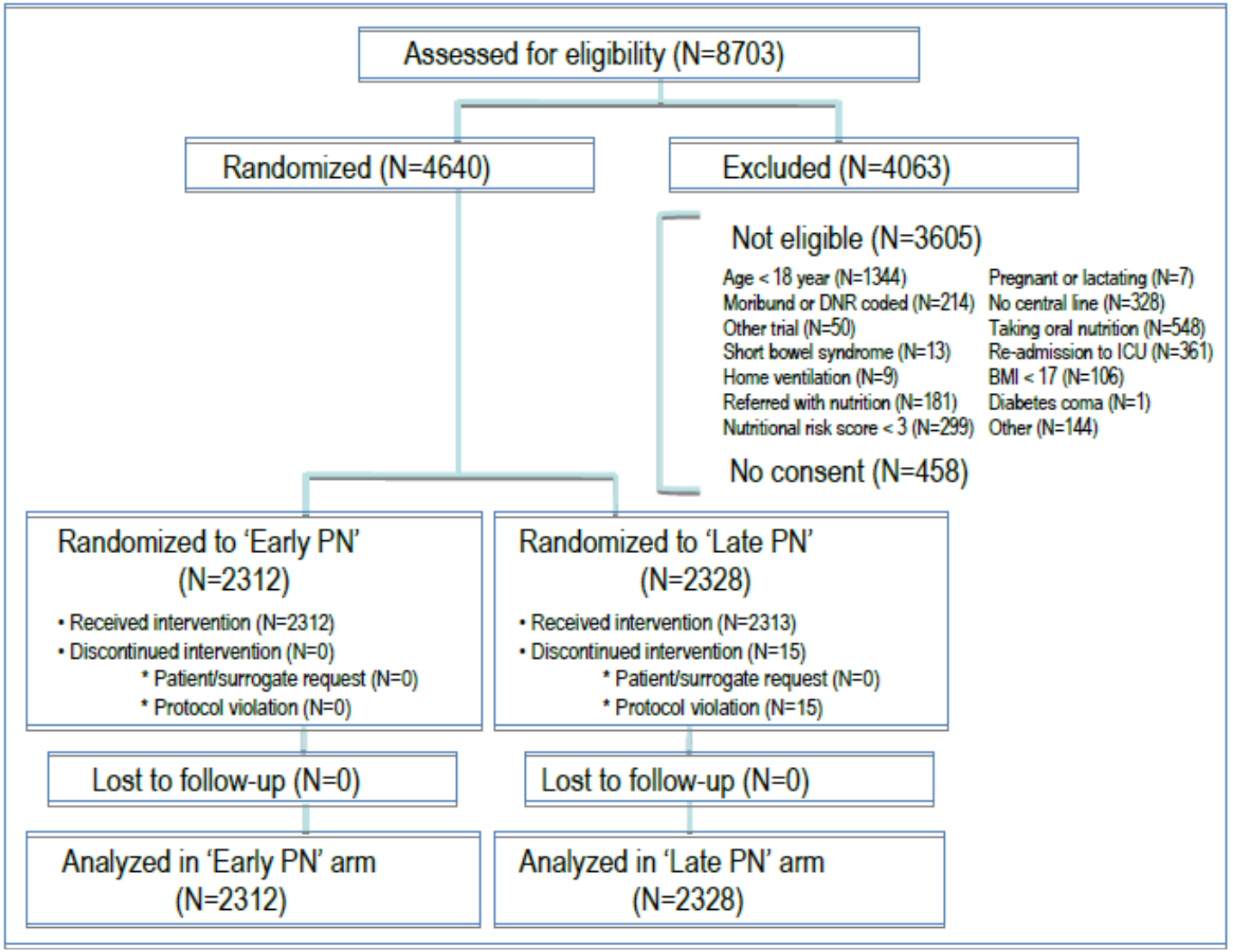
- Same intervention :
  - Supplemental PN started early during the ICU course
- *Same results :* ***no benefit of early supplemental PN***

No

- Different study populations
- Different interventions
- Different primary outcomes
- *Differences is secondary outcomes : increased rate of complications / LOS in one study – difference in late infection rate – duration MV*

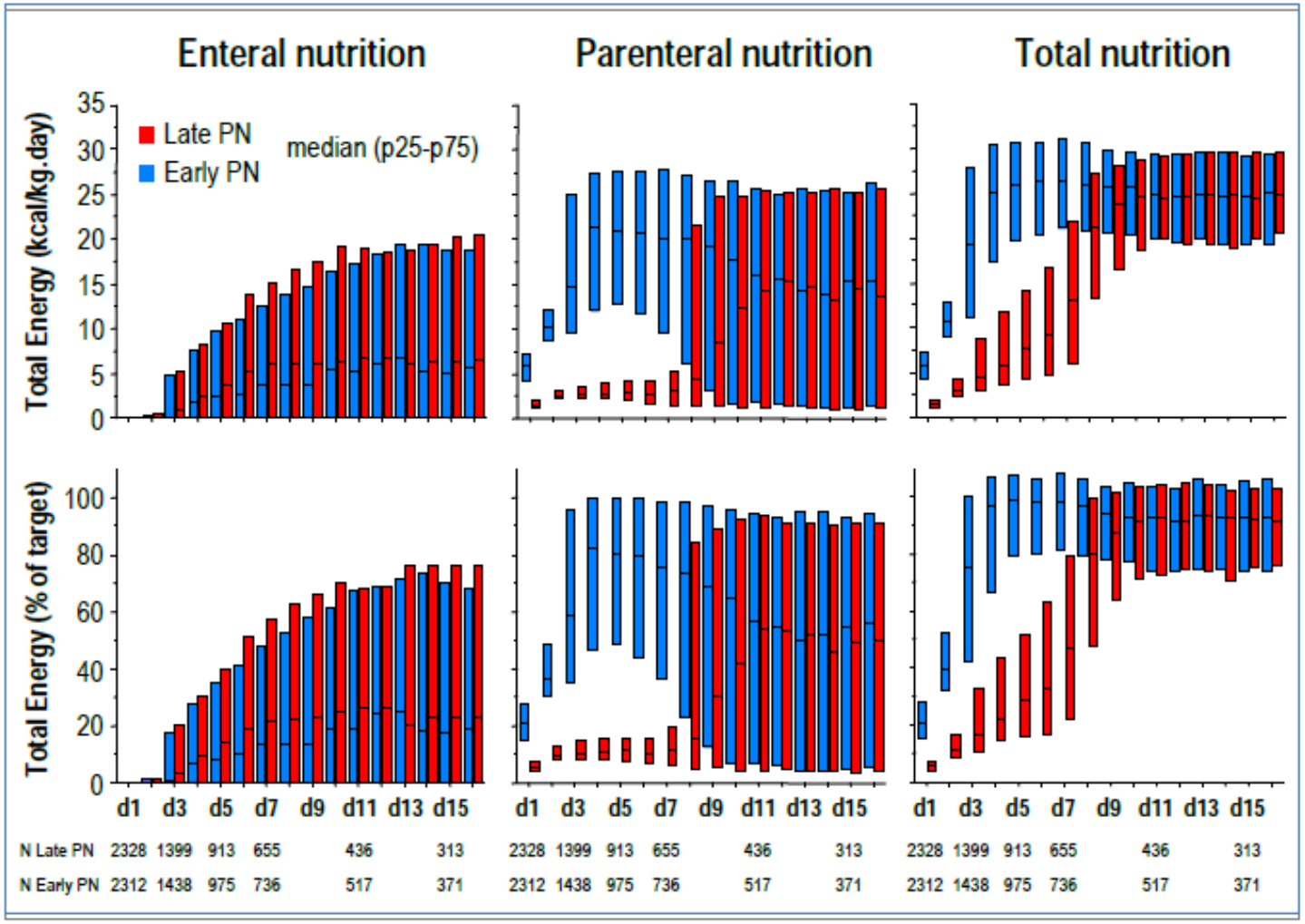
The EPaNIC trial

Figure 1: Consort diagram



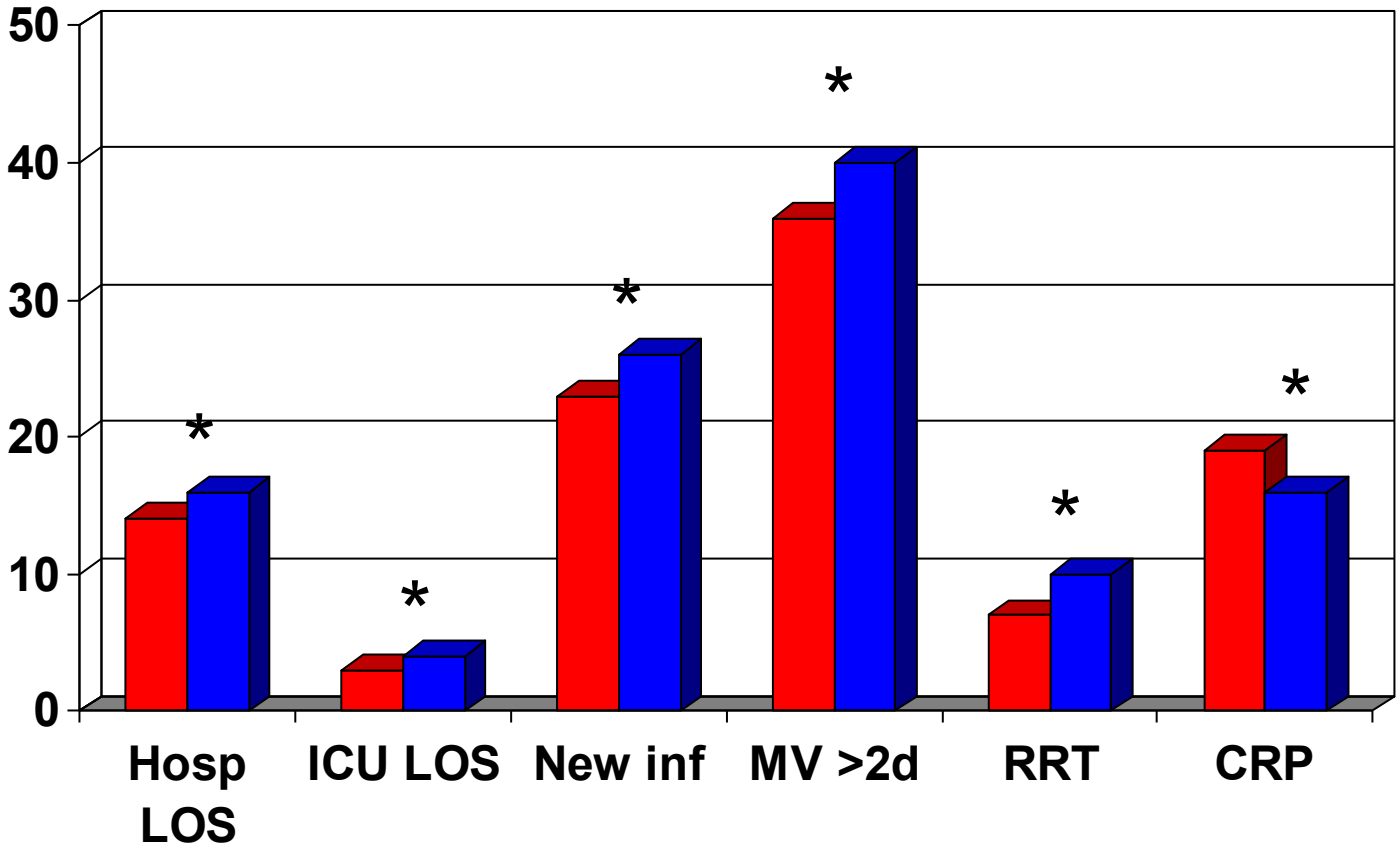
Caloric intake in the EPaNIC trial

Figure 2: Nutrition



Outcomes – EPaNIC trial

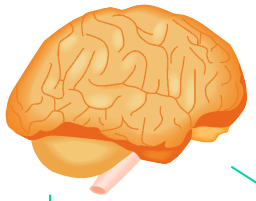
Casaer et al NEJM 2011

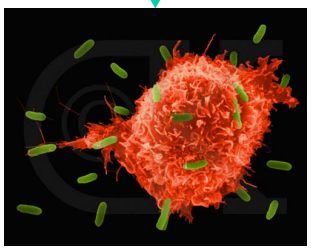


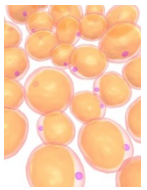
Prise alimentaire chez l'agressé?

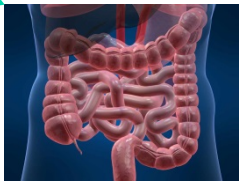
- Inappétence lors d'états inflammatoires aigus (grippe..)
- La réponse métabolique à l'agression est triphasique
- A la phase aigüe, un excès de calories peut être nocif
- Comment l'organisme régule-t-il la prise alimentaire après l'agression?

Stressor
Trauma
surgery
Infection









Epinephrine
Norepinephrine
Sympathetic drive

Cytokines
Switch to T-cell phenotype
Inflammatory mediators

Adipokines

GI tract hormones

?

UNCONTROLLED CATABOLISM

RESISTANCE TO ANABOLIC SIGNALS

Energy expenditure and substrate use

Body composition

Hypothalamic regulation of appetite

Simpson Bloom Exp Rev Endo Metab 2008;3:577

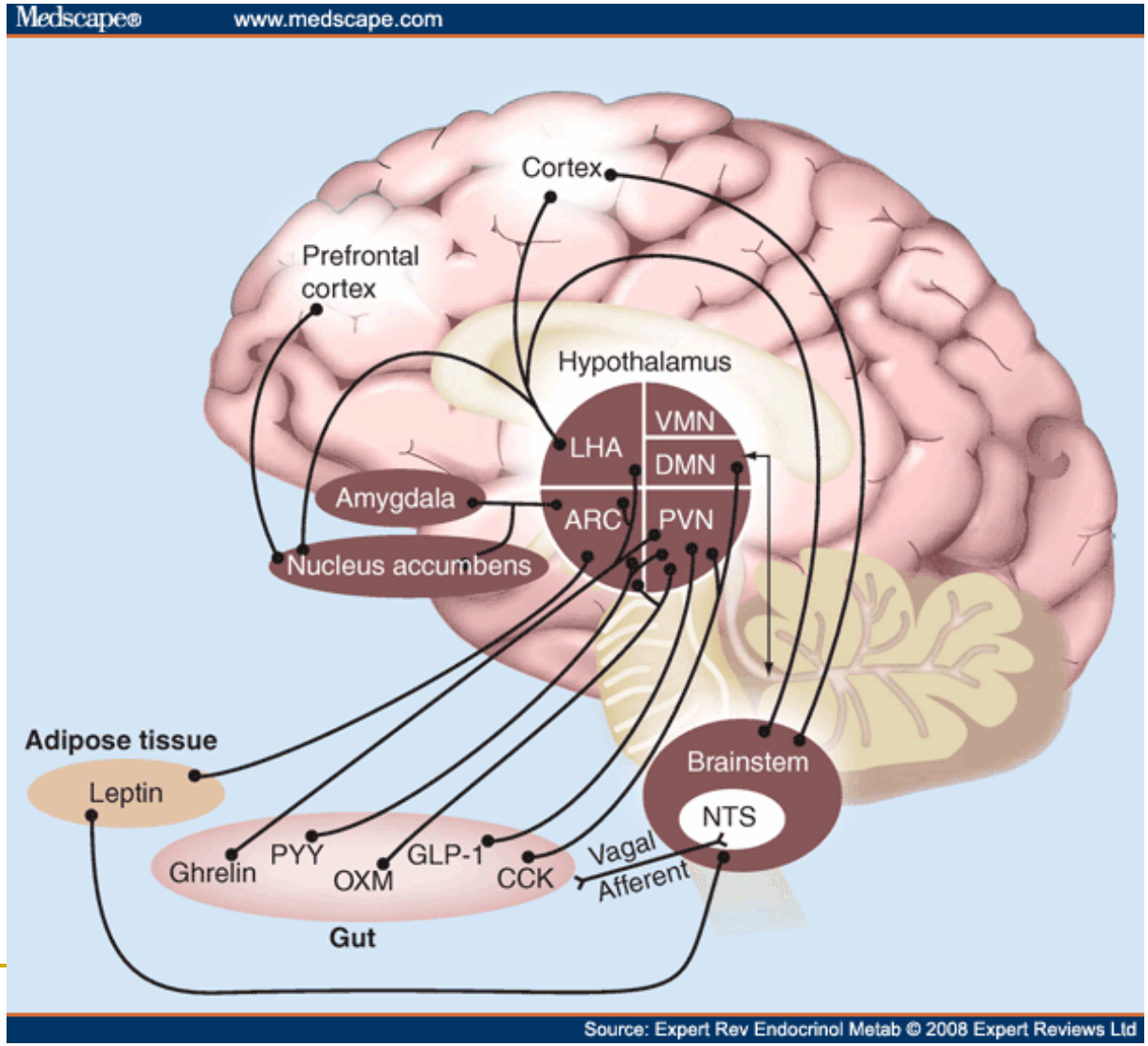
Arcuate nucleus of the hypothalamus

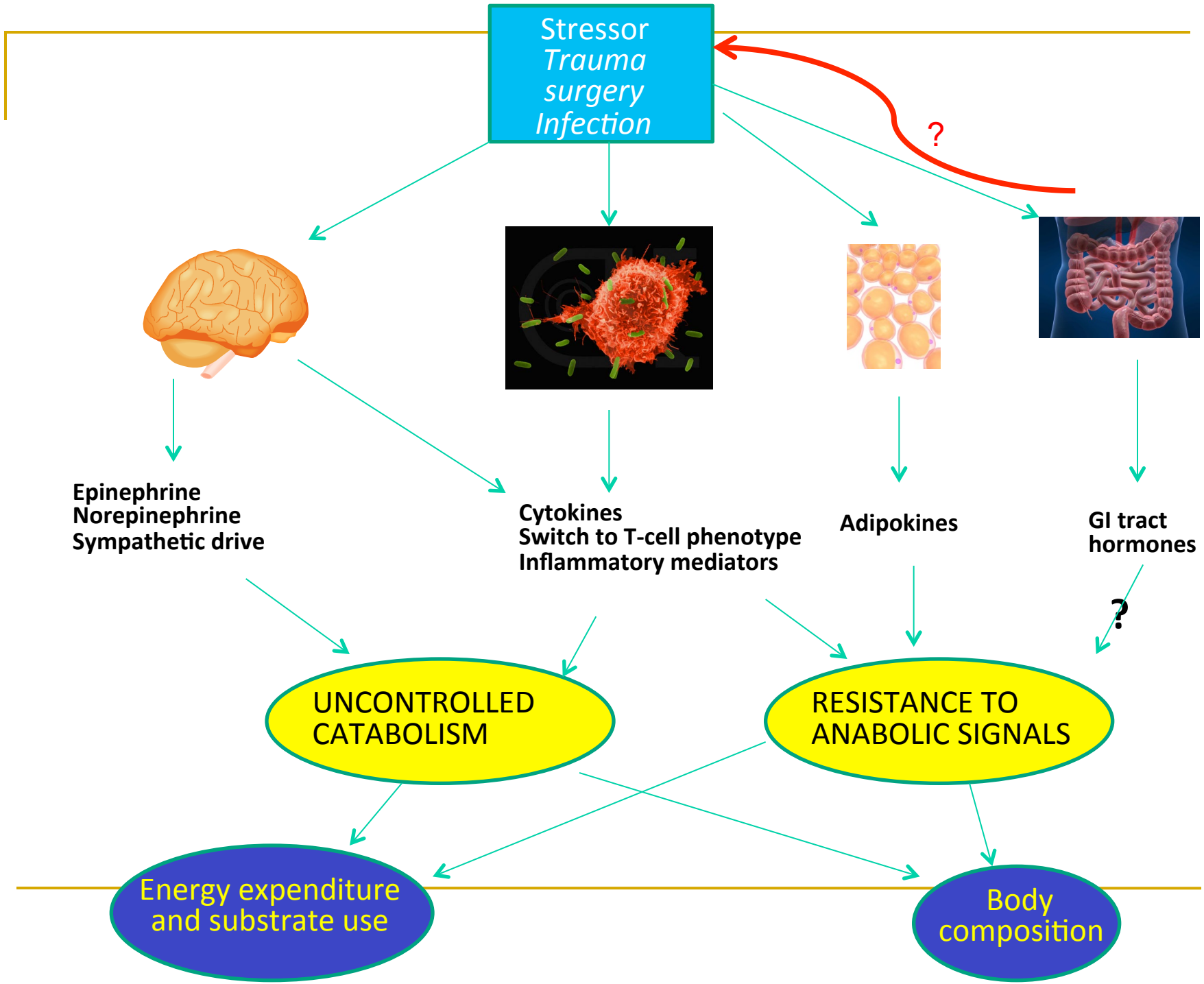
- ***Mediators released from gut / adipose tissue can cross the blood brain barrier***

Brainstem – nucleus of the solitary tract

stimulated by the vagus nerve

- ***gut derived factors, visceral distension concentration of nutrients in portal vein***




Stressor
Trauma
surgery
Infection
?
Epinephrine
Norepinephrine
Sympathetic drive
Cytokines
Switch to T-cell phenotype
Inflammatory mediators
Adipokines
GI tract
hormones
?
UNCONTROLLED
CATABOLISM
RESISTANCE TO
ANABOLIC SIGNALS
Energy expenditure
and substrate use
Body
composition

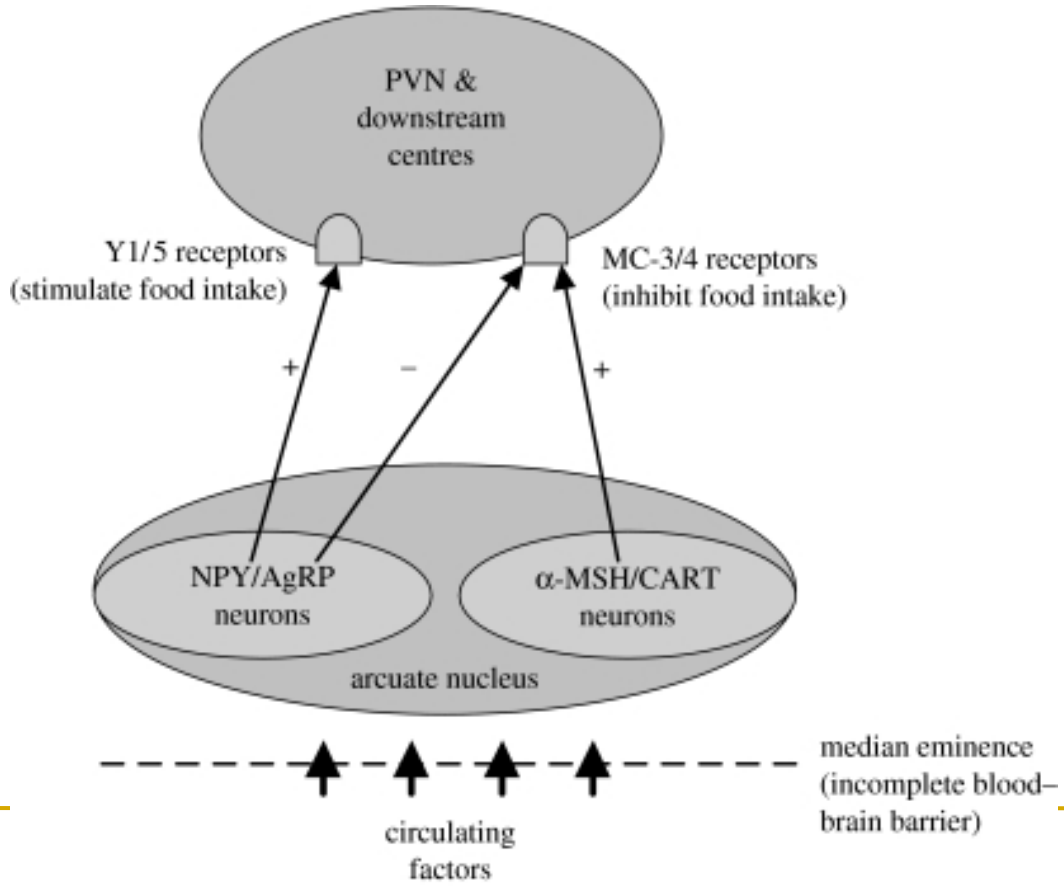
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2006) **361**, 1187–1209
doi:10.1098/rstb.2006.1856
Published online 15 June 2006

Gastrointestinal hormones regulating appetite

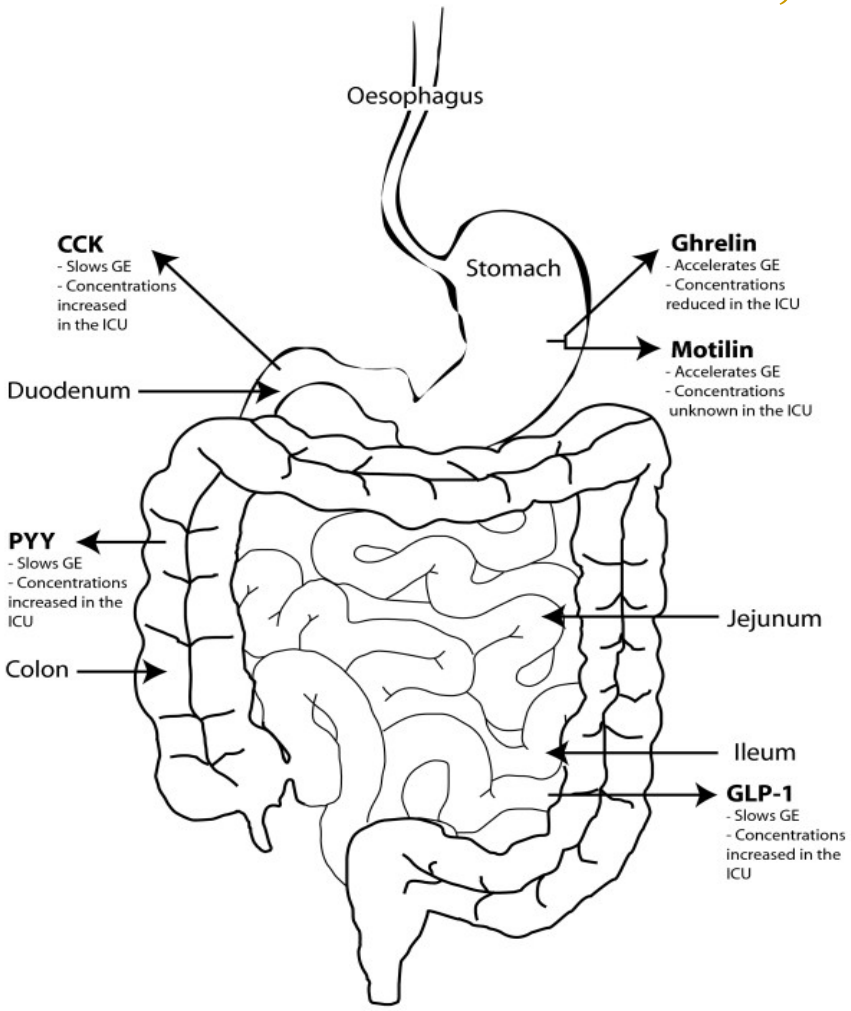
Owais Chaudhri, Caroline Small and Steve Bloom*

Department of Metabolic Medicine, Imperial College Faculty of Medicine, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK



The gut as an endocrine organ in the critically ill.

Deane A et al Crit Care 2010;14:228

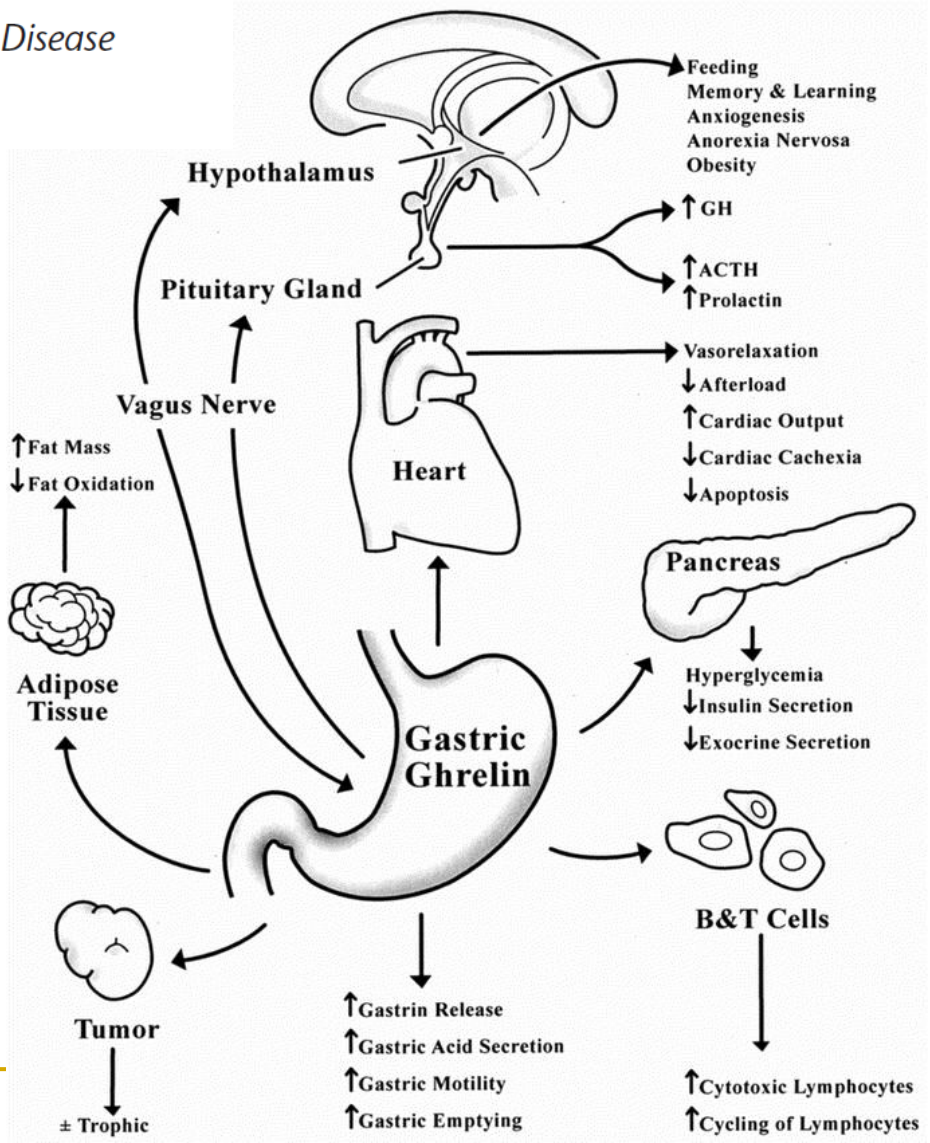


Ghrelin

Integrative Neuroendocrine Peptide in Health and Disease

James T. Wu, MD, and John G. Kral, MD, PhD

(*Ann Surg* 2004;239: 464–474)



0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(10):3930–3934

doi: 10.1210/jc.2007-1194

Bacterial Endotoxin Induces Biphasic Changes in Plasma Ghrelin in Healthy Humans

Greisa Vila, Christina Maier, Michaela Riedl, Peter Nowotny, Bernhard Ludvik, Anton Luger, and Martin Clodi

Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, A-1090, Vienna, Austria

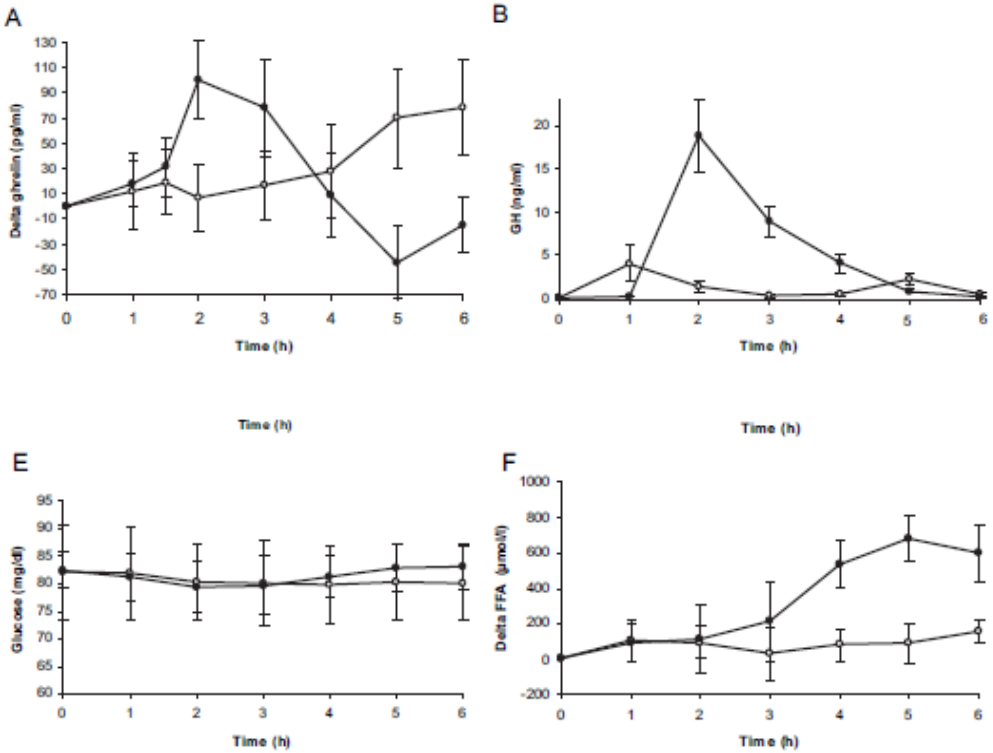
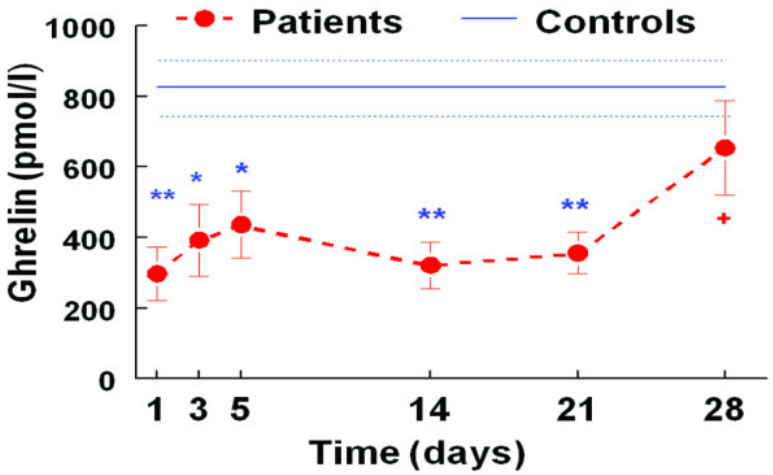


FIG. 3. Hormone and metabolic changes induced by endotoxin. LPS infusion (time point 0) induced within 2 h a rapid increase in plasma ghrelin followed by a second decline reaching a nadir at 5 h (A). LPS increased significantly GH (B), ACTH (C), cortisol (D), and FFA (F) but had no significant effects on plasma glucose (E). Data are presented as mean ± SEM (●, LPS; ○, placebo).

GHRELIN

Gut failure in the ICU.
Puleo F, Arvanitakis M, Van Gossum A, Preiser JC.
Semin Respir Crit Care Med. 2011 Oct;32 (5):626-38.

- Secreted from the stomach during fasting period;
- Secretion suppressed by meal ingestion;
- Stimulates appetite;
- Exogenous ghrelin accelerate gastric emptying in humans;



Fasting plasma ghrelin reduced in critically ill patients

Could play a role in delayed gastric emptying, decreased appetite and weight loss.

Wren AM et al. J Clin Endocrinol Metab 2001
Tack J, et al. Aliment Pharmacol Ther 2005
Nematy M, et al. Crit Care 2006

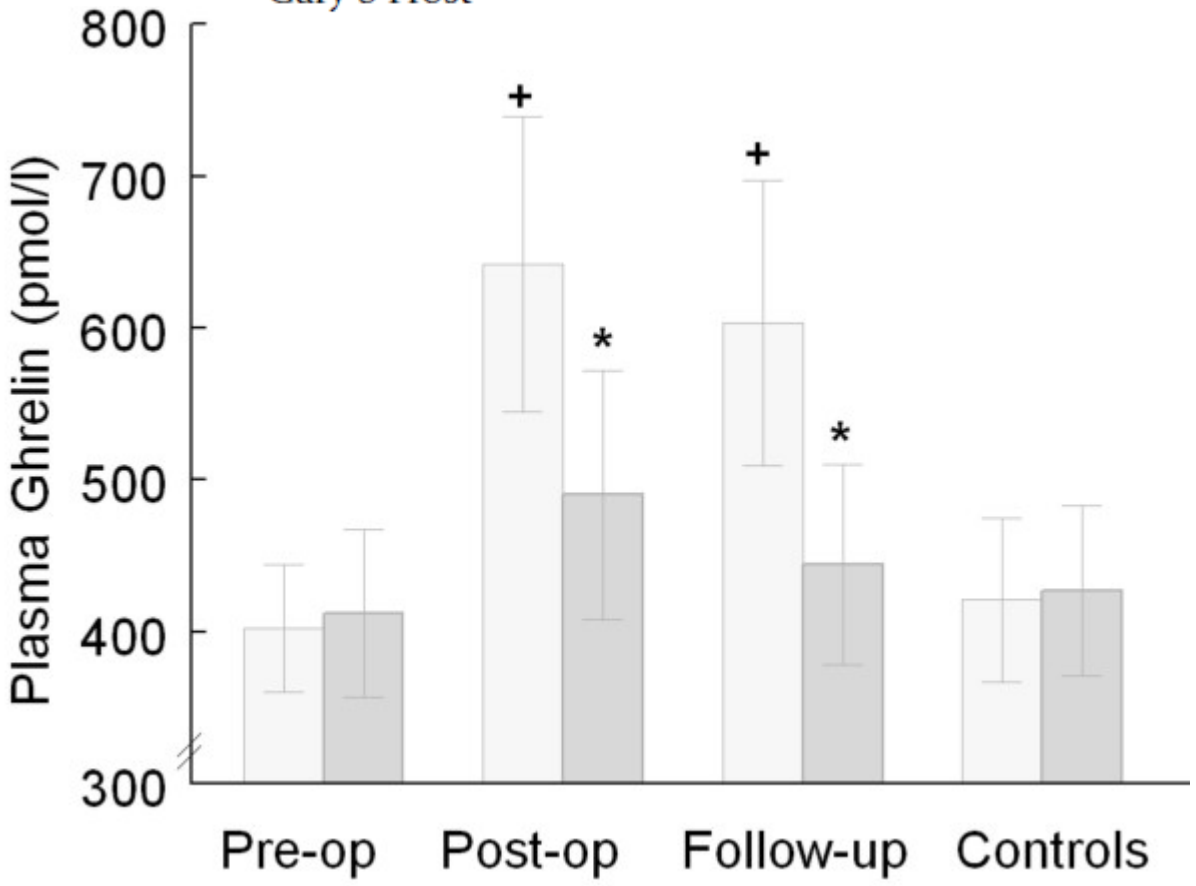
Brief communication

Open Access

Postprandial ghrelin suppression is exaggerated following major surgery; implications for nutritional recovery

Mohsen Nematy[1,2], Audrey E Brynes[1], Philip I Hornick[3], Michael Patterson[4], Mohammad A Ghatei[4], Stephen R Bloom[4], Stephen J Brett[5] and Gary S Frost*[6]

Nutrition & Metabolism 2007, 4:20

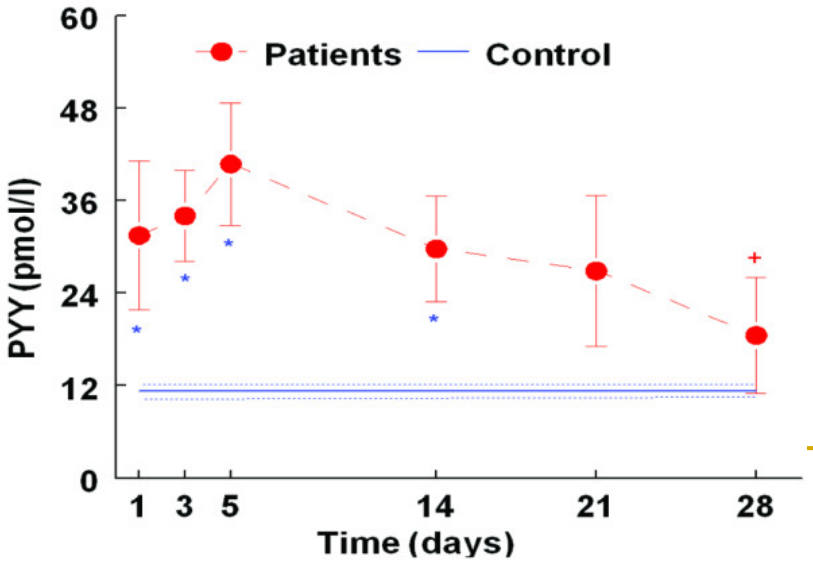


Fasting (light grey bars) and postprandial (dark grey bars) plasma ghrelin concentrations (mean ± SEM) 45 minutes following the start of a test meal in 17 coronary artery bypass grafting patients (CABG) and matched controls,
+ $p < 0.05$ fasting postop versus fasting preop & controls, fasting follow-up versus fasting preop & controls ;
** $p < 0.05$ Δ change postop & follow-up versus preop & controls (ANOVA).*

Peptide YY (PYY)

Gut failure in the ICU.
Puleo F, Arvanitakis M, Van Gossum A, Preiser JC.
Semin Respir Crit Care Med. 2011 Oct;32 (5):626-38.

- Secreted by colon, rectum, pancreas, small intestine, stomach;
- Pharmacological doses slow gastric emptying, small intestine transit and inhibits appetite;
- Fasting concentration of PYY increased in critically ill;



Adrian TE, et al. Gastroenterology 1985
Nematy M, et al. Crit Care 2006

0148-6071/06/3006-0530$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 30, No. 6
Printed in U.S.A.

Brief Communication

Peptide YY (PYY) Is Increased in Elderly Patients With Femoral Neck Fractures: A Prospective Cohort Study

Mohsen Nematy, MD*‖; Chris A. Powell, BSc, MBChB†; Audrey E. Brynes, PhD*:
Michael Pearse, FRCP(orth)†; Michael Patterson, BSc‡; Mohammad A. Ghatei, PhD‡;
Steve R. Bloom, MD, DSc‡; and Gary S. Frost, PhD, SRD§

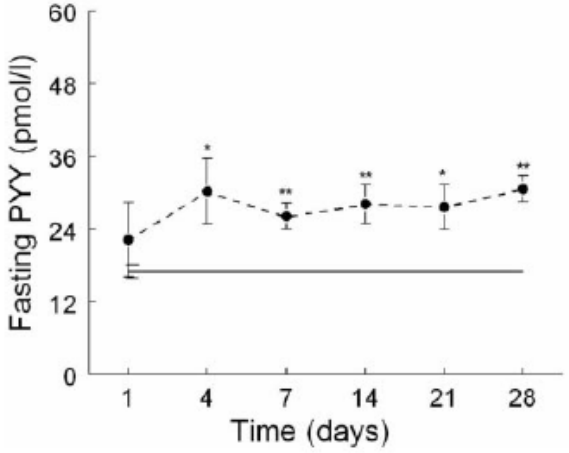


FIGURE 1. Longitudinal fasting PYY concentrations in 17 elderly patients with femoral neck fracture (FNF; solid circles) and matched control subjects (solid line). The overall repeated-measures ANOVA was significant at $p < .01$. *Post hoc* analysis of control *vs* FNF is represented as $*p < .05$; $**p < .005$ *vs* controls.

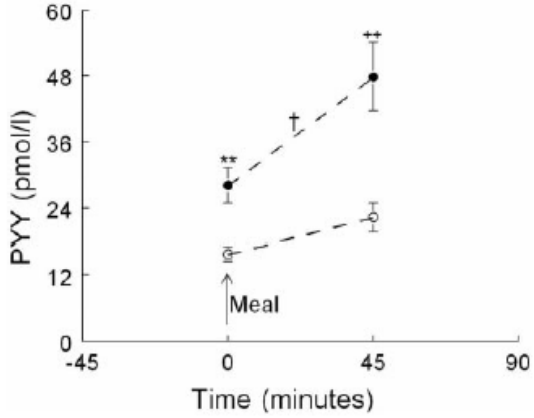


FIGURE 2. Fasting and postprandial pattern of PYY in 13 patients with femoral neck fracture (FNF; solid circles) and matched control subjects (open circles). $**p < .005$ fasting patients *vs* controls; †Δ PYY patients *vs* control subjects; $++p < .005$ postprandial patients *vs* controls.

The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients*

Nam Q. Nguyen, MBBS (Hons), FRACP, PhD; Robert J. Fraser, MBBS, FRACP, PhD; Laura K. Bryant, BHSc; Carly Burgstad, BHSc; Marianne J. Chapman, BMBS, FANZCA, FJFICM; Max Bellon, Dip Med Tech, A Dip Nuc Med; Judith Wishart, BSc; Richard H. Holloway, MBBS, FRACP, MD; Michael Horowitz, MBBS, FRACP, PhD

Crit Care Med 2008;36:1469

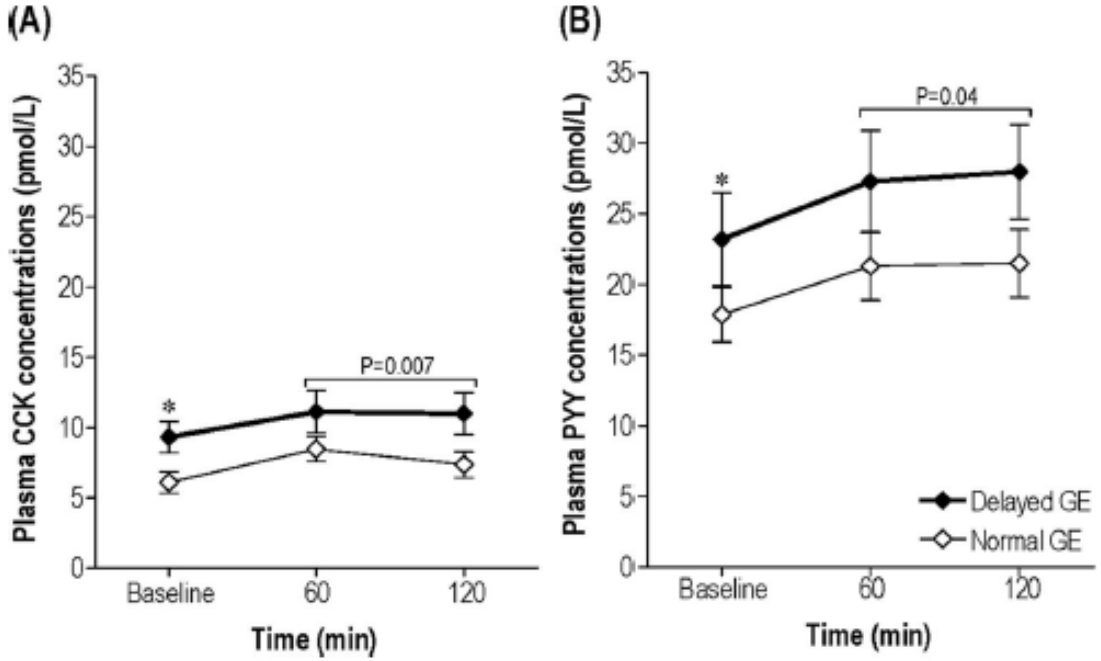
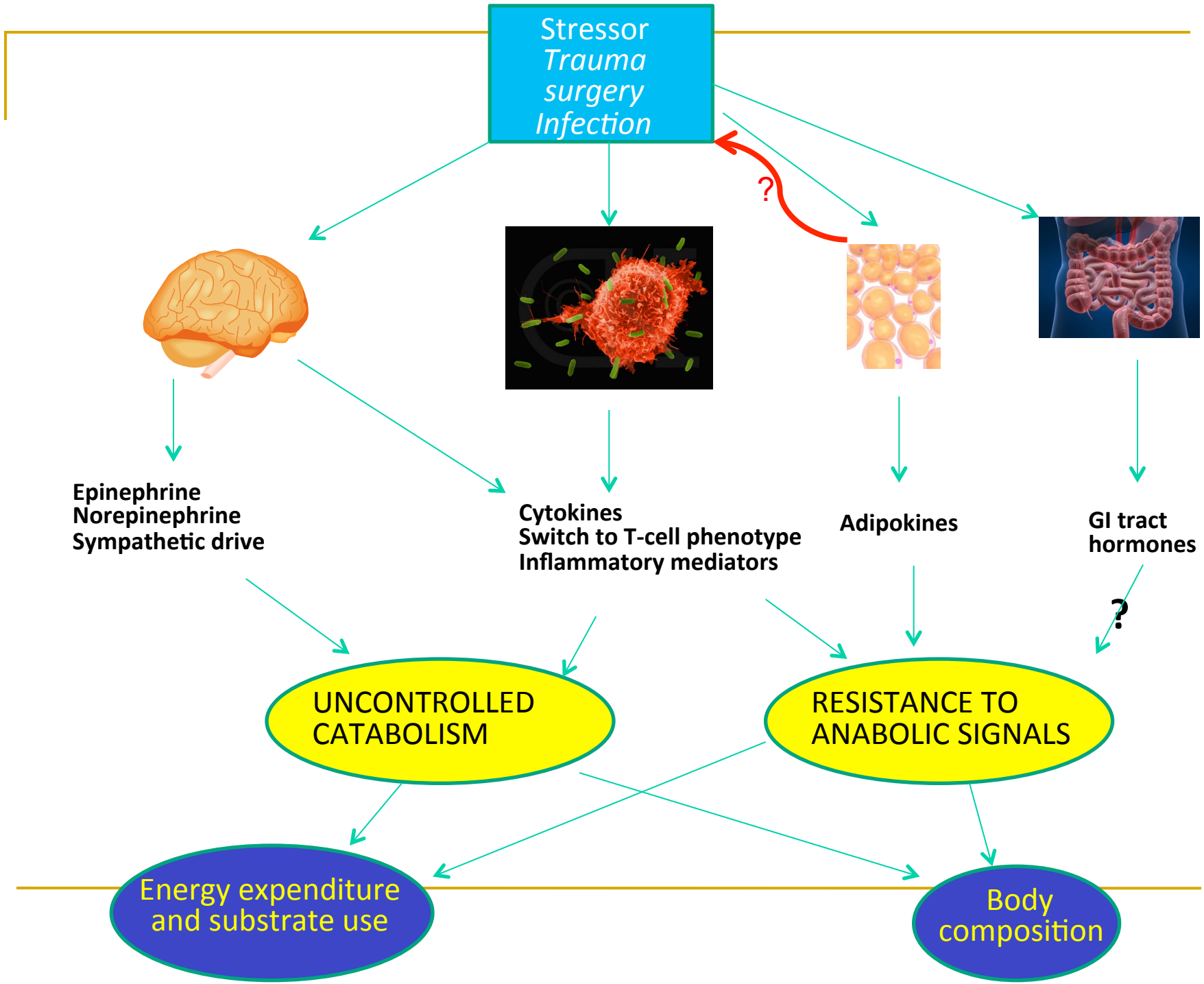


Figure 3. Plasma concentrations of cholecystokinin (*CCK*) (*A*) and peptide YY (*PYY*) (*B*) during fasting and postprandially in critically ill patients who had normal (◇) and delayed (◆) gastric emptying (*GE*). *$p < 0.05$, patients with normal GE.

In summary

- Circulating levels of orexigenic hormones, typically ghrelin, are decreased
- Circulating levels of anorexigenic hormones, typically PYY are increased


Stressor
Trauma
surgery
Infection
?
Epinephrine
Norepinephrine
Sympathetic drive
Cytokines
Switch to T-cell phenotype
Inflammatory mediators
Adipokines
GI tract
hormones
?
UNCONTROLLED
CATABOLISM
RESISTANCE TO
ANABOLIC SIGNALS
Energy expenditure
and substrate use
Body
composition

Endotoxin and Cytokines Induce Expression of Leptin, the *ob* Gene Product, in Hamsters

A Role for Leptin in the Anorexia of Infection

Carl Grunfeld,* Connie Zhao,‡ John Fuller,* Allan Pollock,* Arthur Moser,* Jeffrey Friedman,‡ and Kenneth R. Feingold*
**Department of Medicine, University of California, San Francisco and Medical Service, Department of Veterans Affairs Medical Center, San Francisco, California 94121; and ‡Laboratory of Molecular Genetics and Howard Hughes Medical Institute, The Rockefeller University, New York 10021*

(*J. Clin. Invest.* 1996. 97:2152–2157.)

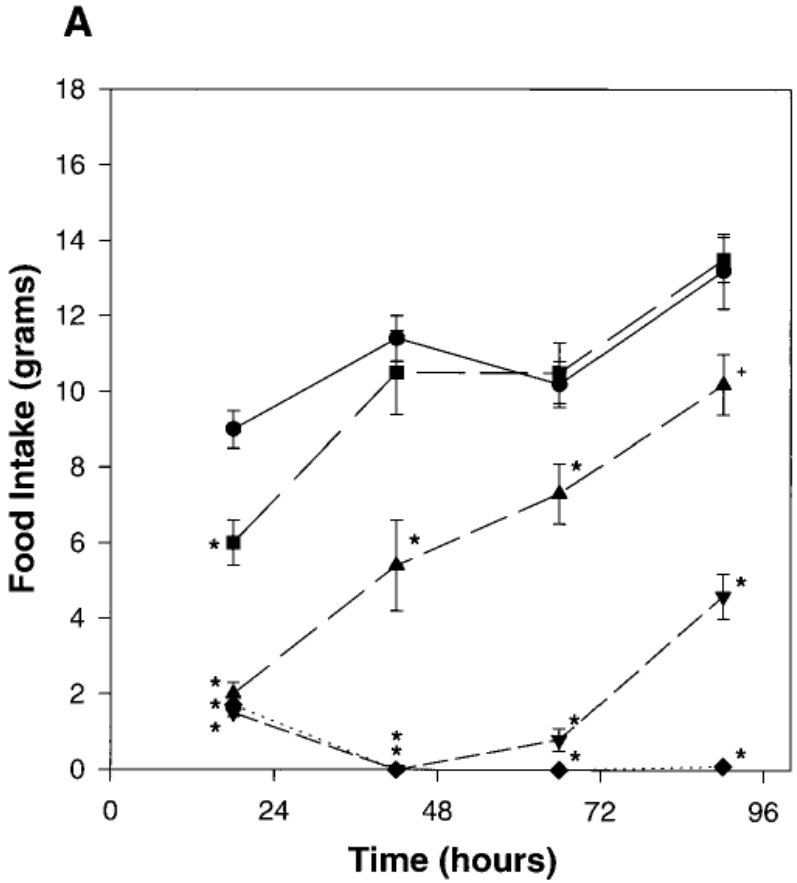


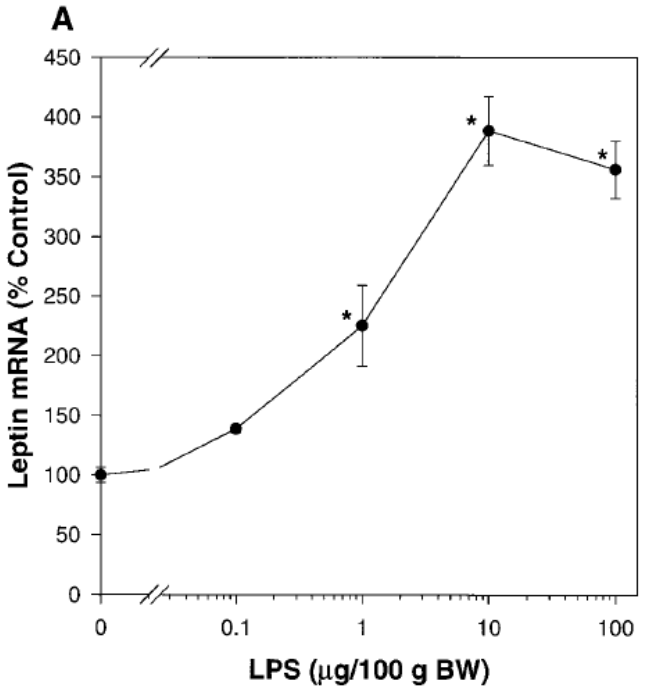
Figure 1. The effect of LPS on food intake and body weight in hamsters. At 4:00 p.m. hamsters were given either normal saline (*circles*) or 0.1 μg (*squares*), 1 μg (*triangles*), 10 μg (*inverted triangles*), or 100 μg (*diamonds*)/100 g BW of LPS. Animals were maintained in individual Nalgene metabolic cages. Food intake (*A*) and weight (*B*) were measured at the times indicated. $n = 5$ for each group. Values are mean±SEM. $^{*}P < 0.01$ vs. control. $^{***}P < 0.05$ vs. control.

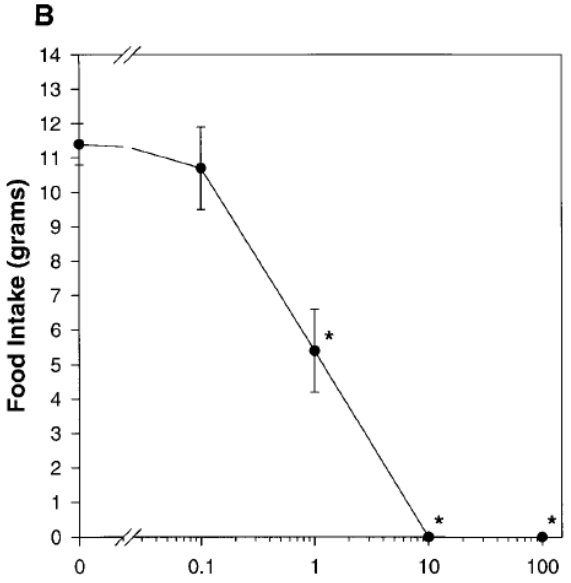
Endotoxin and Cytokines Induce Expression of Leptin, the *ob* Gene Product, in Hamsters

A Role for Leptin in the Anorexia of Infection

Carl Grunfeld,* Connie Zhao,‡ John Fuller,* Allan Pollock,* Arthur Moser,* Jeffrey Friedman,‡ and Kenneth R. Feingold*
**Department of Medicine, University of California, San Francisco and Medical Service, Department of Veterans Affairs Medical Center, San Francisco, California 94121; and ‡Laboratory of Molecular Genetics and Howard Hughes Medical Institute, The Rockefeller University, New York 10021*

(*J. Clin. Invest.* 1996. 97:2152–2157.)





Multiple Cytokines and Acute Inflammation Raise Mouse Leptin Levels: Potential Role in Inflammatory Anorexia

Pasha Sarraf,* Robert C. Frederich,‡ Ewa M. Turner,* Grace Ma,*
Nora T. Jaskowiak,* Dennis J. Rivet III,* Jeffrey S. Flier,‡
Bradford B. Lowell,‡ Douglas L. Fraker,* and H. Richard Alexander*

The Journal of Experimental Medicine • Volume 185, Number 1, January 6, 1997 171–175

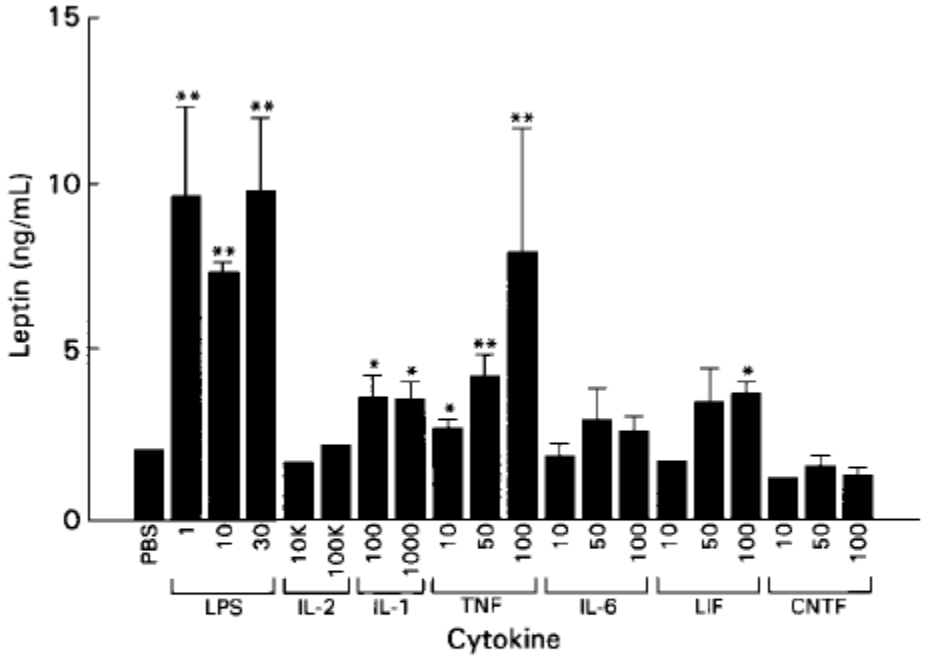


Figure 2. Leptin levels after i.p. administration of various cytokines and LPS. Mice were injected with LPS (mg/kg) or recombinant cytokine in the doses shown (IL-2, IL-1: U/mouse; TNF, IL-6, LIF, CNTF: μg/kg) or PBS after a 7-h fast and sera and adipose tissue harvested 5 h later. Further details are in Materials and Methods. Each bar represents the mean ± SEM serum leptin level of 6–7 mice. Significance compared with the PBS-treated animals is indicated as $^{*}P < 0.05$, $^{**}P < 0.01$.

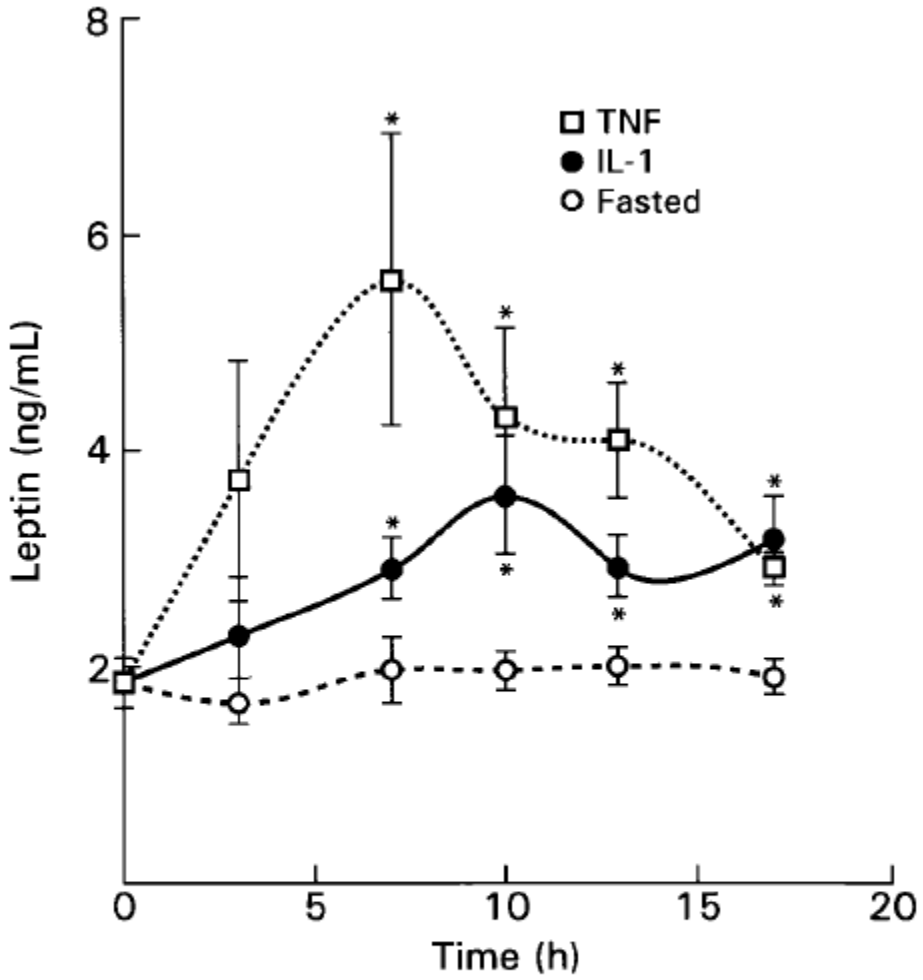


Figure 4. Kinetics of leptin in sera from mice injected with 100 μg/kg of TNF or 1,000 U of IL-1, after a 7-h fast. All animals were food-deprived during the experimental period. Each point represents mean ± SEM leptin level of 5–6 mice, except for the 13-h points, which represent 10–14 mice. Compared with fasted controls, significant differences are indicated as $^{*}P < 0.05$.

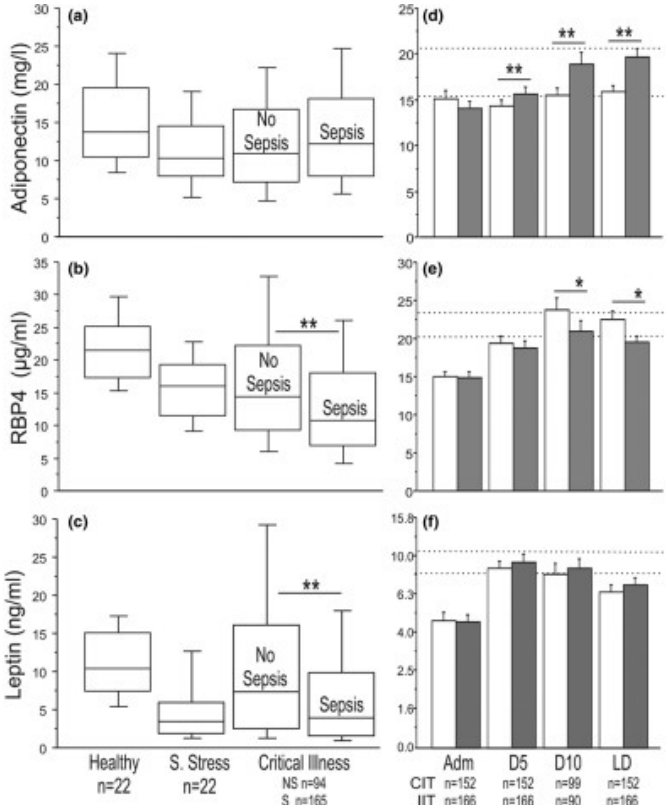
Research

Open Access

Adiponectin, retinol-binding protein 4, and leptin in protracted critical illness of pulmonary origin

Lies Langouche[1], Sarah Vander Perre[1], Jan Frystyk[2], Allan Flyvbjerg[2], Troels Krarup Hansen[3] and Greet Van den Berghe[1]

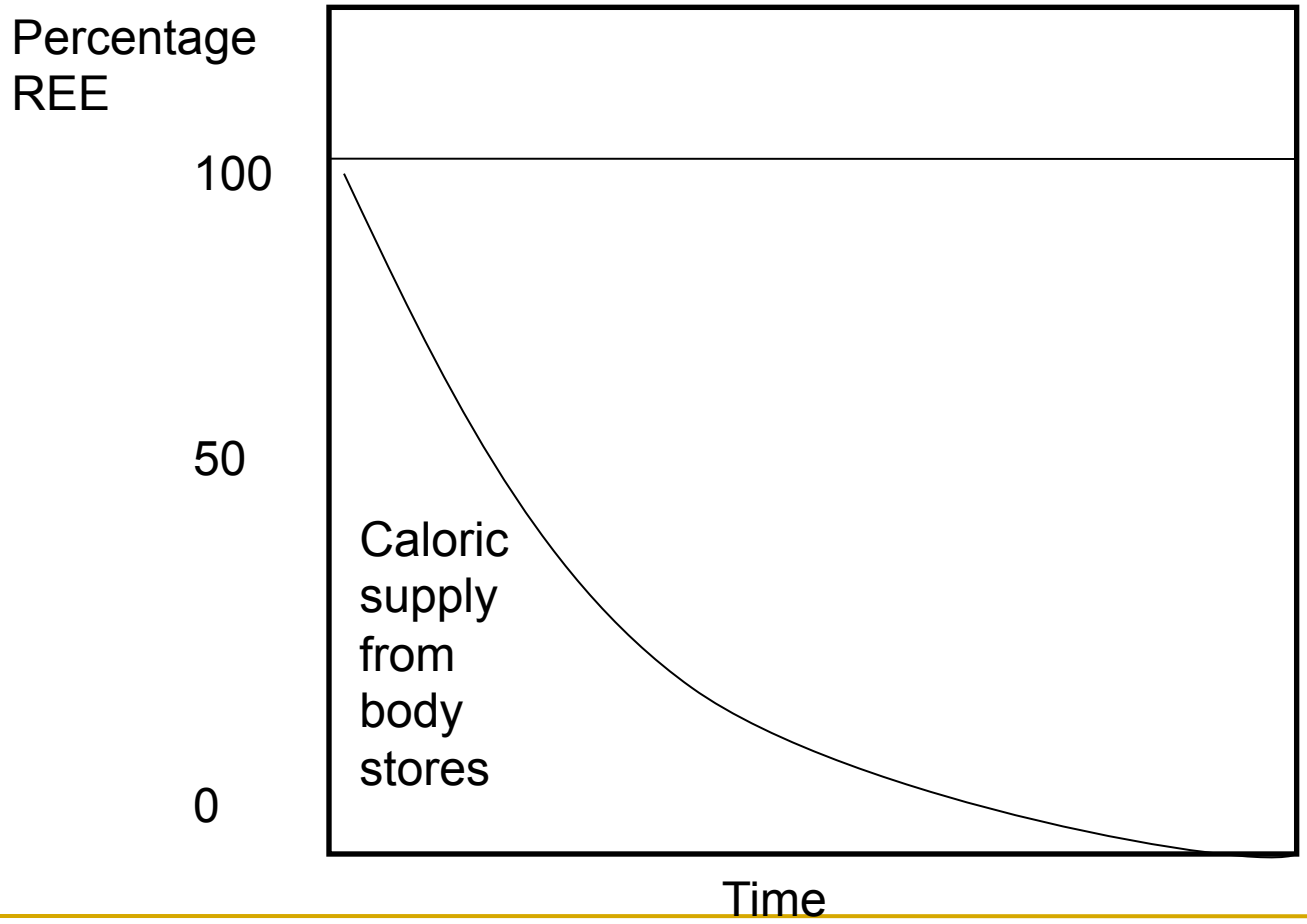
Critical Care 2009, **13**:R112 (



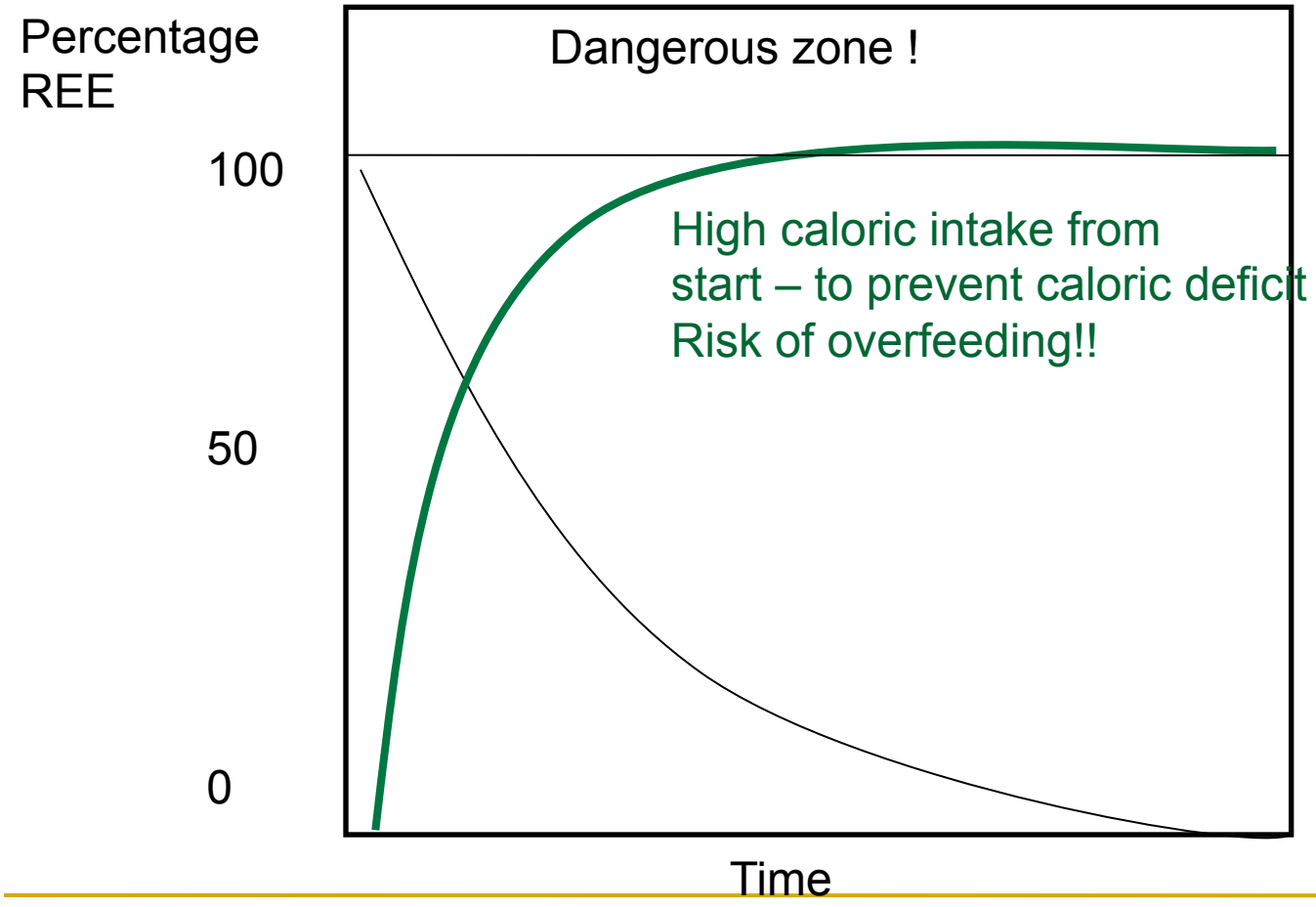
Circulating adipokines during critical illness. **(a-c)** Impact of acute illness: Results from healthy volunteers, patients not critically ill undergoing elective surgery, and critically ill patients on admission to the ICU are presented as box plots (boxes are medians and interquartile ranges; whiskers are 10th and 90th percentiles). **(d-f)** Critically ill patients who received CIT (white bars) or IIT (gray bars). Reference values (mean ± SEM) of healthy controls are indicated by two horizontal dotted lines. Adm = admission day; D5 = day 5; D10 = day 10; LD = the last day of ICU stay; ICU = intensive care unit. Data are presented as mean ± SEM. $^{*}P \leq 0.05$; $^{**}P \leq 0.01$. For statistical analysis, we subtracted corresponding admission-day values, and for leptin, we used log-transformed data as indicated on the figure.

Implications pratiques???

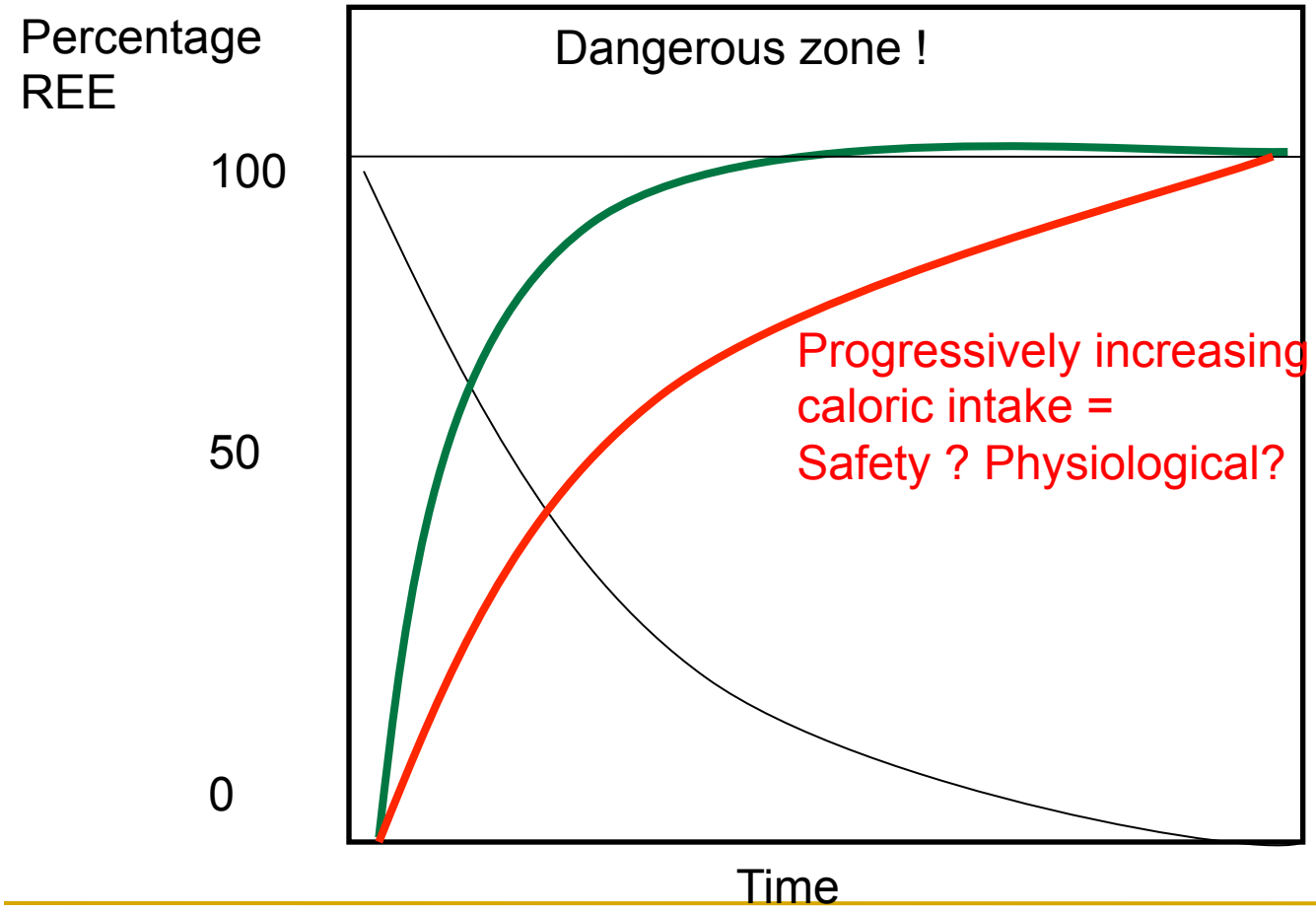
The daily clinical question : How many calories should be prescribed?



How many calories should be prescribed?



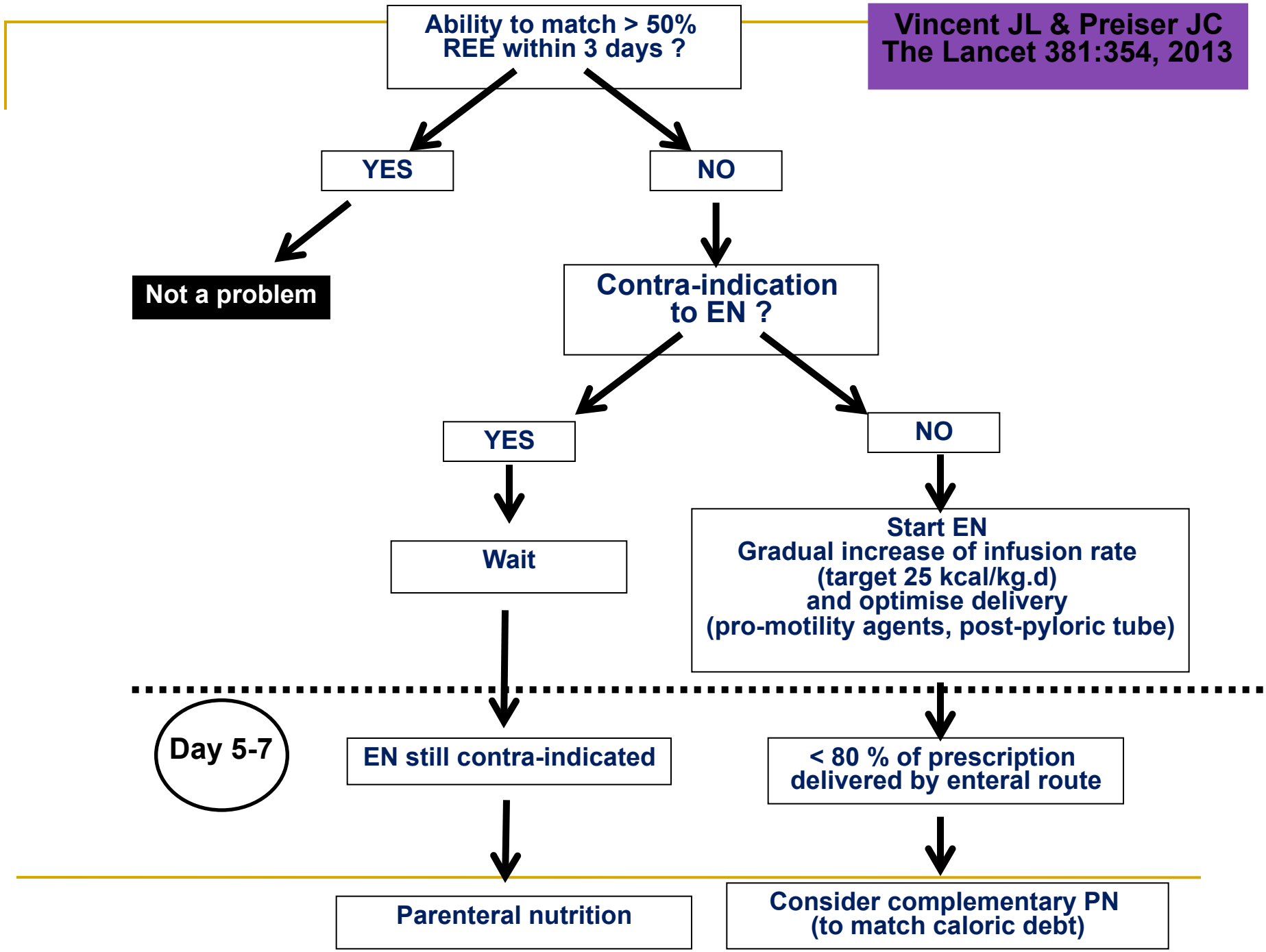
How many calories should be prescribed?

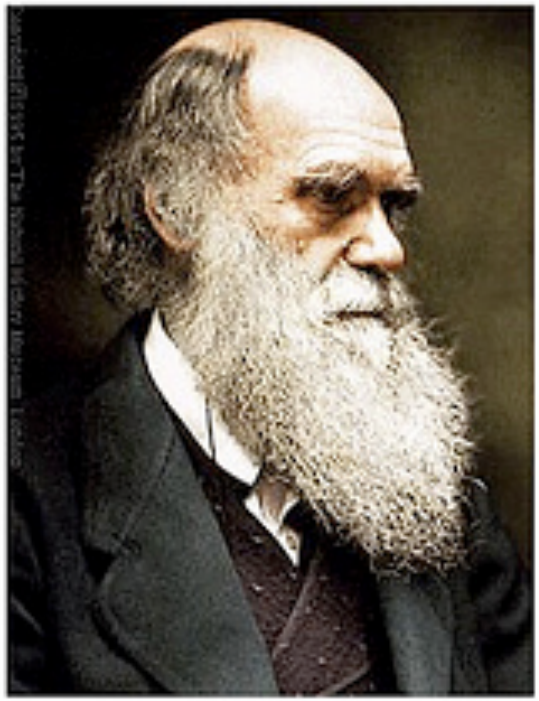


RFE nutrition

2.2 Il faut probablement limiter le déficit énergétique précoce (dépenses moins apports cumulés) durant la 1ère semaine pour réduire la morbi-mortalité en réanimation (Accord Fort)

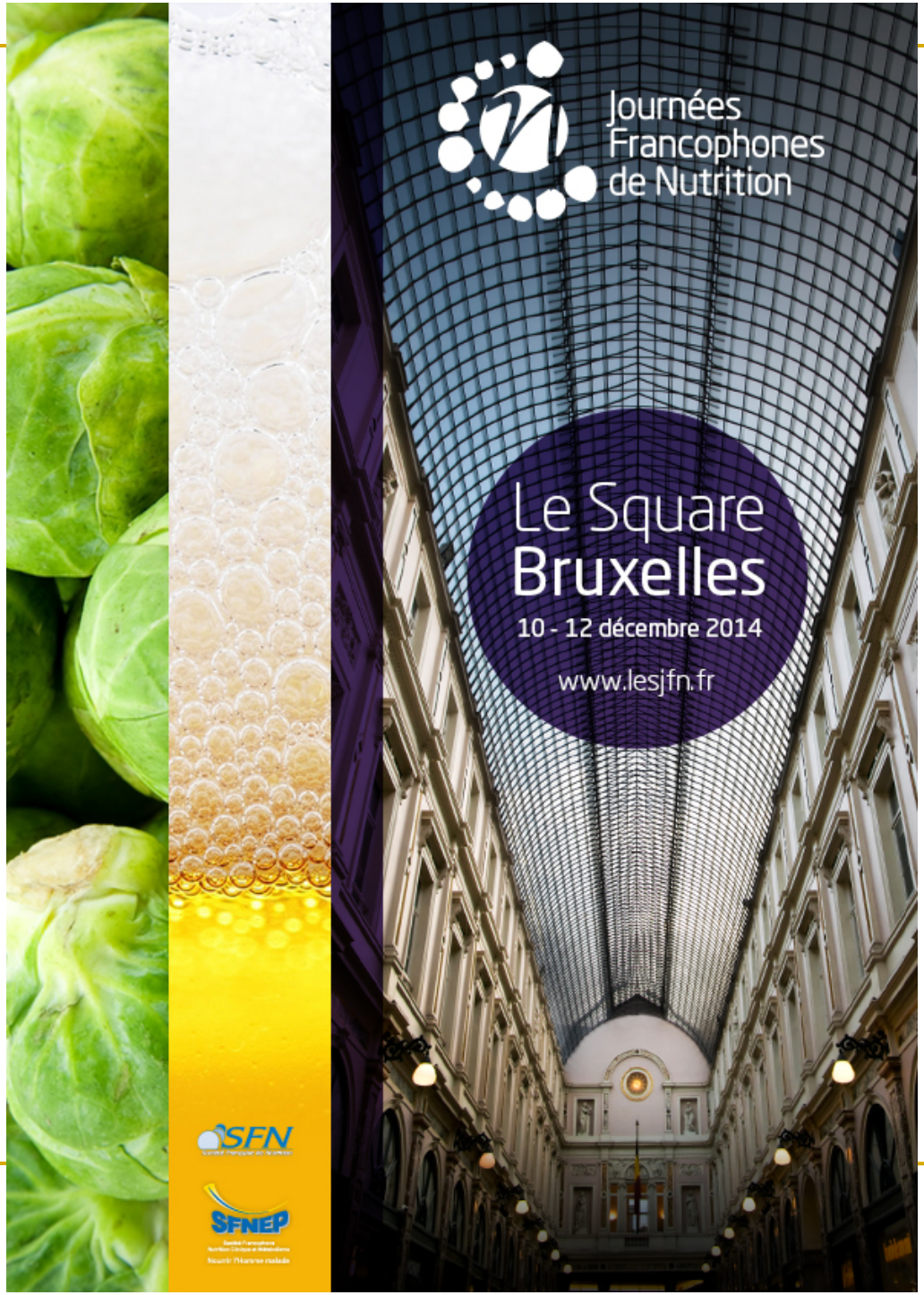
- ***En fonction de l'intensité de l'agression, un déficit énergétique peut s'installer précocement pendant la première semaine (> 100 kcal/kg cumulés). Limiter plus que corriger complètement ce déficit énergétique précoce constitue probablement la stratégie d'assistance nutritionnelle la plus raisonnable. En effet, sur- ou sous-compenser les besoins énergétiques de façon excessive majore le risque de complications.***


Ability to match > 50% REE within 3 days ?
Vincent JL & Preiser JC
The Lancet 381:354, 2013
YES
NO
Not a problem
Contra-indication to EN ?
YES
NO
Wait
Start EN
Gradual increase of infusion rate
(target 25 kcal/kg.d)
and optimise delivery
(pro-motility agents, post-pyloric tube)
Day 5-7
EN still contra-indicated
< 80 % of prescription delivered by enteral route
Parenteral nutrition
Consider complementary PN
(to match caloric debt)



- L’anorexie constitue l’un des mécanismes adaptatifs plausibles à la phase aigue de l’agression

- Les hormones digestives et les adipokines sont vraisemblablement impliquées dans cette réponse


Journées
Francophones
de Nutrition
Le Square
Bruxelles
10 - 12 décembre 2014
www.lesjfn.fr
SFN
SFNEP