HOMEOSTASIS

Concepts of Homeostasis

- Claude Bernard:
  - Stability of the “milieu intérieur” is the primary condition for freedom and independence of existence.
  - i.e. body systems act to maintain internal constancy.
- Walter Cannon:
  - Term “Homeostasis”.
  - Coordinated physiological process which maintains most of the steady states of the organism.
  - i.e. complex homeostatic responses involving the brain, nerves, heart, lungs, kidneys and spleen work to maintain body constancy.
- ~~Responses to injury are beneficial to the host and allow healing/survival.~~

Concepts of Homeostasis……

- Classical homeostatic control system:
  - Signal detector
  - Processor
  - Effector
  - Negative feedback loop
- Open loop system:
  - Also referred to as non-feedback system
  - Type of continuous control system in which the output has no influence or effect on the control action of the input signal.
  - Only with medical/surgical resolution of the primary abnormality results in classical homeostasis.

Concepts of Homeostasis……

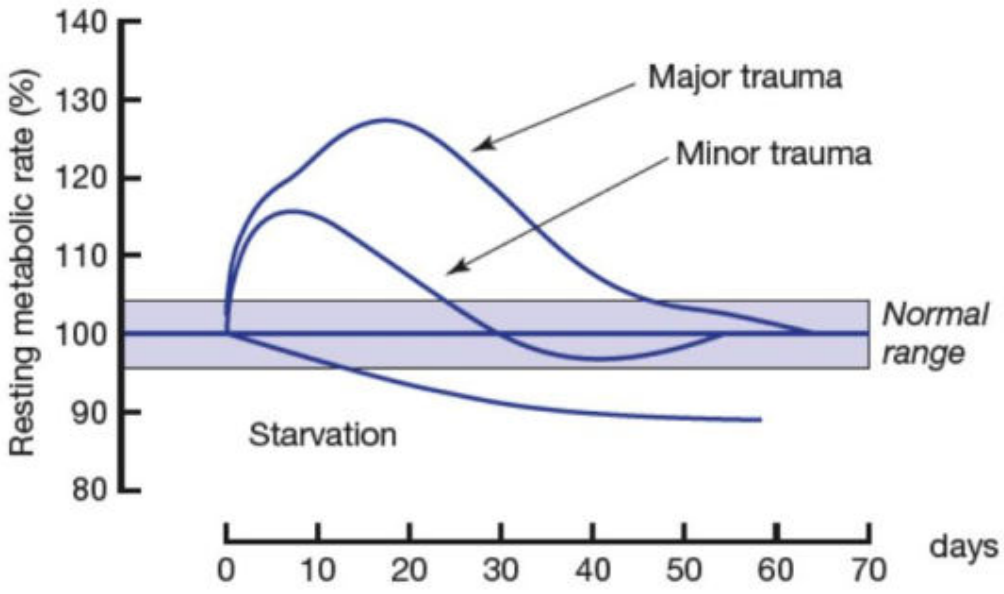
- Elective surgical practice:
  - Reduce the need for a homeostatic response by minimizing the primary insult
  - e.g. minimal access surgery and ‘stress-free’ perioperative care.
- Emergency surgery:
  - Presence of tissue trauma/ sepsis/ hypovolaemia often compounds the primary problem.
  - It requires:
    - To augment artificially homeostatic responses (e.g. resuscitation)
    - And to close the ‘open’ loop by intervening to resolve the primary insult (e.g. surgical treatment of major abdominal sepsis)
    - And provide organ support (critical care)
  - While the patient comes back to a situation in which homeostasis can achieve a return to normality.

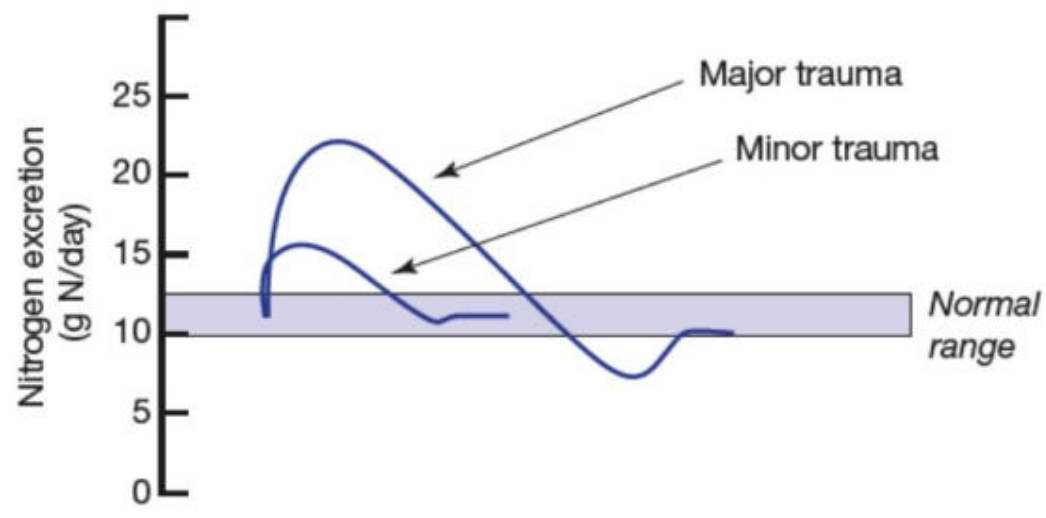
Graded Nature of the Injury Response

- Response to injury:
  - More severe the injury- Greater the response.
    - Applies to Physiological/ Metabolic/ Immunological changes.
    - Following elective surgery of intermediate severity-
      - Changes may be a transient and modest.
      - Mild rise in temp./ heart rate/ respiratory rate/ energy expenditure and white cell count.
    - Following major trauma/sepsis-
      - Changes are accentuated.
      - Resulting in SIRS/ hyper metabolism/ marked catabolism/ shock and even multiple organ dysfunction (MODS).
  - Genetic variability plays a key role in determining the intensity of the inflammatory response.

Graded Nature of the Injury Response….

Response to injury:





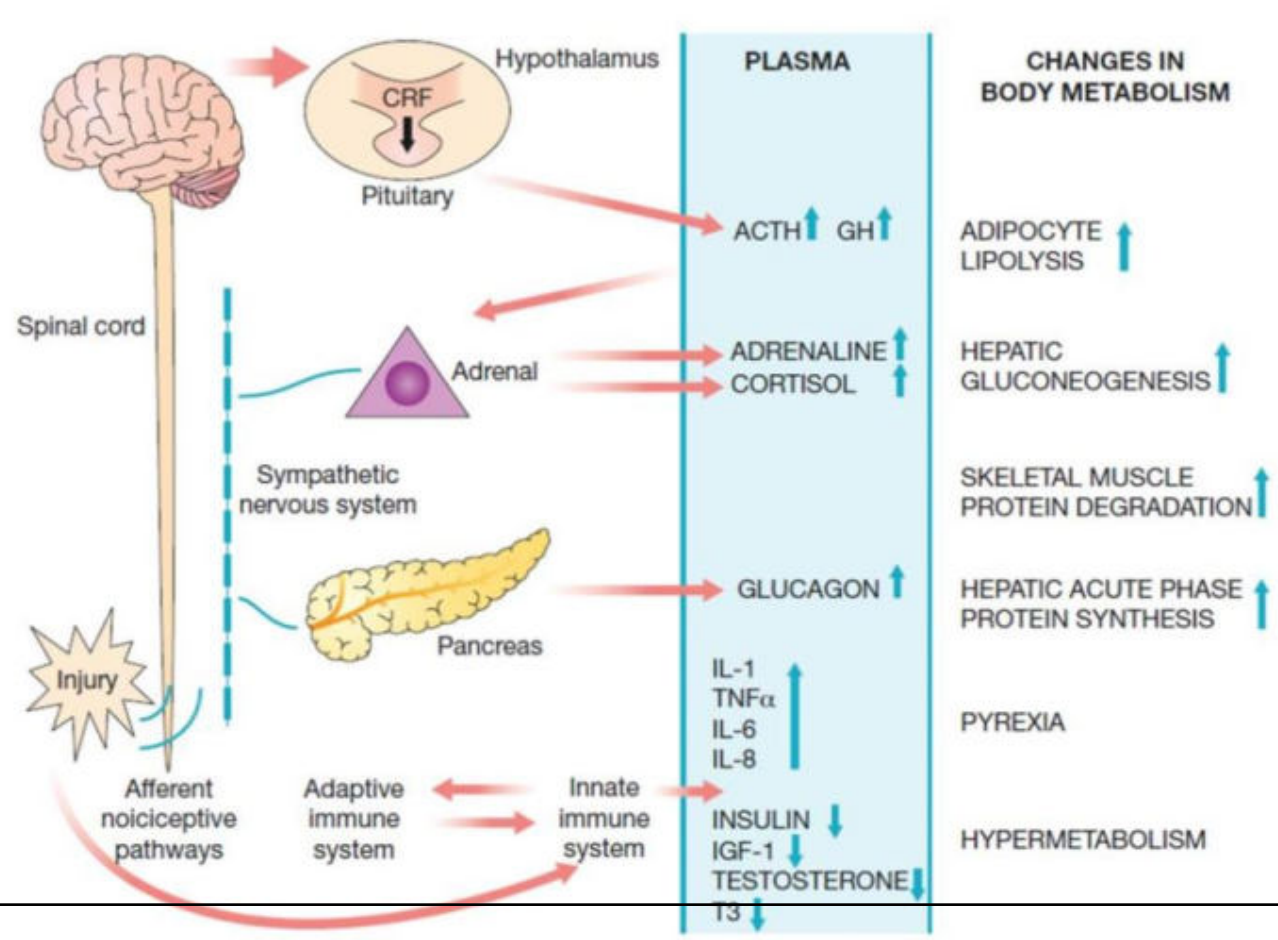
Hypermetabolism and increased nitrogen excretion are closely related to the magnitude of the initial injury and show a gradedresponse.

Graded Nature of the Injury Response….

- Immunological sequelae of major injury:
  - Evolve from a Pro-inflammatory State
    - Driven primarily by the innate immune system (macrophages, neutrophils, dendritic cells).
  - Finally- Compensatory Anti-Inflammatory Response Syndrome (CARS)
    - Characterized by suppressed immunity- diminished resistance to infection.
    - Patients who develop infective complications-
      - CARS leads to ongoing systemic inflammation/ acute phase response and continued catabolism.

Mediators of the Metabolic Response to Injury

- 'Classical Neuroendocrine Pathways' of the stress response consist of:
  - Afferent nociceptive neurons
  - Spinal cord
  - Thalamus
  - Hypothalamus
  - and pituitary



Mediators of the Metabolic Response to Injury…..

- **Corticotrophin- Releasing Factor** (CRF)- released from the hypothalamus
  - Increases **ACTH** release- from the anterior pituitary.
  - ACTH acts on the adrenals- increase the secretion of **cortisol**.
- Hypothalamic activation of the **Sympathetic Nervous System**-
  - Release of Adrenaline and Glucagon.
- Intravenous infusion of a **cocktail** of these 'counter-regulatory' hormones (glucagon, glucocorticoids and catecholamine)-
  - Results in many aspects of the metabolic response.

Mediators of the Metabolic Response to Injury…..

- Other mediators:
  - Alterations in insulin release and sensitivity.
  - Hypersecretion of prolactin and growth hormone (GH) in the presence of low circulatory insulin-like growth factor-1 (IGF-1).
  - Inactivation of peripheral thyroid hormones and gonadal function.

Neuroendocrine response to injury/critical illness

- Neuroendocrine response to severe injury/critical illness is biphasic:
  - Acute phase:
    - Actively secreting pituitary and elevated counter-regulatory hormones (cortisol, glucagon, adrenaline).
    - Changes are thought to be beneficial for short term survival.
  - Chronic phase:
    - Hypothalamic suppression and low serum levels of the respective target organ hormones.
    - Changes contribute to chronic wasting.

Immunological changes to injury/critical illness

- Innate immune system (principally macrophages) interacts in a complex manner with the adaptive immune system (T cells, B cells):
  - Also affects the metabolic response to injury.
- Pro-inflammatory cytokines (IL-1/ TNFα/ IL-6 and IL-8):
  - Produced within the first 24 hours of injury.
  - Act directly on the Hypothalamus-
    - Cause pyrexia.
    - Augment the hypothalamic stress response.
  - Act directly on skeletal muscle- induce proteolysis.
  - Act on liver- Induce acute phase protein production.
  - A complex role in the development of peripheral insulin resistance.

Immunological changes to injury/critical illness.....

- Endogenous Cytokine Antagonists enter the circulation:
  - Within hours of the Upregulation of Pro-inflammatory Cytokines.
  - e.g. interleukin-1 receptor antagonist [IL-1Ra] and TNF-soluble receptors [TNF-sR-55 and 75].
  - Act to control the pro-inflammatory response.
  - A complex adaptive changes includes:
    - Development of a Th2-type counter-inflammatory response.
      - Regulated by IL-4, -5, -9 and -13 and transforming growth factor beta [TGFβ].
- If accentuated and prolonged in critical illness- characterized as the CARS.
  - Results in immunosuppression- increased susceptibility to nosocomial infection.

Immunological changes to injury/critical illness.....

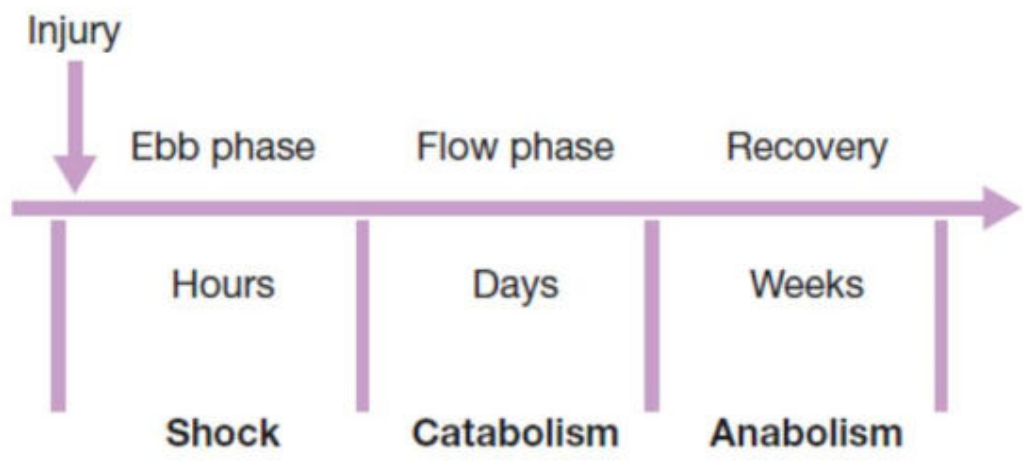
- Duration and magnitude of acute inflammation as well as the return to homeostasis are influenced by-
  - Specialized proresolving mediators (SPM)- include essential fatty acid-derived lipoxins, resolvins, protectins and maresins.
  - Uptake and clearance- of apoptotic polymorphonuclear neutrophils and microbial particles
  - Reduce- proinflammatory cytokines and lipid mediators
  - Enhance the removal of cellular debris.

Immunological changes to injury/critical illness.....

- Systemic inflammatory response syndrome following major injury:
  - Is driven initially by proinflammatory cytokines (e.g. IL-1, IL-6 and TNFα).
  - Is followed rapidly by increased plasma levels of cytokine antagonists and soluble receptors (e.g. IL-1Ra, TNF-sR).
  - If prolonged or excessive may evolve into a counterinflammatory response syndrome.

The 'Ebb and Flow' model of metabolic response

- Natural physiological response to injury includes:
  - Immobility/rest
  - Anorexia
  - Catabolism
- Sir David Cuthbertson divided the metabolic response to injury:
  - Into 'ebb' and 'flow' phases



Ebb phase

- Begins at the time of injury and lasts for approximately 24–48 hours.
- Characterized by-
    - hypovolemia/ decreased BMR/ reduced cardiac output/ hypothermia and lactic acidosis.
- Predominant hormones regulating the ebb phase- catecholamines/ cortisol/ aldosterone.
- Magnitude of response depends on:
    - Degree of blood loss.
    - Stimulation of somatic afferent nerves at the site of injury.
- Main physiological role of the ebb phase:
    - **Conserve** both circulating volume and energy stores for recovery and repair.

Flow phase

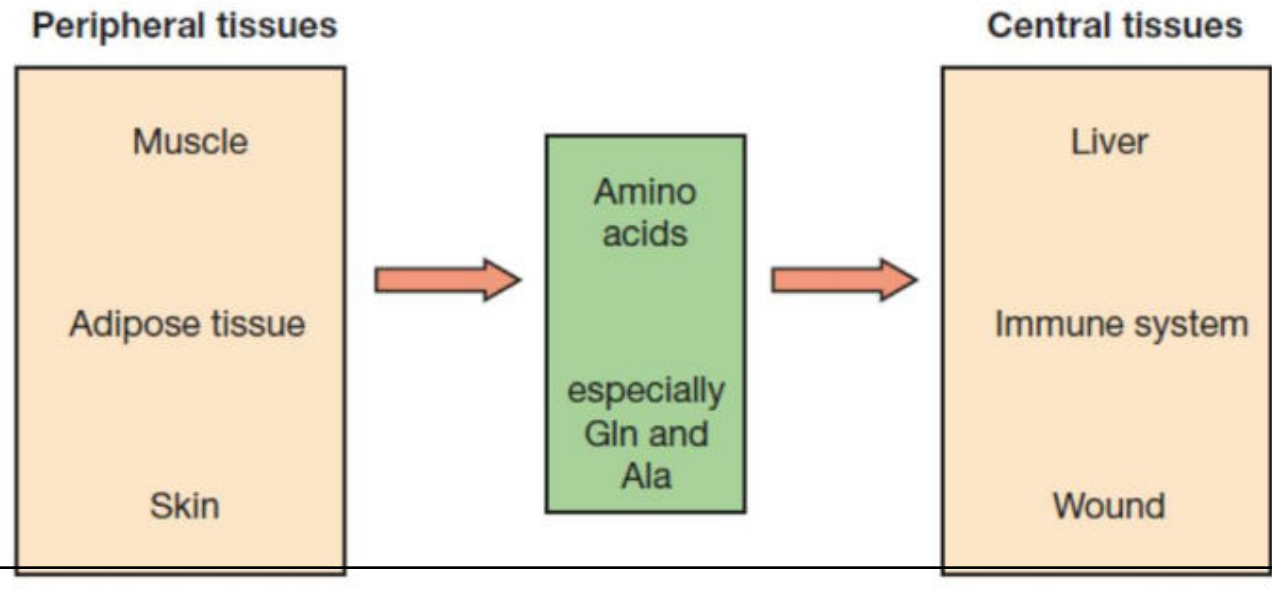
- Following resuscitation, ebb phase evolves into a hypermetabolic flow phase.
- This phase involves:
    - Mobilization of body energy stores- for recovery and repair
    - and subsequent replacement of lost or damaged tissue.
- Characterized by:
    - Tissue edema (from vasodilatation and increased capillary leakage)
    - Increased basal metabolic rate (hyper metabolism)/ Increased cardiac output
    - Raised body temperature/Leukocytosis
    - Increased oxygen consumption
    - And increased gluconeogenesis.

Flow phase.....

- Flow phase may be subdivided into:
  - Catabolic phase
    - lasting approximately 3–10 days.
    - Increased production of counter-regulatory hormones (catecholamines, cortisol, insulin and glucagon) and inflammatory cytokines(e.g. IL-1, IL-6 and TNFα).
    - Significant fat and protein mobilization- significant weight loss and increased urinary nitrogen excretion.
    - Increased production of insulin- associated with significant insulin resistance and poor glycemic control.
    - Increased risk of complications- further aggravate the neuroendocrine and inflammatory stress responses and creates a vicious catabolic cycle.
  - Anabolic phase
    - may last for weeks if extensive recovery and repair are required following serious injury.

Key Catabolic Elements of the Flow Phase

- During the response to injury, not all tissues are catabolic.
- Essence of coordinated response is-
  - Reprioritise limited resources away from peripheral tissues towards key viscera and wound.



Key Catabolic Elements of the Flow Phase

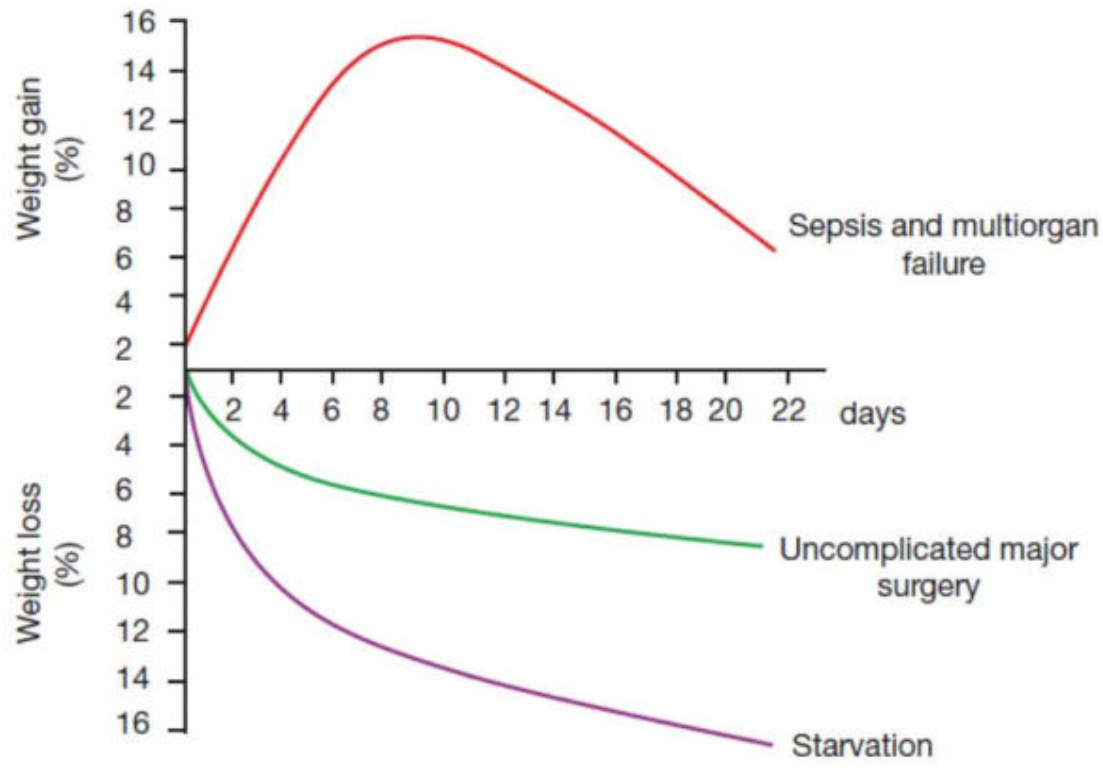
- Hypermetabolism:
  - Caused by an acceleration of energy-dependent metabolic cycles.
  - limited in modern practice on account of elements of routine critical care.
- Skeletal muscle wasting:
  - Provides amino acids for the metabolic support of central organs/tissues.
  - Mediated at a molecular level- by activation of the ubiquitin–proteasome pathway.
  - Can result in-
    - Immobility
    - Contribute to hypostatic pneumonia
    - If prolonged and excessive- leads to death

Key Catabolic Elements of the Flow Phase

- Hepatic acute phase response:
  - Represents a reprioritisation of body protein metabolism towards the liver and is characterised by:
    - Positive reactants (e.g. CRP): plasma concentration ↑
    - Negative reactants (e.g. albumin): plasma concentration ↓
- Insulin resistance
  - Following surgery or trauma- hyperglycemia develops as a result of
    - Increased glucose production
    - Combined with decreased glucose uptake in peripheral tissues.
  - Decreased glucose uptake is a result of insulin resistance which is transiently induced.

CHANGES IN BODY COMPOSITION FOLLOWING INJURY

- Catabolism:
  - Decrease in fat mass and skeletal muscle mass
- Body weight may paradoxically increase
  - Expansion of extracellular fluid space



Avoidable factors that compound the response to injury

- Continuing haemorrhage
- Hypothermia
- Tissue oedema
- Tissue underperfusion
- Starvation
- Immobility