PATHOPHYSIOLOGY OF DISEASE

Pathophysiology:

- Defined as the physiology of altered health
- Deals with cellular and organ changes that occur with disease as well as the effects of these changes on whole body function
- Focuses on the mechanisms of the disease, allowing for preventative and therapeutic health care measures

Disease

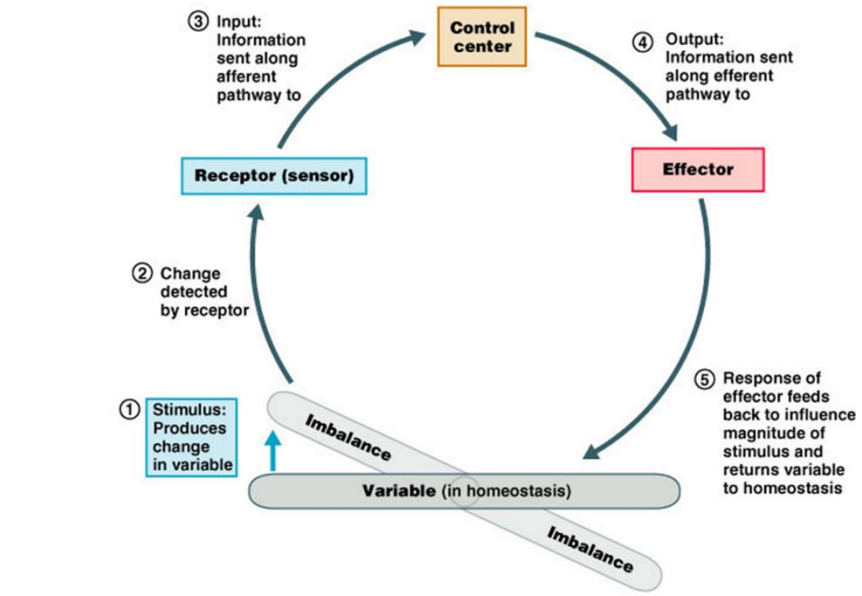
- A disruption of homeostasis
- Can be caused due to error in homeostatic sensors, regulatory centers, or effectors
- Results from a sum of deviations from the normal state
- Is a dynamic state

HOMEOSTASIS

- Defined as the ability to maintain relatively stable internal conditions
- A dynamic state of balance in which internal conditions vary within narrow limits
- Almost all organ systems are involved in either directly or indirectly contributing to homeostasis

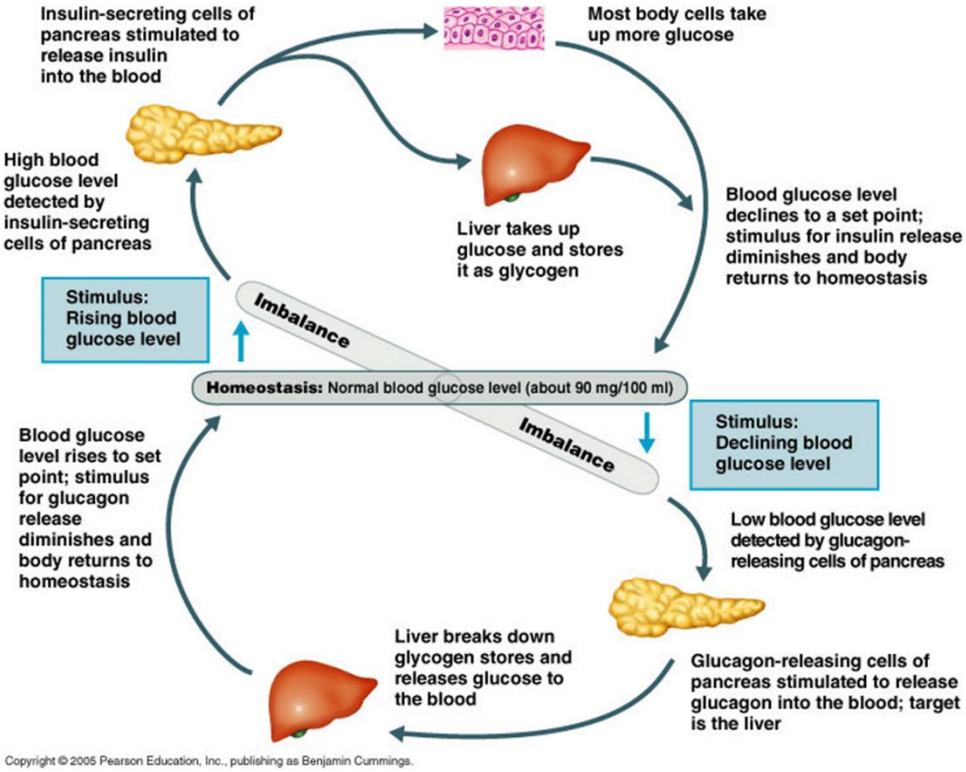
HOMEOSTATIC CONTROL MECHANISMS

- Communication by and between the endocrine and nervous systems are crucial
- **A**fferent information **A**rrives, **E**fferent information **E**xits
- Variable:
  - factor being controlled
- Receptor:
  - sensor that monitors the environment and responds to changes by sending information to the control center
- Control center:
  - message arrives here via an afferent pathway; determines the level at which the variable is the be maintained; analyzes the input and determines the appropriate response
- Effector:
  - provides means for the control center's response; information arrives via an efferent pathway, causes feedback to influence the stimulus in a negative or positive feedback loop



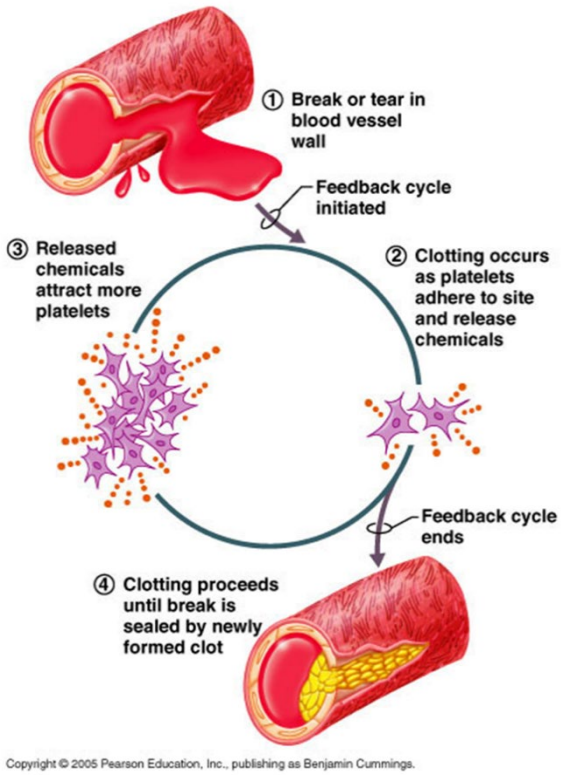
NEGATIVE FEEDBACK LOOP

- Majority of control mechanisms are negative feedback loops
- Output acts to shut off the original stimulus or to reduce its intensity
- Causes the variable to change in the opposite direction
- The goal is to prevent sudden changes within the body
- Examples: blood sugar, blood volume, body temperature, rate and depth of breathing, blood pressure control



POSITIVE FEEDBACK LOOP

- Enhances the original stimuli so the output is accelerated
- Causes the variable to deviate further from its set point
- Controls infrequent events that do not require continuous adjustment
- Important in labour contractions and blood clotting



HOMEOSTATIC IMBALANCE

- Internal environment becomes less stable with age
- Also occurs when negative feedback mechanisms are overwhelmed
- Cell needs to adapt to changes in its environment to survive
- Cells do well at responding to changes in their environment and maintaining their healthy status
- When the stress or injury is too great, the cell will develop maladaptive changes and could result in cell death
- Cells also need to adapt in structure and function as the body ages

FEELING FEVERISH: A CASE STUDY IN HOMEOSTASIS

- Thermoregulation adjusts heat production, heat conservation and heat loss to maintain body temperature at normal homeostatic levels
    - Normal body temperature fluctuates during the day, ranging between 36.1 and 37.2^{o}C
- During **pyrexia**, commonly referred to as fever, there is an adjustment in homeostasis that creates a higher set-point than 'normal temperature'
    - Fever occurs when the thermostat of the body, the hypothalamus, is reset to a higher base temperature
    - A patient is considered to have a fever when their body temperature is above 38.1 ^{o}C
- To maintain the higher temperature, there are adjustments in heat production, conservation and loss

ETIOLOGY

- Fevers are caused by pyrogens
- Pyrogens are defined as any substance or agent that tends to cause an increase in body temperature
- Endogenous pyrogens:
    - proteins that induce fever
    - released by cells of the immune system, usually in response to a trigger from an exogenous pyrogen
    - many have been identified, including cytokines, interleukins 1 and 6, interferons and tumor necrosis factors
- Exogenous pyrogens:
    - Can be endotoxins, which are lipopolysaccharides present in the outer membrane of Gram-negative pathogens (eg *Escherichia coli)*
    - Antigen-antibody complexes also act as exogenous pyrogens

PATHOGENESIS OF PYREXIA DURING AN INFECTION

- As macrophages phagocytose the infectious pathogens, it results in the release of a variety of endogenous pyrogens, which cause a downstream enzymatic cascade that eventually results in the release of prostaglandin
- Prostaglandin is the substance that causes the hypothalamus to increase the temperature set-point
- Once the set-point has been increased, the variable of body temperature will need to increased to bring the homeostatic loop back into balance
    - the patient will feel cold and make voluntary behavioural responses to feeling cold; these responses will help increase body temperature
    - the hypothalamic centre is stimulated to conserve heat by vasoconstriction and generate heat by shivering.
- When production of cytokines decreases, prostaglandin production goes down and the hypothalamus will return to its normal set-point
    - the fever 'breaks'
    - the patient will feel hot and make behavioural changes to increase heat loss

FUNCTION OF PYREXIA DURING AN INFECTION

- In response to infection, fever has 5 benefits:
    1. Raised body temperature kills heat sensitive microorganisms, as well as decreasing their growth and replication rate
    2. Serum levels of iron, zinc and copper decrease; these minerals are needed for bacterial replication
    3. Lysosomes breakdown at increased temperature, resulting in auto-destruction of some infected cells, limiting viral replication in infected cells
    4. Heat increases the immune response through activation of neutrophils and lymphocytes
    5. Phagocytosis is enhanced by increased body temperature
    6. Body metabolism is increased, which facilitates healing and recovery

References:

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Martini, F., Nath, J., and Bartholomew, F. 2018. *Fundamentals of Anatomy and Physiology.* 11th edition. Toronto: Pearson Education; 1296 pp.