THE PHYSIOLOGICAL IMPACT OF TRAUMA AND INFECTION

=

The Metabolic Response to Stress

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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 8–1. Metabolic responses to injury.

Extent of Injury	Neuroendocrine, Metabolic, Cytokine, and Immune Responses
Minimal surgery: Laparoscopy, thoracoscopy, inguinal hernia repair, no large incision into body cavity	Minimal and appropriate. Minor changes in the homeostatic thermostat.
Major surgery and non-life-threatening injury: Large incision into a body cavity or multisystem injury	Major changes that seem to be interrelated and coordinated. Homeostasis as we understand it seems evident.
Life-threatening injuries, operations, or illnesses	Biologic chaos—dyshomeostasis. The individual is overwhelmed by the multiplicity of changes that should be protective but become self-destructive.

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

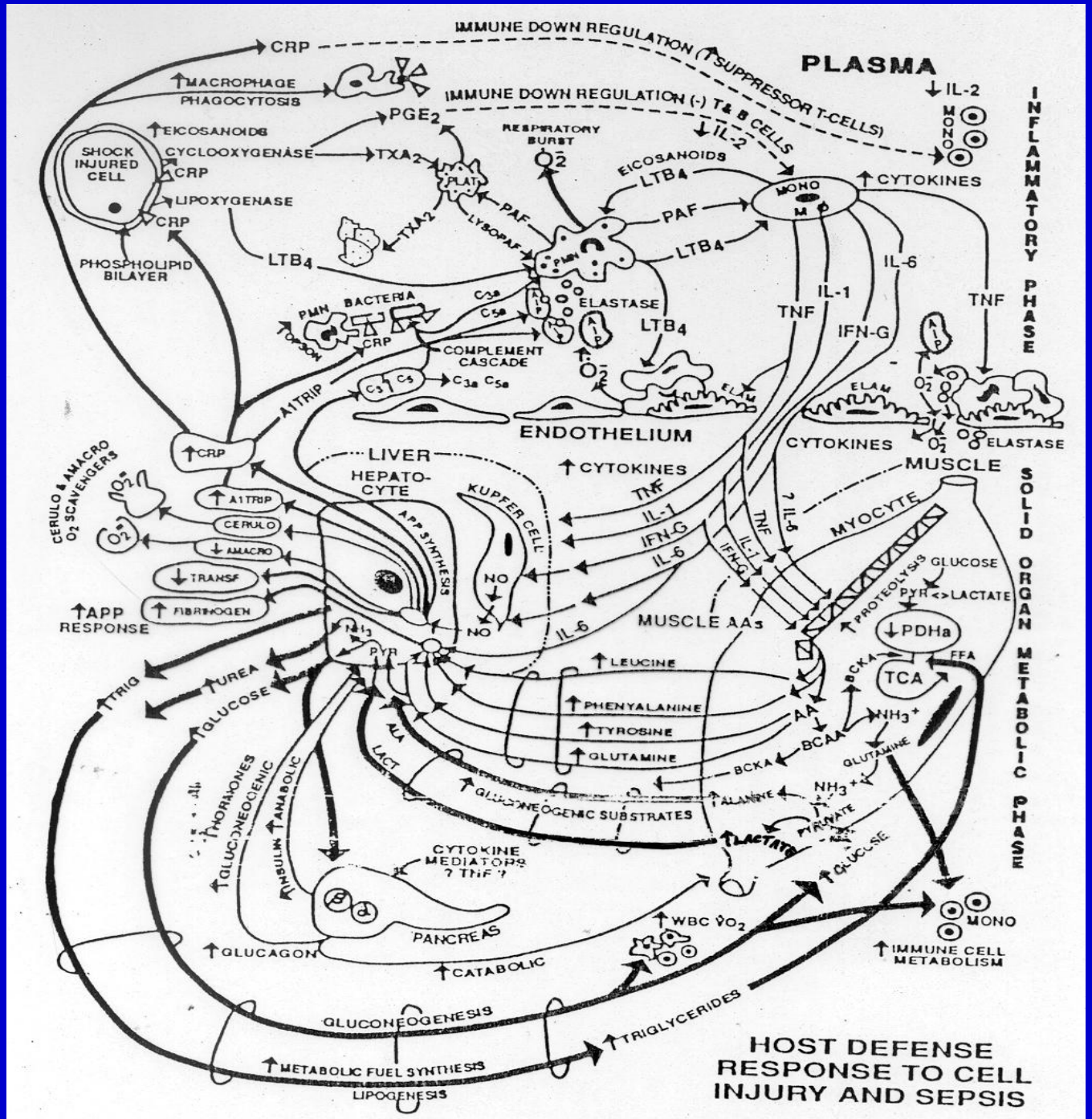
response

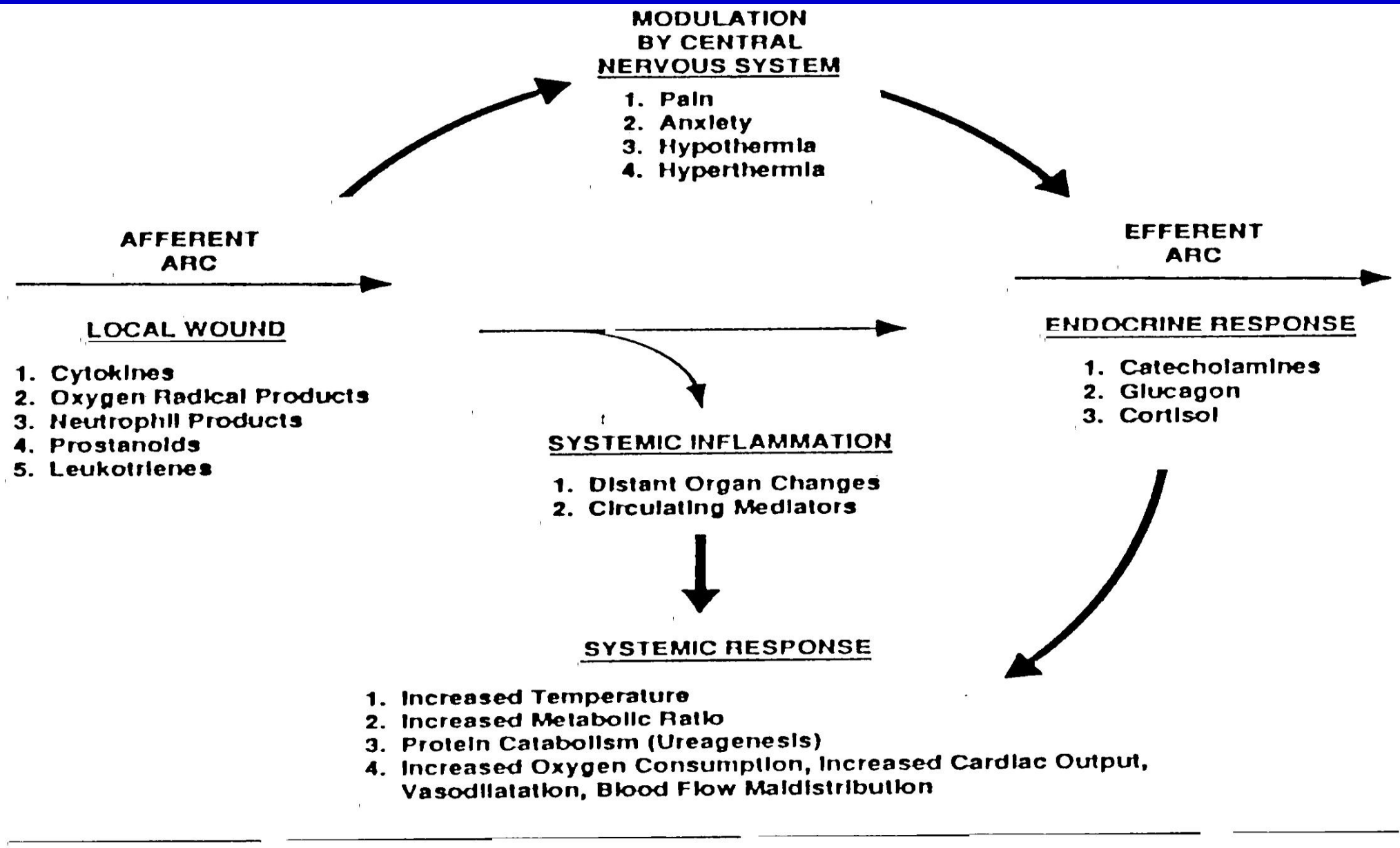
=

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

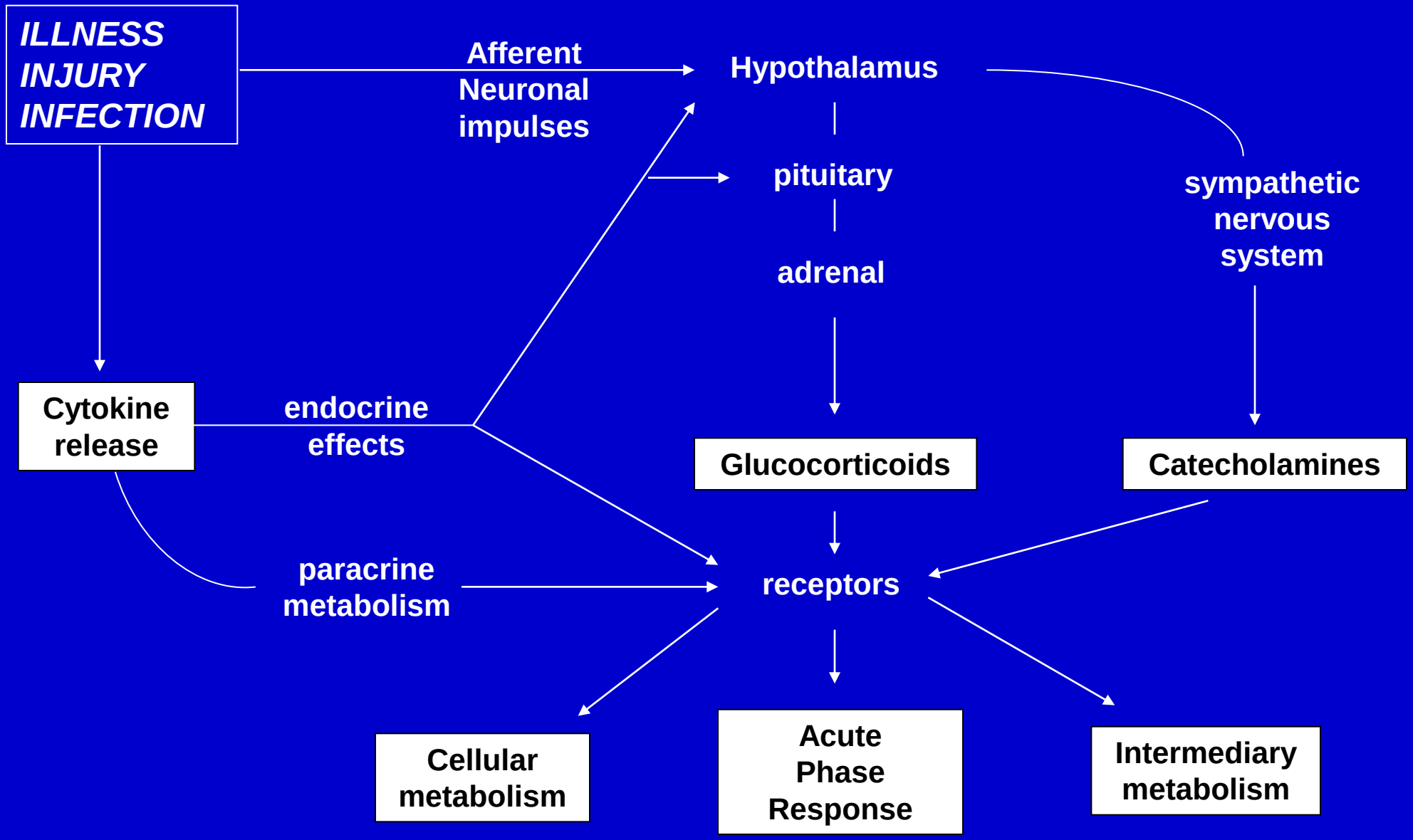
= Host defense!

= Maintenance of HOMEOSTASIS


IMMUNE DOWN REGULATION (↑SUPPRESSOR T-CELLS)
CRP
PLASMA
↓IL-2
MACROPHAGE
PHAGOCYTOSIS
IMMUNE DOWN REGULATION (-) T & B CELLS
↓IL-2
MONO
INFLAMMATORY PHASE
PGE2
EICOSANOIDS
RESPIRATORY BURST
O2-
SHOCK INJURED CELL
CYCLOOXYGENASE
TXA2
PLAT
EICOSANOIDS
LTB4
↑CYTOKINES
CRP
LIPOXYGENASE
PAF
LYSOPAF
PAF
MONO M Φ
CRP
TXA2
PMN
LTB4
LTB4
PHOSPHOLIPID BILAYER
IL-6
IL-1
TNF
TNF
PMN
BACTERIA
C3a
C5a
ELASTASE
A1-P
LTB4
IFN-G
CRP
COMPLEMENT CASCADE
A1-P
O2-
A1TRIP
C3 C5
C3a C5a
ELAM
ELAM
ENDOTHELIUM
CYTOKINES
O2-
ELASTASE
CRP
LIVER
↑CYTOKINES
MUSCLE
CERULO & AMACRO O2 SCAVENGERS
HEPATO-CYTE
KUPFER CELL
TNF
IL-1
IFN-G
IL-6
MYOCYTE
SOLID ORGAN METABOLIC PHASE
O2-
↑A1TRIP
↑CERULO
↓AMACRO
↓TRANSF
↑FIBRINOGEN
APP SYNTHESIS
NO
NO
IL-6
MUSCLE AA's
PROTEOLYSIS
GLUCOSE
PYR <> LACTATE
↑APP RESPONSE
NH3
PYR
↓PDHa
↑LEUCINE
BCKA
TCA
FFA
↑TRIG
↑UREA
↑GLUCOSE
↑PHENYALANINE
↑TYROSINE
↑GLUTAMINE
AA
BCAA
NH3+
BCKA
GLUTAMINE
ALA
LACT
↑ALANINE
NH3+
↑GLUCONEOGENIC SUBSTRATES
PYRUVATE
↑LACTATE
↑GLUCOSE
↑HORMONES GLUCONEOGENIC
↑INSULIN ANABOLIC
CYTOKINE MEDIATORS ? TNF ?
↑WBC VO2
MONO
↑GLUCAGON
PANCREAS
↑CATABOLIC
↑IMMUNE CELL METABOLISM
GLUCONEOGENESIS
↑TRIGLYCERIDES
↑METABOLIC FUEL SYNTHESIS
LIPOGENESIS
HOST DEFENSE RESPONSE TO CELL INJURY AND SEPSIS



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

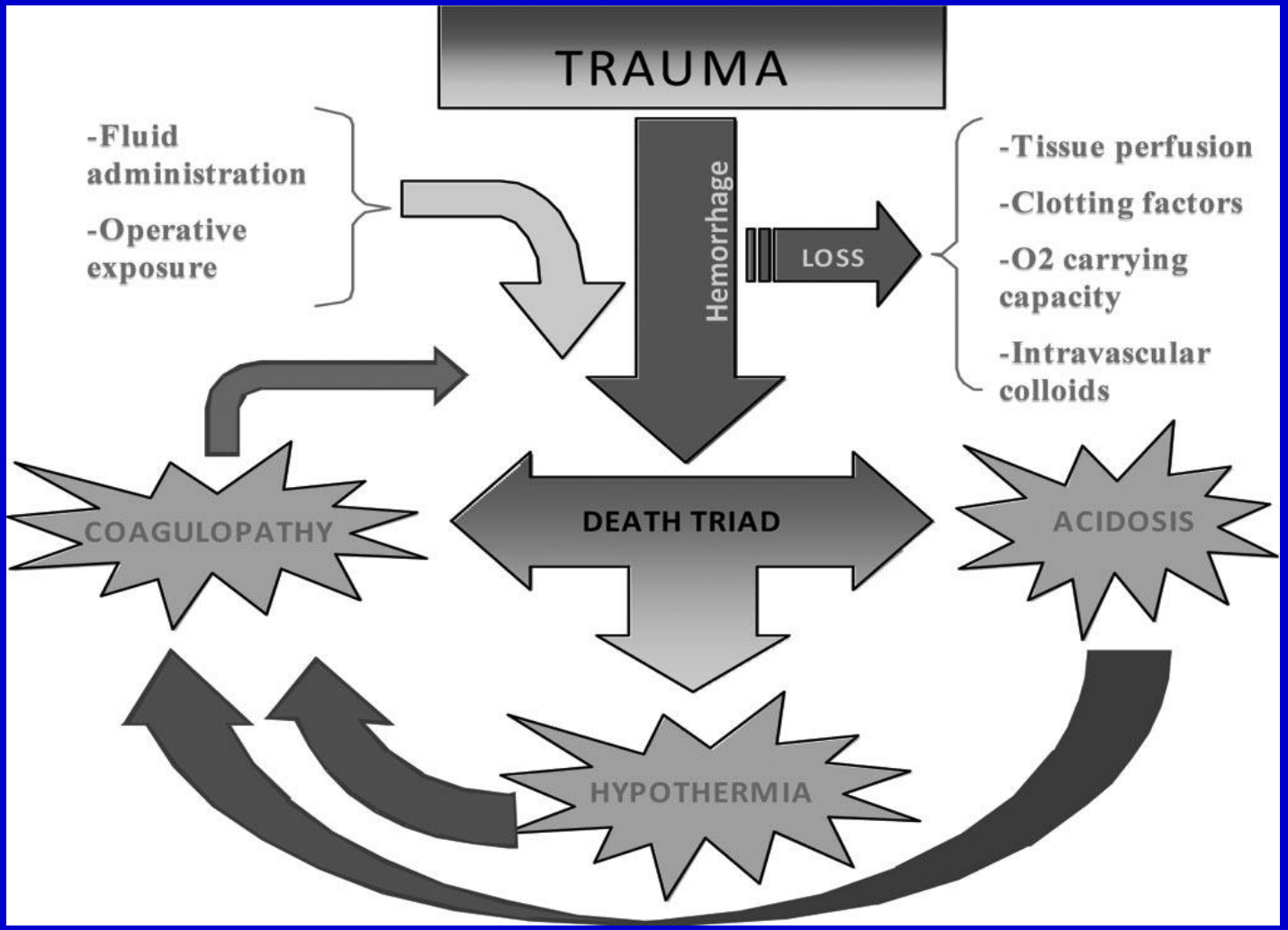


Table 8–6. Hormonal changes and systemic effects of injury.

Major changes
Stress hormones increased
Cortisol
Catecholamines
Glucagon
Volume control hormones increased
Renin-angiotensin, aldosterone
Arginine vasopressin (ADH)
Sex hormones decreased
Thyroid T_3 decreased
Thyroid rT_3 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

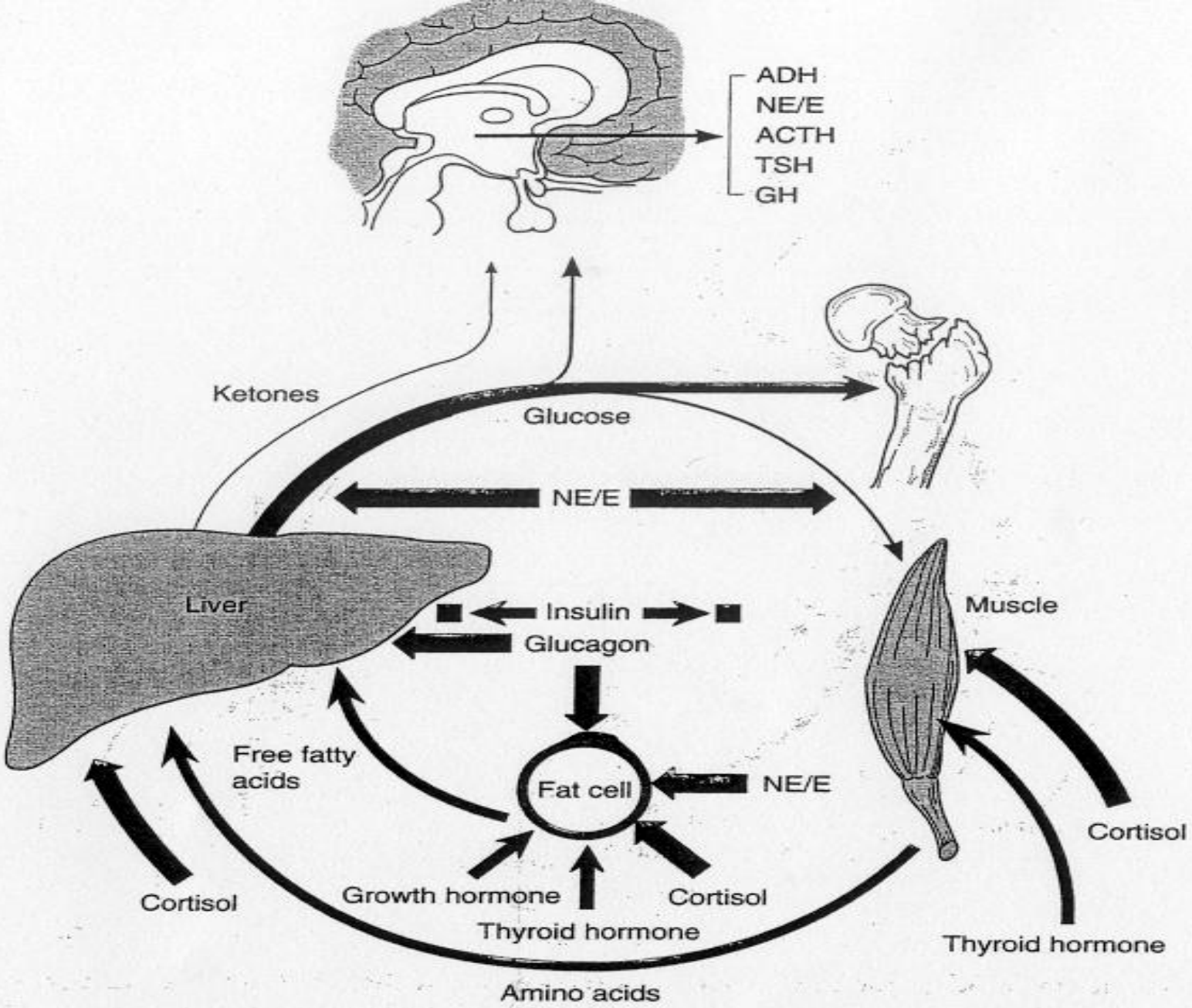


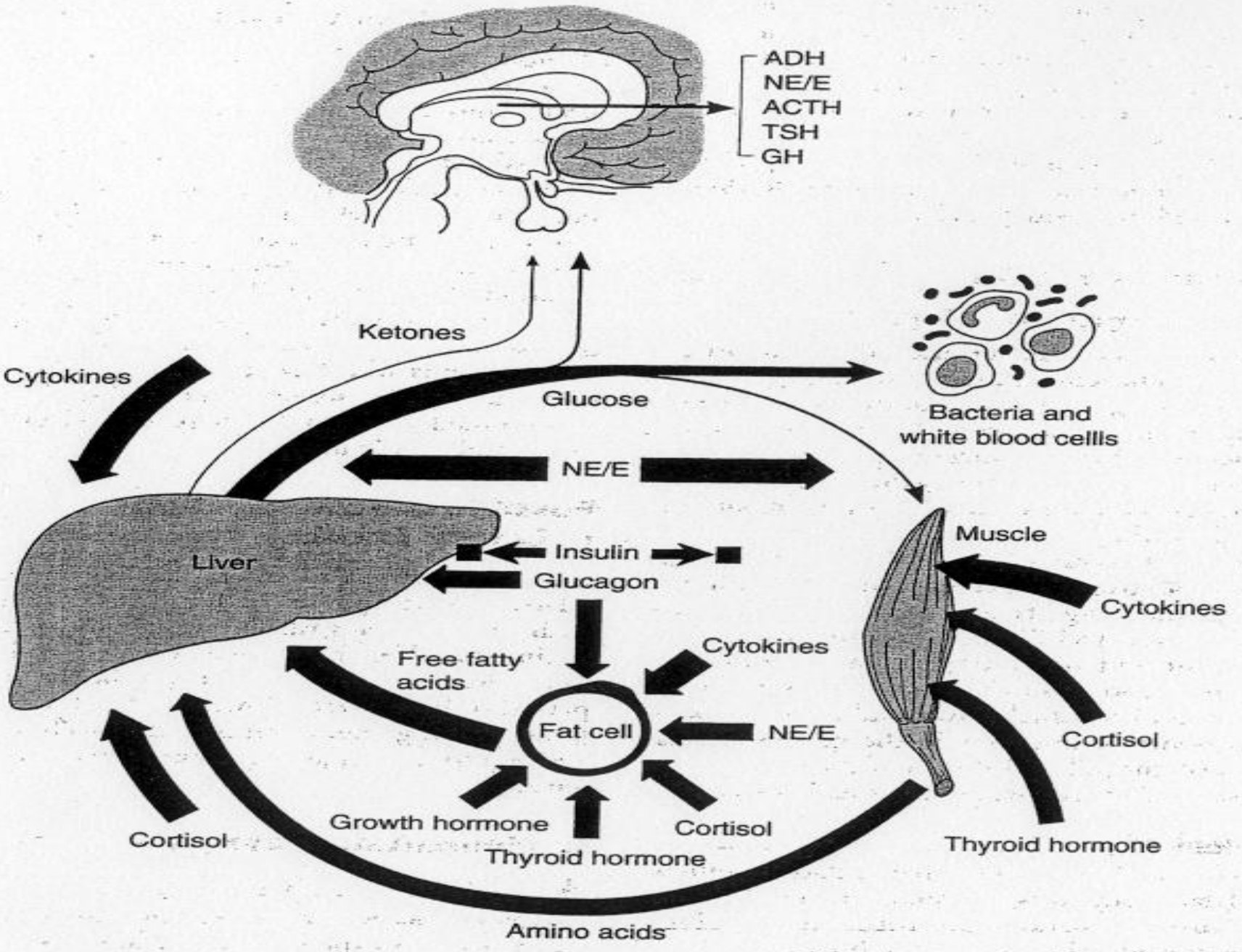
Figure 11–5. The metabolic response to trauma is a result of neuroendocrine stimulation, which accelerates protein breakdown, stimulates gluconeogenesis, and produces glucose intolerance.

Table 8–7. Components of the catabolic or acute phase response.

Skeletal muscle proteolysis through the ubiquitin-proteasome pathway
Decreased muscle protein synthesis
Initial increased gut mucosal synthesis and export
Hepatic protein synthesis (acute phase reactants)
Hepatic gluconeogenesis
Lung response (glutamine)
Kidney response

Visceral

Humoral



re 11–6. During sepsis, cytokines (IL-1, IL-2, TNF) released by lymphocytes and macrophages contribute to ca-
ism 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, superoxides, proteases
Immune complexes
Histamine
Nitric oxide (NO_2), endothelium-derived relaxing factor (EDRF)
Myocardial depressant factor (MDF)
Adhesion molecules
Coagulation cascades
Serotonin

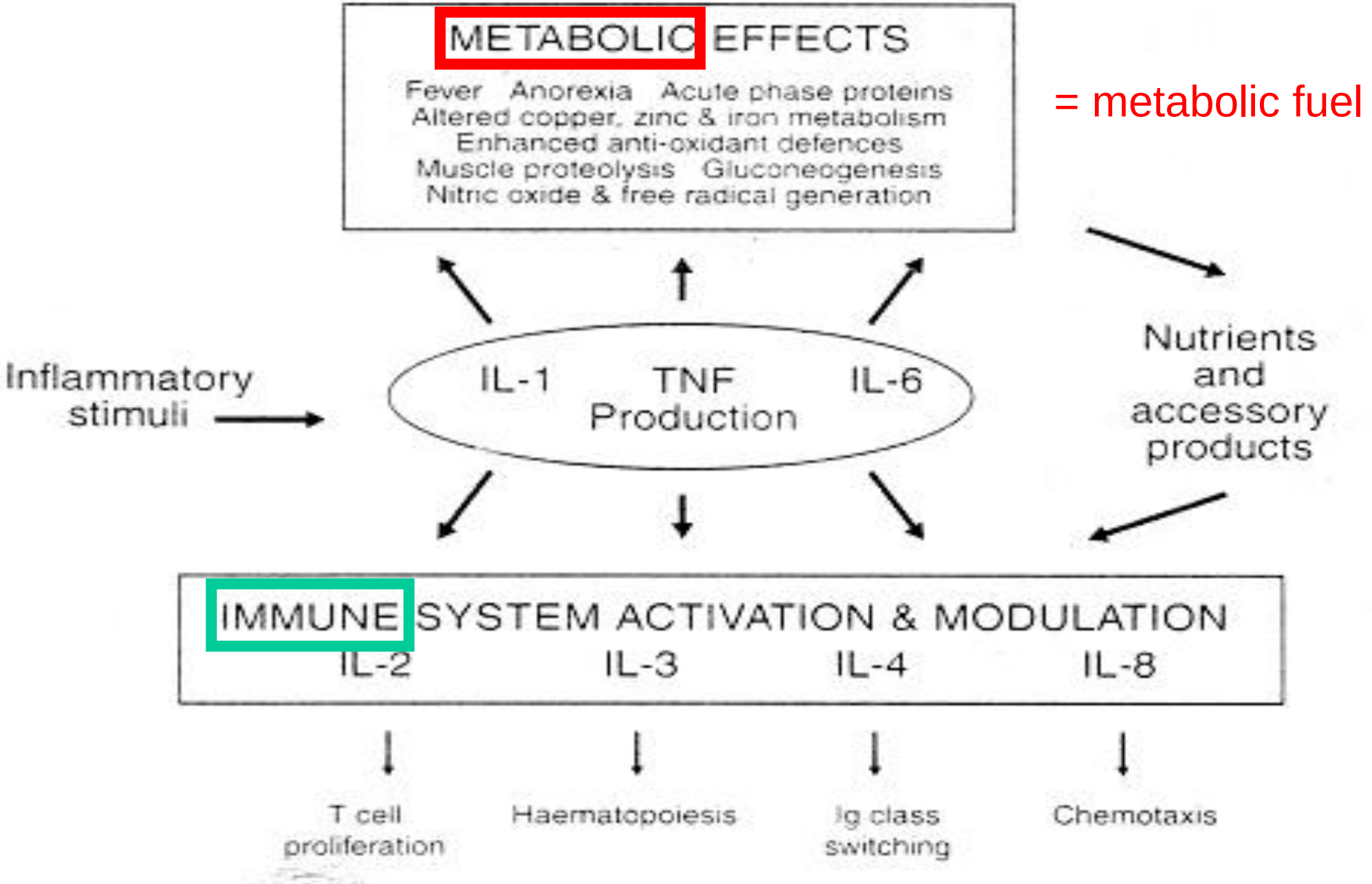
Table II. The pro-inflammatory cytokines*

Cytokine	Source	Main cell targets	Main actions
Interleukin 1α Interleukin 1β	Monocytes, macrophages	Neutrophils, T and B lymphocytes, thymocytes, skeletal muscle, hepatocytes	Immunoregulation, inflammation, fever (endogenous pyrogen), anorexia, sleep, acute-phase protein synthesis, muscle proteolysis, ↑ gluconeogenesis, lymphocyte activation, IL-6 and CSF (colony-stimulating factors) production
Interleukin 6	Monocytes, fibroblasts, T cells	T and B lymphocytes, thymocytes, hepatocytes	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
Tumour necrosis factor α	Monocytes, macrophages	Fibroblasts, endothelium, skeletal muscle, hepatocytes	As for IL-1, induces IL-1, induces IFN-γ secretion

*Adapted from reference 26.

Table III. The major human acute phase proteins[7,22]

Positive APP			Negative APP
Low rise: ± 50% increase	Moderate rise: 2 - 4x increase	Marked rise: up to 1 000x increase	Decreased plasma concentrations
Caeruloplasmin	Orosomucoid	C-reactive protein	Albumin
Complement C3	α_1-acid glycoprotein	Serum amyloid A	Pre-albumin
Complement C4	α_1-antitrypsin		Transferrin
	α_1-antichymotrypsin		RBP
	Haptoglobin		Fibronectin
	Fibrinogen		



Cytokine link to Metabolic + Immune reactions

BUT…….

The process can go the wrong way !

(Murphy's 1st law ?)

TIME TO SOURCE CONTROL !!!!!

Prevention is the best cure for MODS + MOF

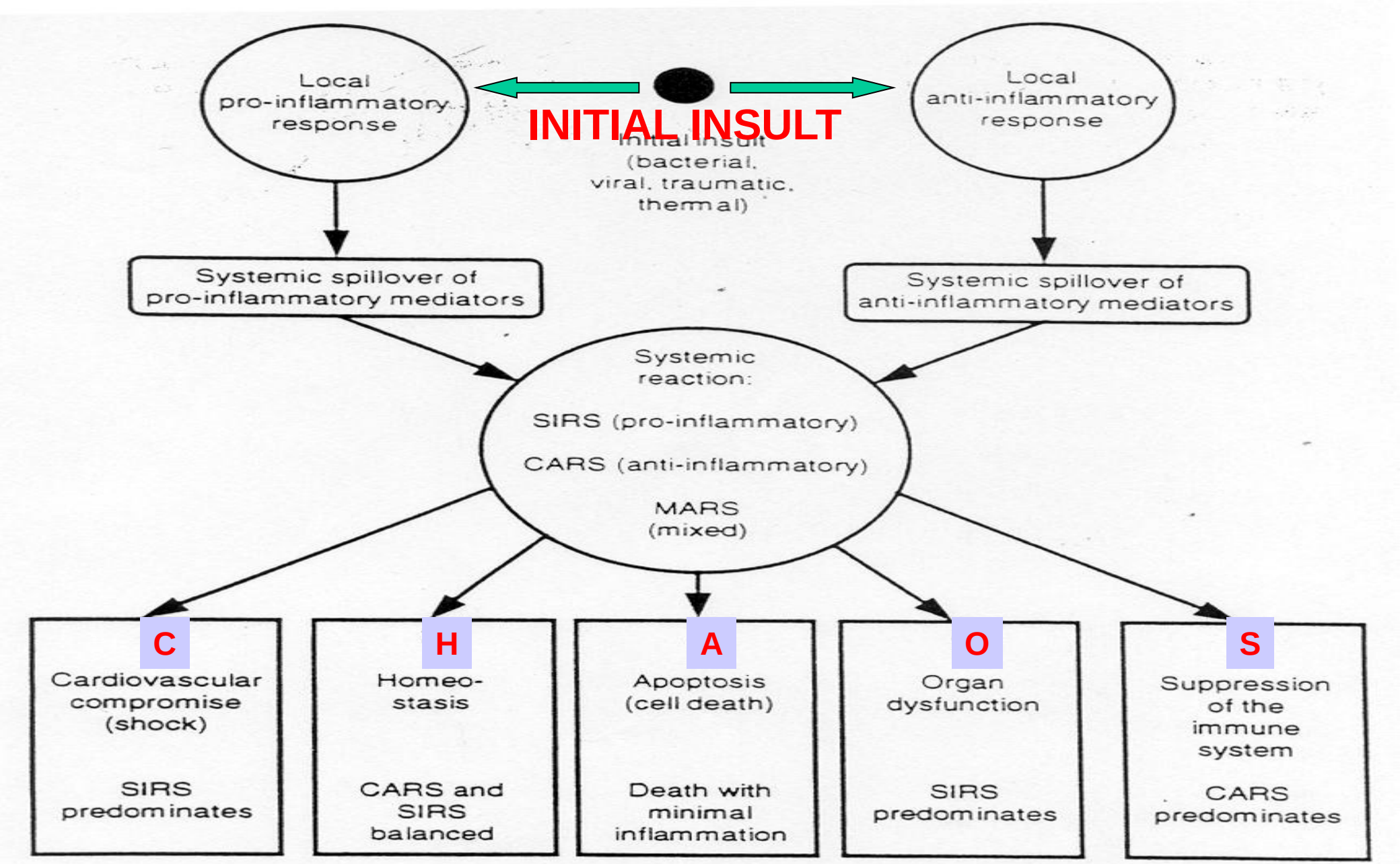


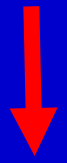
FIGURE 4. New concepts for the clinical sequelae of sepsis, SIRS, CARS, and MARS. (This figure is an adaptation of Figure 1 by Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 1996; 24:1125-28.)

HOST DEFENSE

"Psycho-neuro-endocrino-immunology"

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 ➡ Resuscitation ➡ Hypermetabolism ➡ MODS ➡ MOFS

Resuscitation in progress

Early……Transition in emphasis over time……....Later

The Solution:

Tissue oxygen delivery

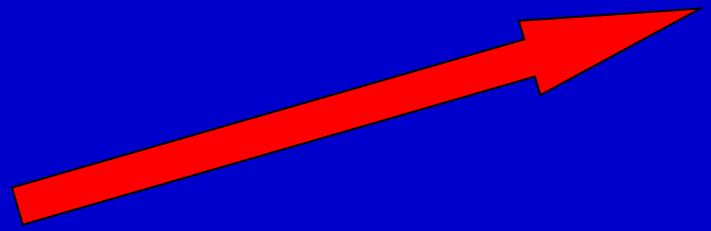
= perfusion deficit

Cardiopulmonary resuscitation

Cell metabolic regulation

= substrate deficit

Metabolic resuscitation



Cell metabolic regulation

Tissue oxygen delivery

HOMEOSTASIS

SUCCESSFUL SUPPORTIVE THERAPY

FOR CRITICALLY ILL PATIENTS

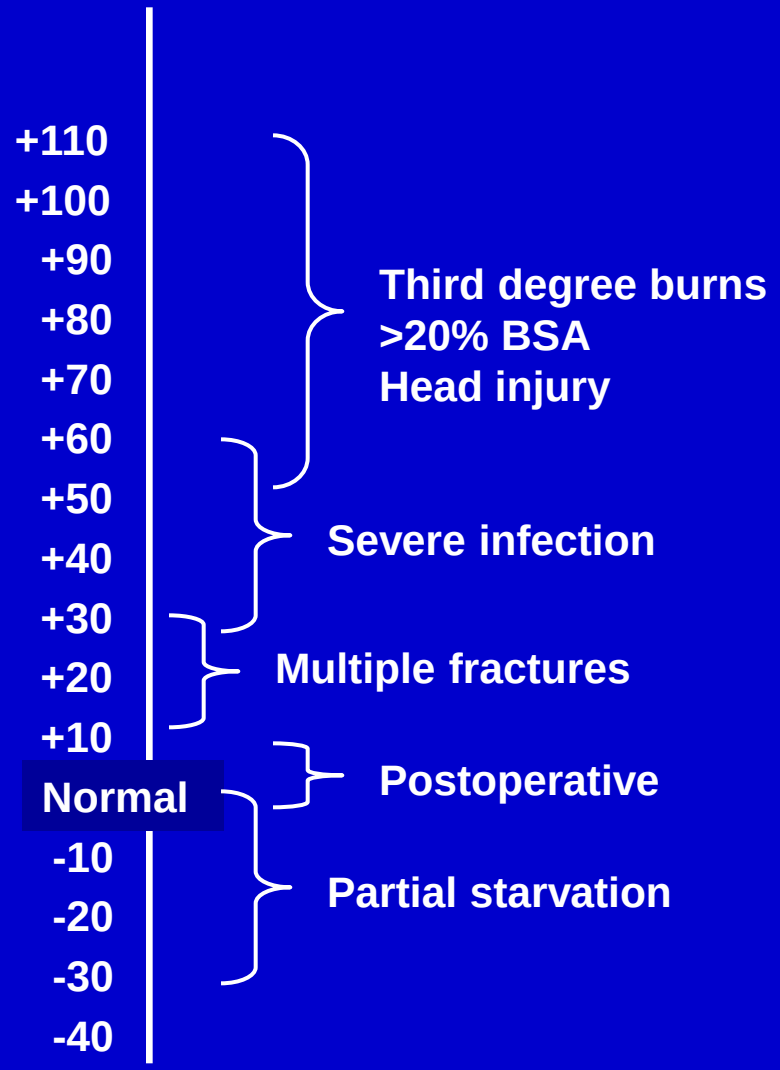
DEPENDS ON METABOLIC

RESUSCITATION

Characteristics of Metabolic Phases Occurring After Severe Injury

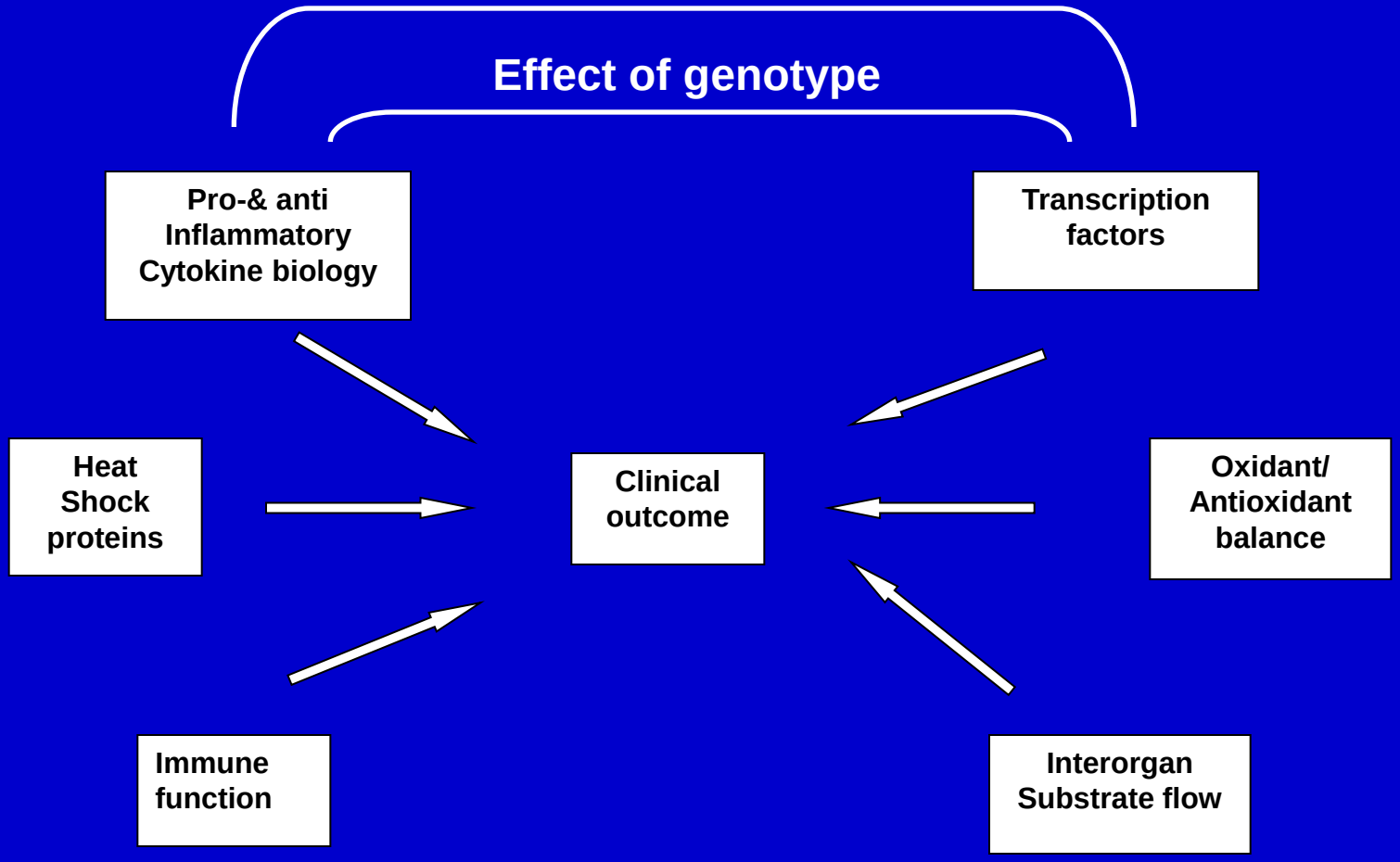
Ebb Phase Response "Conservation"	Flow Phase: Acute Response "Preparation"	Flow Phase: Adaptive Response "Rebuilding"
Hypovolemic Shock	Catabolism predominates	Anabolism predominates
↓ tissue perfusion	↑ glucocorticoids	Hormonal response gradually diminishes
↓ metabolic rate	↑ glucagon	↓ hypermetabolic rate
↓ oxygen consumption	↑ catecholamines	Associated with recovery
↓ blood pressure	Release of cytokines, lipid mediators	Potential for restoration of body protein.
↓ body temperature	Production of acute phase proteins	Wound healing depends in part on nutrient intake
	↑ excretion of nitrogen ↑ metabolic rate ↑ oxygen consumption Impaired utilization of fuels	

Effects of injury, sepsis and nutritional depletion on resting energy expenditure



Genetic Influences

Modulation by nutrients



The Latest on Inflammation !

- Human genome project
- Baseline level of preconditioning

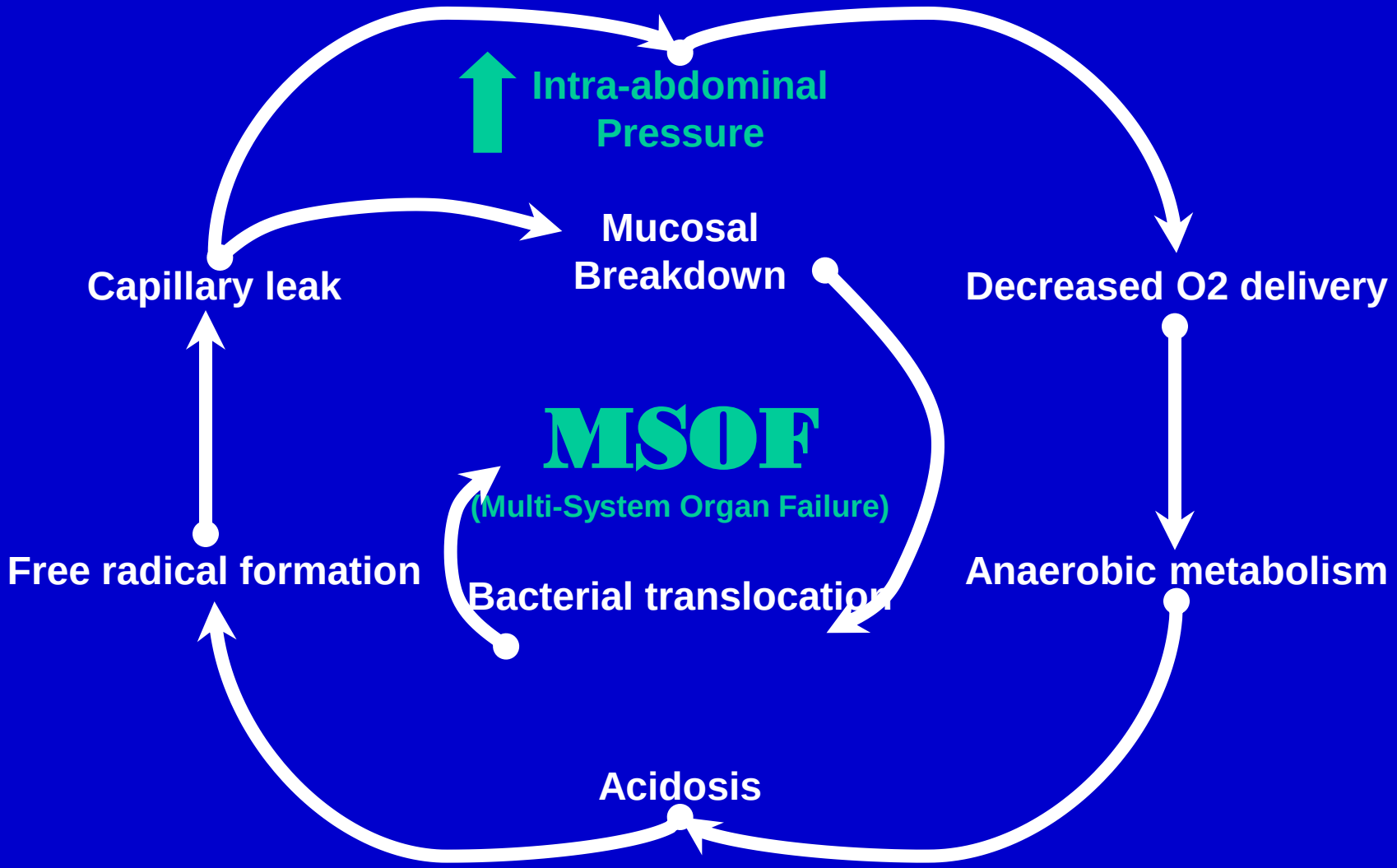
  = ability of the host to tolerate and respond to an insult without severe disturbance to homeostasis
- Degree of preconditioning
- Simultaneous pro- and anti-inflammatory responses

Suliburk et al Eur Surg Res 2008; 40: 184 - 189

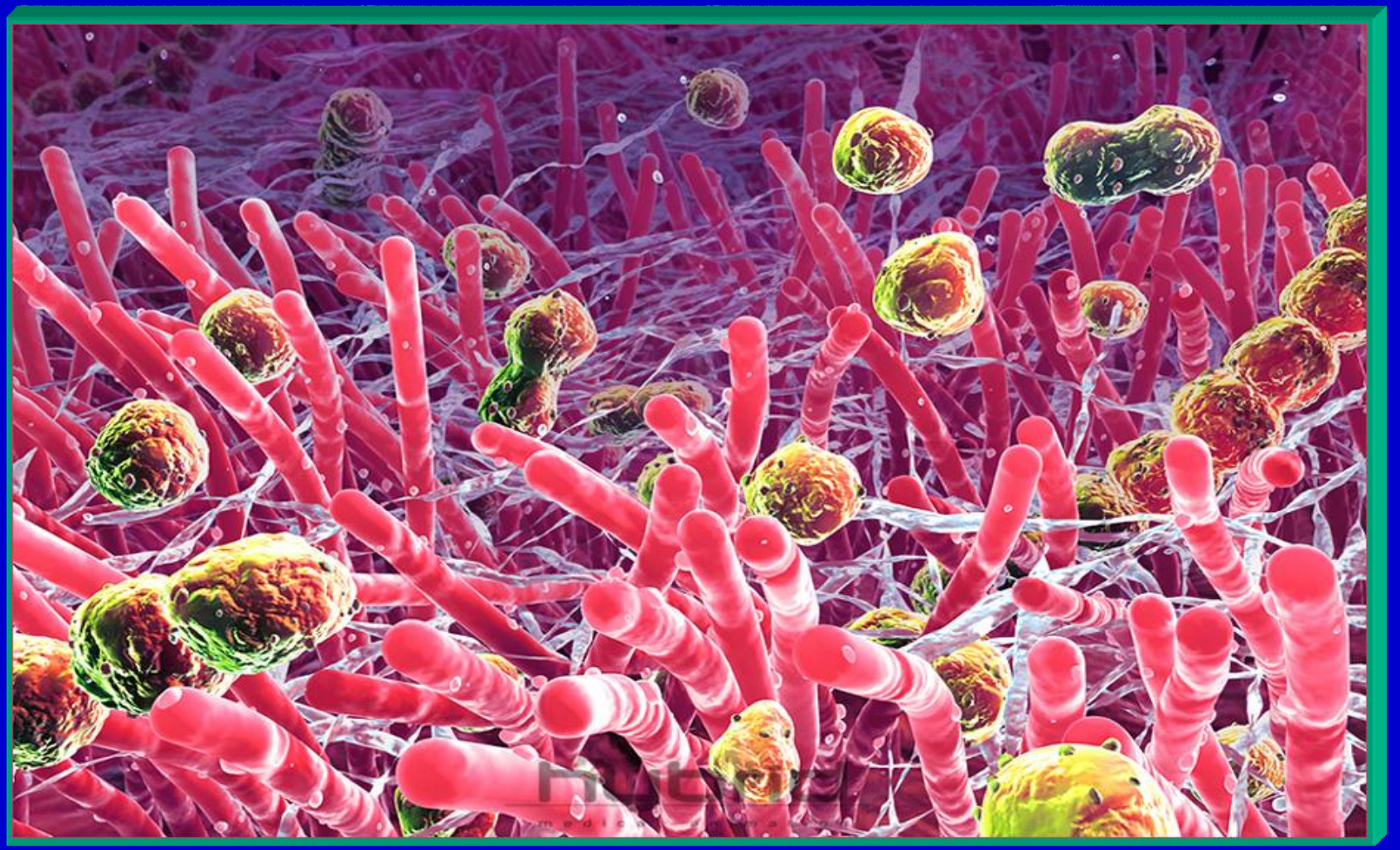
Table 1. Summary: Hyperglycemia and immune function

Component of immune system	Effect of hyperglycemia
▪ Polymorphonuclear cells	Impaired phagocytosis Impaired chemotaxis Decreased bactericidal activity Decreased adherence Increased apoptosis
▪ Lymphocytes Monocytes	Decreased response (all subsets) Impaired chemotaxis Impaired phagocytosis Decreased respiratory burst
▪ Immunoglobulins	Non-enzymatic glycosylation Decreased concentrations (IgA, IgG, IgM)
▪ Collectins (SP-A, SP-D)	Non-enzymatic glycosylation Impaired opsonization

Gut as Motor of MODS - A Vicious Circle?



The Mucosal Barrier: Is It the Motor for MOF ?

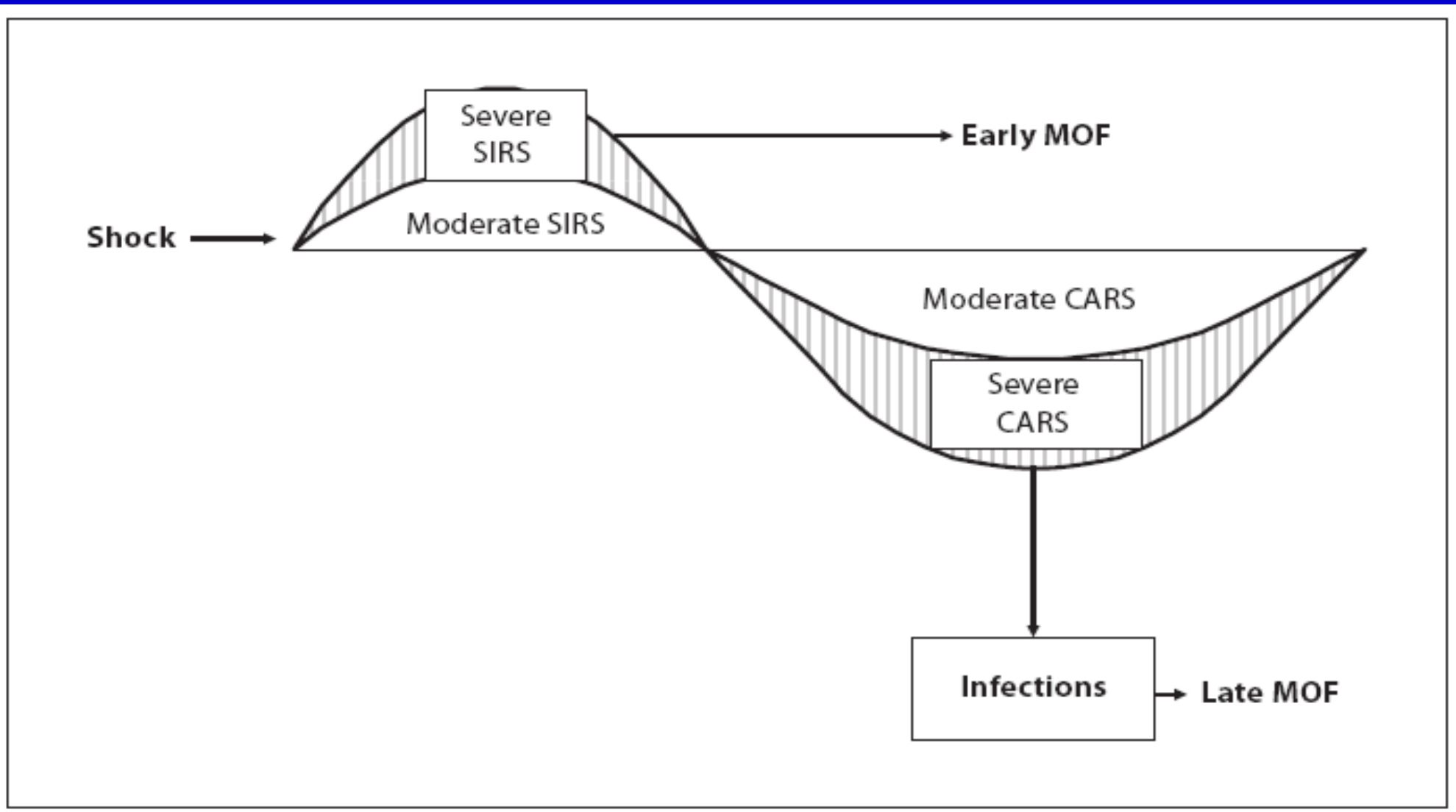


The Latest on Inflammation !

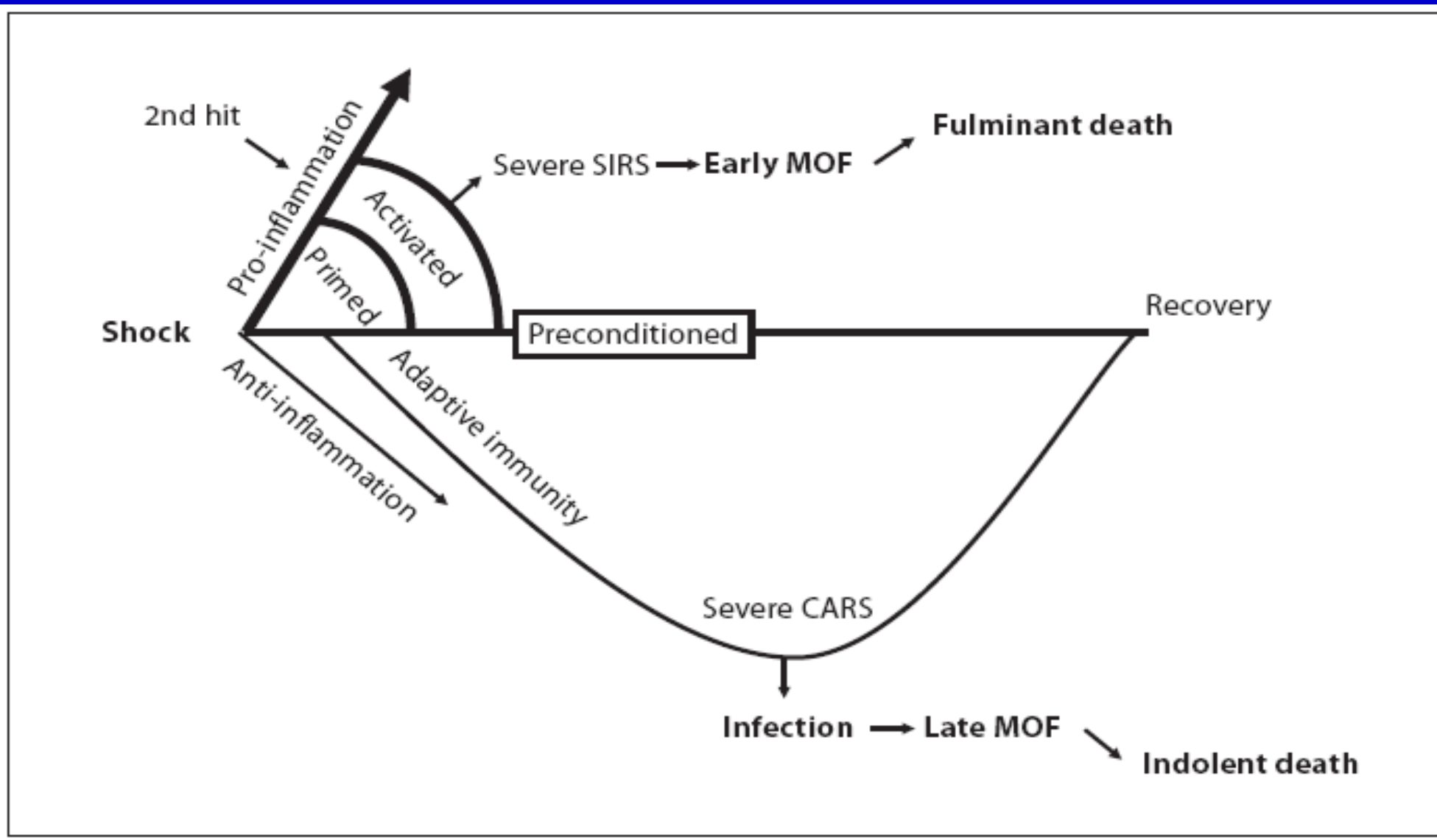
- Despite improvement in care, Multiple Organ Failure continues to cause significant morbidity + mortality
- “Shock” >>>organ ischaemia>>>critical for development of MODS + MOF
- MOF is a gut-derived phenomenon

  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

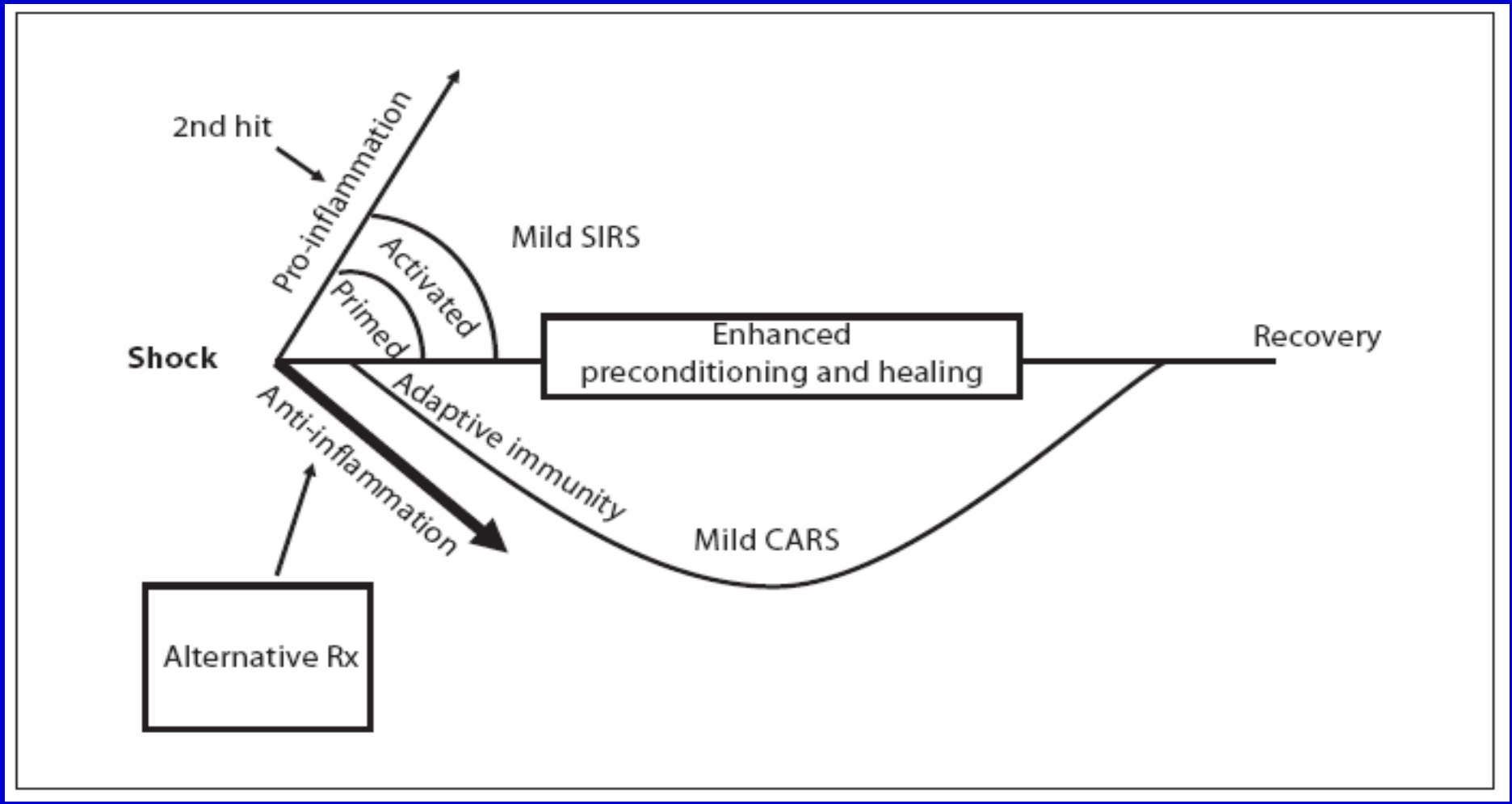
Suliburk et al Eur Surg Res 2008; 40: 184 - 189



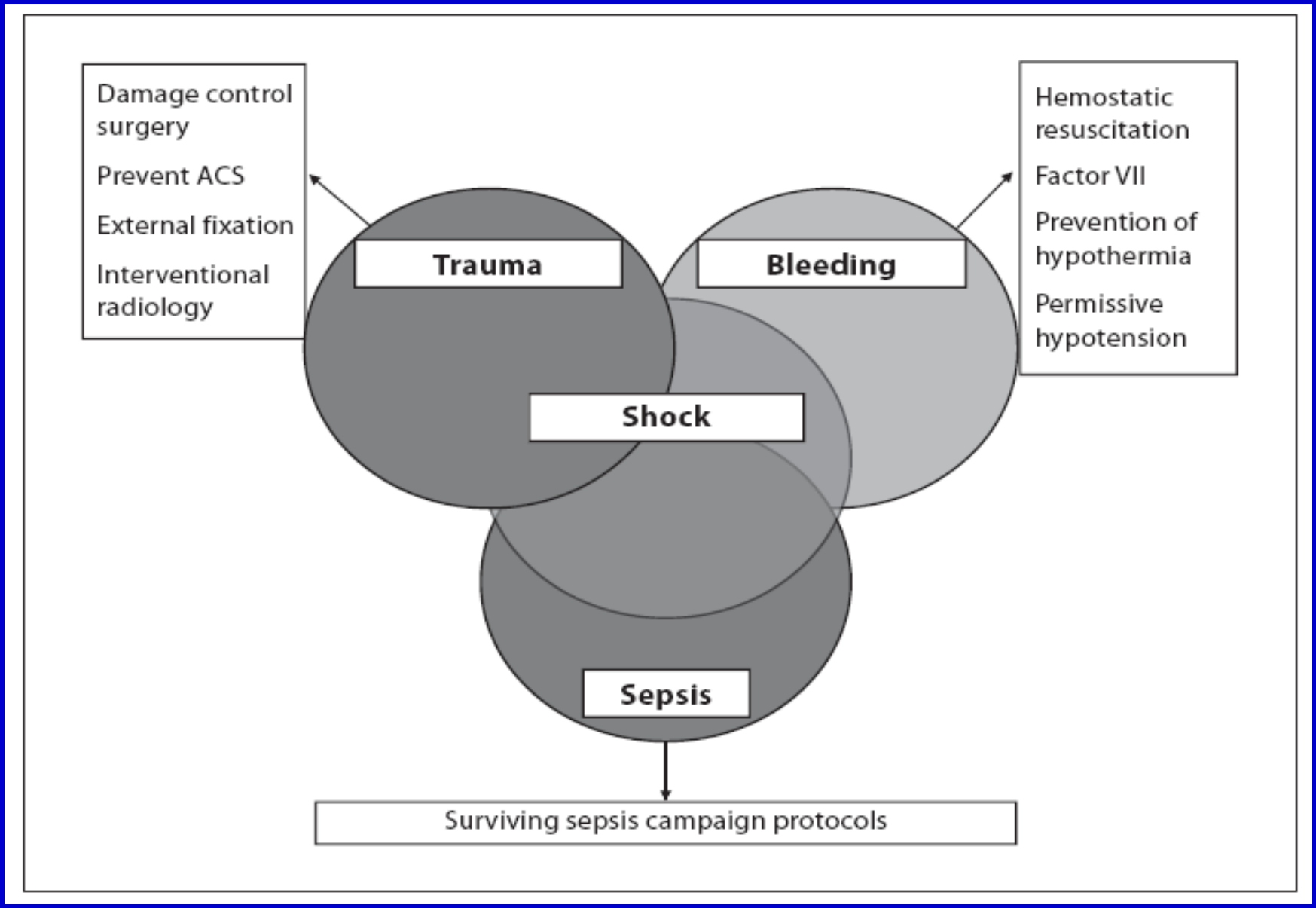
View of MOF in the 1990s: dysfunctional inflammation causes MOF.



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 a possessing their own unique characteristics and treatments.

CONCLUSION

RF Grimble

1

The “psycho-neuro-immuno-endocrine response” to injury or infection functions to enhance the possibility of survival without treatment

2

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

3

For the infected individual, marshalling of resources to combat invading pathogens must assume a priority over all other physiologic demands.

4

After the invasion has been repulsed and the damaged done by the invader repaired, priorities normally given to other physiological processes can be restored.

5

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 direct toward providing nutrients for the system.

7

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.

8

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.

MUST READ's !!!

1. **The Gut in Systemic Inflammatory Response Syndrome and Sepsis - Enzyme Systems Fighting Multiple Organ Failure**

   J. Suliburk et al

   Eur Surg Res 2008;40:184–189

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

   Crit Care Clin 26 (2010) 527–547