THE PHYSIOLOGICAL IMPACT OF TRAUMA AND INFECTION

= The Metabolic Response to Stress

JP Pretorius
Head: Department of Critical Care
Head: Clinical Unit Surgical/Trauma ICU
University of Pretoria &
Steve Biko Academic Hospital
Characteristics of Surgical Stress

- Hypermetabolism
- Protein catabolism
- Insulin resistance
- Salt and water sequestration

The metabolic response to stress ...... and much, much MORE !!!!!
Metabolic Response

- ↑ BMR
- Negative Nitrogen balance
- Increased gluconeogenesis
- Increased synthesis of acute phase proteins

BUT......how does this reaction or process evolve or develop ?

WHAT stimulates or initiates this change ?
Table 8-3. **Stimuli resulting from injury.**

1. An injury and a major operation are similar in that they produce the same stimuli. Factors that trigger a biologic response and reset the homostatic thermostat are as follows:
   - Anxiety, fear, pain
   - Starvation
   - Immobilization
   - Anesthetic agents
   - Tissue injury
   - Blood and body fluid (extracellular fluid) loss
   - Drugs
   - Infection

2. Factors that produce only minor transient changes (an inguinal hernia, laparoscopic cholecystectomy, open cholecystectomy, modified radical mastectomy):
   - Pain, fear, fatigue
   - Anesthesia and drugs
   - Immobilization
   - Transient starvation

3. Factors that produce major, extensive efforts:
   - Multisystem injury
     - Long bone and pelvic fractures
     - Organ injury—spleen, liver, lung, bowel, heart
   - The wound
     - Tissue injury
     - Tissue necrosis
     - Major burns
   - Invasive sepsis
   - Shock
   - Prolonged starvation
<table>
<thead>
<tr>
<th>Extent of Injury</th>
<th>Neuroendocrine, Metabolic, Cytokine, and Immune Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal surgery: Laparoscopy, thoracoscopy, inguinal hernia repair, no large incision into body cavity</td>
<td>Minimal and appropriate. Minor changes in the homeostatic thermostat.</td>
</tr>
<tr>
<td>Major surgery and non-life-threatening injury: Large incision into a body cavity or multisystem injury</td>
<td>Major changes that seem to be interrelated and coordinated. Homeostasis as we understand it seems evident.</td>
</tr>
<tr>
<td>Life-threatening injuries, operations, or illnesses</td>
<td>Biologic chaos—dyshomeostasis. The individual is overwhelmed by the multiplicity of changes that should be protective but become self-destructive.</td>
</tr>
</tbody>
</table>
A Constellation of Changes in the Host

PEARLS!.....

• Injury and infection invoke a constellation of changes in the host
• A transitory ebb or shock or hypometabolic phase develops first (conservation, protection)
• This is followed by a flow or hypermetabolic phase (mobilisation, preparation, self-preservation)
• The magnitude of the response is proportional to the extent of the injury
• Comorbid conditions will impact on the response
• Therapeutic procedures will impact on the response

Will modulation of the stress response benefit or improve survival?
A Constellation of Changes in the Host

How are the different components of this composite and intricate process related?

... the "psycho-"

to the "neuro-"

to the "endocrine-"

to the "metabolic-"

to the "immunologic" component ????

Does it reflect order or chaos?

What does getting sick means?
Table 8–2. Phases of the response to moderate injury.

1. **Injury phase.** Lasts 2–5 days or longer. Duration is related to the magnitude or “dose” of injury and the presence or absence of complications.

2. **Turning point.** The neuroendocrine response turns off. A transient period. May occur overnight or develop over 1 or 2 days.

3. **Anabolic phase.** Gain in muscular strength. Phase of positive nitrogen balance. Lasts 3–12 weeks or longer.

4. **Late anabolism.** Gain in weight and body fat. Phase of positive caloric balance. **Lasts months to years.**
The *Psycho-neuro-endocrino-immune* response

= A total body, all systems, all cells compensatory response intent on self-preservation

= Host defense!

= Maintenance of HOMEOSTASIS
Schema of the host stress response to injury. The afferent arc initiated by the postinjury inflammation initiates an efferent hormonal response, which can be amplified by central nervous system stress. The result is hypermetabolism and catabolism.
Schema of the metabolic response to stress
Components involved in the development of the Coagulopathy of Trauma
Table 8-6. Hormonal changes and systemic effects of injury.

Major changes
- Stress hormones increased
  - Cortisol
  - Catecholamines
  - Glucagon
- Volume control hormones increased
  - Renin-angiotensin, aldosterone
  - Arginine vasopressin (ADH)
- Sex hormones decreased
- Thyroid T₃ decreased
- Thyroid rT₃ increased
- Wound mediators increased

Results
- Hypermetabolism
- Proteolysis
- Wound healing begins in spite of negative nitrogen balance
- Lipolysis
- Extracellular water gain
- High glucose production for anaerobic cells of wound healing
Figure 11-5. The metabolic response to trauma is a result of neuroendocrine stimulation, which accelerates protein breakdown, stimulates gluconeogenesis, and produces glucose intolerance.
<table>
<thead>
<tr>
<th>Visceral</th>
<th>Humoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle proteolysis through the ubiquitin-proteosome pathway</td>
<td></td>
</tr>
<tr>
<td>Decreased muscle protein synthesis</td>
<td></td>
</tr>
<tr>
<td>Initial increased gut mucosal synthesis and export</td>
<td></td>
</tr>
<tr>
<td>Hepatic protein synthesis (acute phase reactants)</td>
<td></td>
</tr>
<tr>
<td>Hepatic gluconeogenesis</td>
<td></td>
</tr>
<tr>
<td>Lung response (glutamine)</td>
<td></td>
</tr>
<tr>
<td>Kidney response</td>
<td></td>
</tr>
</tbody>
</table>
Figure 11-6. During sepsis, cytokines (IL-1, IL-2, TNF) released by lymphocytes and macrophages contribute to catabolism of muscle protein and adipose tissue and amplify the neuroendocrine response to antecedent trauma.
Cytokines
Platelet-activating factor (PAF)
Complement
Kinins and kallikreins
Endorphins
Neutrophils, superoxydes, proteases
Immune complexes
Histamine
Nitric oxide (NO₂), endothelium-derived relaxing factor (EDRF)
Myocardial depressant factor (MDF)
Adhesion molecules
Coagulation cascades
Serotonin
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Main cell targets</th>
<th>Main actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 1α</td>
<td>Monocytes, macrophages</td>
<td>Neutrophils, T and B lymphocytes, thymocytes, skeletal muscle, hepatocytes</td>
<td>Immunoregulation, inflammation, fever (endogenous pyrogen), anorexia, sleep, acute-phase protein synthesis, muscle proteolysis, ↑ gluconeogenesis, lymphocyte activation, IL-6 and CSF (colony-stimulating factors) production</td>
</tr>
<tr>
<td>Interleukin 1β</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>Monocytes, fibroblasts, T cells</td>
<td>T and B lymphocytes, thymocytes, hepatocytes</td>
<td>Acute-phase protein synthesis (synergises with IL-2 in the production of acute phase proteins by hepatocytes), synergises with IL-3 in haematopoietic cell growth, immune cell differentiation, induces CTL (cytotoxic T lymphocyte) differentiation</td>
</tr>
<tr>
<td>Tumour necrosis factor α</td>
<td>Monocytes, macrophages</td>
<td>Fibroblasts, endothelium, skeletal muscle, hepatocytes</td>
<td>As for IL-1, induces IL-1, induces IFN-γ secretion</td>
</tr>
</tbody>
</table>

*Adapted from reference 26.
Table III. The major human acute phase proteins\textsuperscript{7,22}

<table>
<thead>
<tr>
<th>Positive APP</th>
<th>Negative APP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low rise:</td>
<td>Marked rise:</td>
</tr>
<tr>
<td>± 50% increase</td>
<td>up to 1 000x increase</td>
</tr>
<tr>
<td>Caeruloplasmin</td>
<td>Decreased plasma concentrations</td>
</tr>
<tr>
<td>Complement C3</td>
<td>Albumin</td>
</tr>
<tr>
<td>Complement C4</td>
<td>Pre-albumin</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>Transferrin</td>
</tr>
<tr>
<td>α$_1$-acid glycoprotein</td>
<td>RBP</td>
</tr>
<tr>
<td>α$_1$-antitrypsin</td>
<td>Fibronectin</td>
</tr>
<tr>
<td>α$_1$-antichymotrypsin</td>
<td></td>
</tr>
<tr>
<td>Haptoglobin</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
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</table>
Cytokine link to Metabolic + Immune reactions

**METABOLIC EFFECTS**

- Fever
- Anorexia
- Acute phase proteins
- Altered copper, zinc & iron metabolism
- Enhanced anti-oxidant defences
- Muscle proteolysis
- Gluconeogenesis
- Nitric oxide & free radical generation

**Inflammatory stimuli** → **IL-1** → **TNF Production** → **IL-6** → **Nutrients and accessory products**

**IMMUNE SYSTEM ACTIVATION & MODULATION**

- IL-2
- IL-3
- IL-4
- IL-8

- T cell proliferation
- Haematopoiesis
- Ig class switching
- Chemotaxis

= metabolic fuel
BUT ......

The process can go the wrong way!

(Murphy’s 1st law?)

TIME TO SOURCE CONTROL !!!!!
Prevention is the best cure for MODS + MOF
FIGURE 4. New concepts for the clinical sequelae of sepsis, SIRS, CARS, and MARS. (This figure is an adaptation of Figure 1 by Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 1996; 24:1125-28.)
HOST DEFENSE

“Psycho-neuro-endocrinology”

Controlled, Balanced Integration of:

• Neuro-endocrine response
• Metabolic and biochemical adaptation
• Inflammatory response
• Immunological reactions in blood and tissue

“General Adaptation Syndrome”

Hans Selye
STRESS RESPONSE

The Threat:
Shock $\rightarrow$ Resuscitation $\rightarrow$ Hypermetabolism $\rightarrow$ MODS $\rightarrow$ MOFS

Resuscitation in progress
Early...........Transition in emphasis over time............Later

The Solution:
Tissue oxygen delivery
$= \text{perfusion deficit}$
Cardiopulmonary resuscitation

Cell metabolic regulation
$= \text{substrate deficit}$
Metabolic resuscitation

Cell metabolic regulation

Tissue oxygen delivery
HOMEOSTASIS

SUCCESSFUL SUPPORTIVE THERAPY

FOR CRITICALLY ILL PATIENTS

DEPENDS ON METABOLIC RESUSCITATION
### Characteristics of Metabolic Phases Occurring After Severe Injury

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>“Conservation”</td>
<td>“Preparation”</td>
<td>“Rebuilding”</td>
</tr>
</tbody>
</table>

- **Hypovolemic Shock**  
  - ↓ tissue perfusion  
  - ↓ metabolic rate  
  - ↓ oxygen consumption  
  - ↓ blood pressure  
  - ↓ body temperature

- Catabolism predominates  
  - ↑ glucocorticoids  
  - ↑ glucagon  
  - ↑ catecholamines  
  - Release of cytokines, lipid mediators  
  - Production of acute phase proteins  
  - ↑ excretion of nitrogen  
  - ↑ metabolic rate  
  - ↑ oxygen consumption  
  - Impaired utilization of fuels

- Anabolism predominates  
  - Hormonal response gradually diminishes  
  - ↓ hypermetabolic rate  
  - Associated with recovery  
  - Potential for restoration of body protein.  
  - Wound healing depends in part on nutrient intake
Effects of injury, sepsis and nutritional depletion on resting energy expenditure

-40 -30 -20 -10 Normal

+110 +100 +90 +80 +70 +60 +50 +40 +30 +20 +10

Third degree burns
>20% BSA
Head injury

Severe infection
Multiple fractures

Postoperative
Partial starvation
Genetic Influences

Modulation by nutrients

Effect of genotype

- Pro- & anti-inflammatory Cytokine biology
- Heat Shock proteins
- Immune function
- Clinical outcome
- Transcription factors
- Oxidant/Antioxidant balance
- Interorgan Substrate flow

Effect of genotype
The Latest on Inflammation!

- Human genome project
- Baseline level of preconditioning
  = ability of the host to tolerate and respond to an insult without severe disturbance to homeostasis
- Degree of preconditioning
- Simultaneous pro- and anti-inflammatory responses
Table 1. Summary: Hyperglycemia and immune function

<table>
<thead>
<tr>
<th>Component of immune system</th>
<th>Effect of hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphonuclear cells</td>
<td>Impaired phagocytosis, Impaired chemotaxis, Decreased bactericidal activity, Decreased adherence, Increased apoptosis</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Decreased response (all subsets)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Impaired chemotaxis, Impaired phagocytosis, Decreased respiratory burst</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Non-enzymatic glycosylation, Decreased concentrations (IgA, IgG, IgM)</td>
</tr>
<tr>
<td>Collectins (SP-A, SP-D)</td>
<td>Non-enzymatic glycosylation, Impaired opsonization</td>
</tr>
</tbody>
</table>
Gut as Motor of MODS - A Vicious Circle?

- Intra-abdominal Pressure
- Mucosal Breakdown
- Capillary leak
- Free radical formation
- Bacterial translocation
- Acidosis
- Decreased O2 delivery
- Anaerobic metabolism

MSOF (Multi-System Organ Failure)
The Mucosal Barrier: Is It the Motor for MOF?
The Latest on Inflammation!

- Despite improvement in care, Multiple Organ Failure continues to cause significant morbidity + mortality
- “Shock” >>> organ ischaemia >>> critical for development of MODS + MOF
- MOF is a gut-derived phenomenon
  70’s+80’s > improved resuscitation > ICU > MOF epidemic
- 90’s > understanding of MOF improves outcome – still the prime cause of ICU deaths + prolonged stay
- Roles of Trauma + Sepsis > early and late MOF

View of MOF in the 1990s: dysfunctional inflammation causes MOF.
Current evolving view of MOF: unbalanced early pro-inflammation.
Alternative intervention to balance anti-inflammation will enhance preconditioning, leading to improve healing that will enable patients to recover. Alternative treatments include use of ketamine as a sedative/analgesic agent, immune enhancing nutritional modulation, liberal use of fresh frozen plasma, and body temperature maintenance.
Global view of shock. Shock is common to trauma, bleeding and sepsis, with each sharing some common biologic pathways with the other as well as possessing their own unique characteristics and treatments.
CONCLUSION

RF Grimble

The “psycho-neuro-immuno-endocrine response” to injury or infection functions to enhance the possibility of survival without treatment
Survival of an individual often depends on the effectiveness of regulatory systems in changing the priority given to different physiologic processes, particularly those that exert a large metabolic demand.
For the infected individual, marshalling of resources to combat invading pathogens must assume a priority over all other physiologic demands.
After the invasion has been repulsed and the damaged done by the invader repaired, priorities normally given to other physiological processes can be restored.
The high priority given to combating pathogens is necessary because of the speed with which pathogens multiply after they are established within the host.
Clearly, the provision of nutrients to allow the immune system to function correctly cannot be left to chance.

Thus, cytokines act as modulatory agents by which the activity of the system is changed and metabolic activity of the host is directed toward providing nutrients for the system.
The enhanced production of cytokines and oxidants, which follows pathogenic invasion and injury, although designed to combat the invader, carries the potential to damage the host. Damage is limited by concurrent enhancement of the antioxidant defenses of the host and activation of systems for retaining cytokine production within healthful confines, as discussed earlier.
The future challenge for the clinician and scientist working within the field of nutrition will be in determining how the nature of the nutrient-cytokine interactions, identified in the experimental context, can be used to achieve a healthful diet and clinical benefit.
1. The Gut in Systemic Inflammatory Response Syndrome and Sepsis - Enzyme Systems Fighting Multiple Organ Failure
   J. Suliburk et al
2. Damage Control Resuscitation: The New Face of Damage Control
   Juan C. Duchesne et al
   The Journal of TRAUMA® Injury, Infection, and Critical Care • Volume 69, Number 4, October 2010
3. Enhanced Recovery After Surgery: The Future of Improving Surgical Care
   Krishna K. Varadhan et al