Fever

- Fever, **or pyrexia**, describes an elevation in body temperature that is caused by a cytokine-induced upward displacement of the set point of the hypothalamic thermoregulatory center.

- Called also "hallmark of infection", in fact, many infections are called fevers: Typhoid fever, rheumatic fever, etc.

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Normal Body Temperature Regulation

- The temperature within the deep tissues of the body (core temperature) is normally maintained within a range of 36.0°C to 37°C.
- Within this range, there are individual differences and diurnal variations:
  - Internal core temperatures reach their highest point in late afternoon and evening and their lowest point in the early morning hours.
- Body temperature reflects the difference between heat production and heat loss.
  - Body heat is generated in the tissues of the body, transferred to the skin surface by the blood, and then released into the environment surrounding the body.

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Normal thermoregulation

- Body temperature is set and controlled by the hypothalamus
- Body temperature is maintained within ± 0.5-0.6 °C.
- It varies over the course of the day

Cells constantly produce heat by metabolism

Mechanisms to lose heat:

dilation of surface blood vessels

sweating

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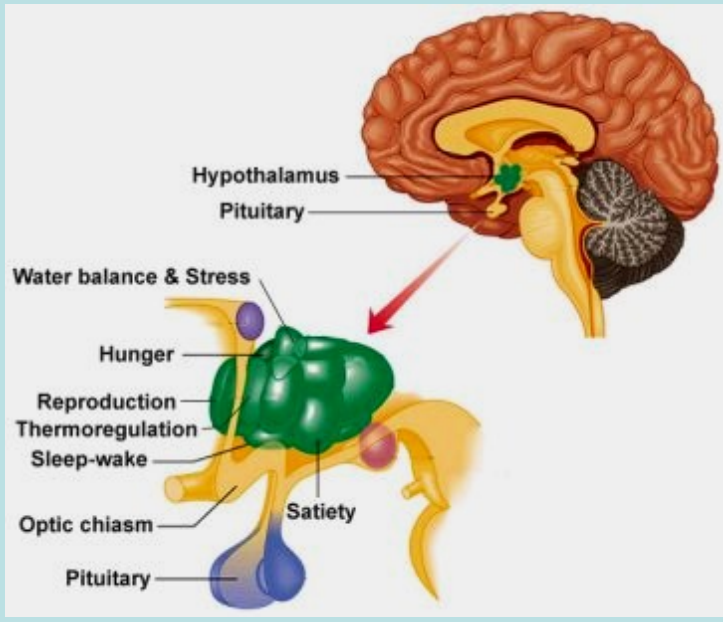
Hypothalamus and its functions



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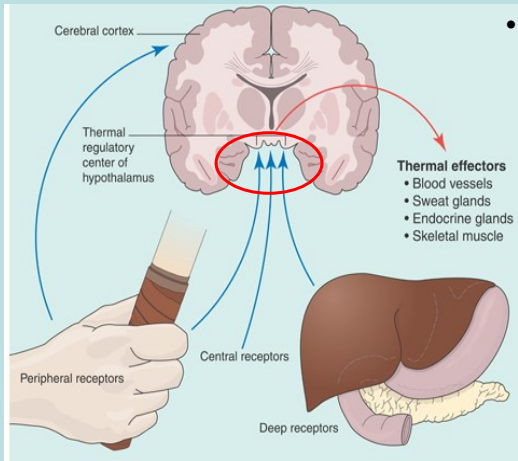
Hypothalamus sensing of Temperature



- Mechanisms are activated in two ways:
  - Thermal receptors in skin provide input to central command
  - Direct stimulation of hypothalamus through changes in temperature of blood perfusing the area

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Body Temperature Regulation

- The thermoregulatory center functions to modify heat production and heat losses as a means of regulating body temperature.
  - The thermoregulatory center in the hypothalamus regulates the core body temperature, not the surface temperature.
- This center integrates input from cold and warm ***thermal receptors*** located throughout the body and generates output responses that conserve body heat or increase its dissipation = ***thermostatic set point.***
  - When body temperature begins to rise above the normal range, heat-dissipating behaviors are initiated;
  - When the temperature falls below the normal range, heat production is increased;
- A core temperature greater than 41°C or less than 34°C usually indicates that the body's ability to thermoregulate is impaired.

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Body Temperature Regulation - Heat Gain

- Mechanisms involved in regulation:
  - Vasoconstriction of the superficial blood vessels - confines blood flow to the inner core of the body;
  - Contraction of the pilomotor muscles that surround the hairs on the skin - reduces the heat loss surface of the skin;
  - Assumption of the huddle position with the extremities held close to the body - reduces the area for heat loss;
  - Shivering - increases heat production by the muscles. It is initiated by impulses from the hypothalamus;
  - Increased production of epinephrine - increases the heat production associated with metabolism;
  - Increased production of thyroid hormone - is a long-term mechanism that increases metabolism and heat production.

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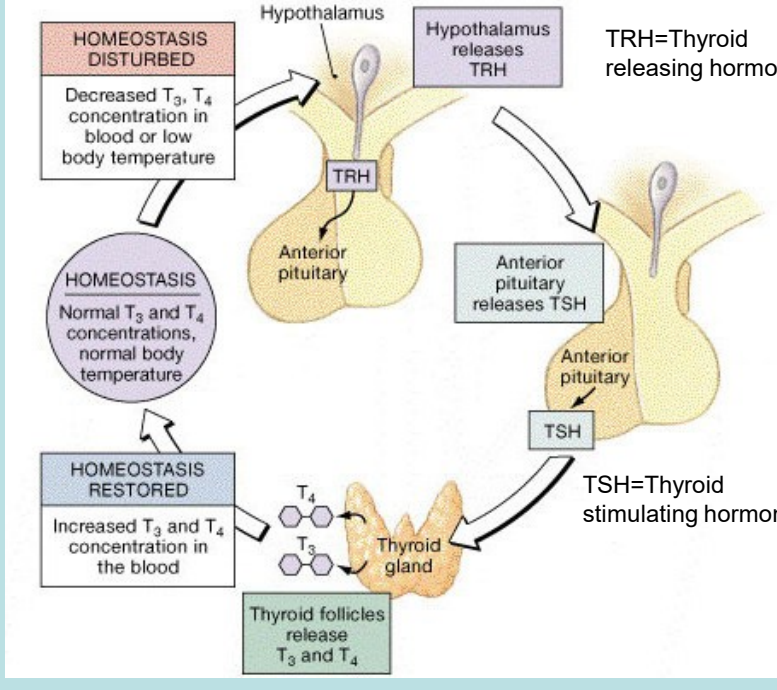

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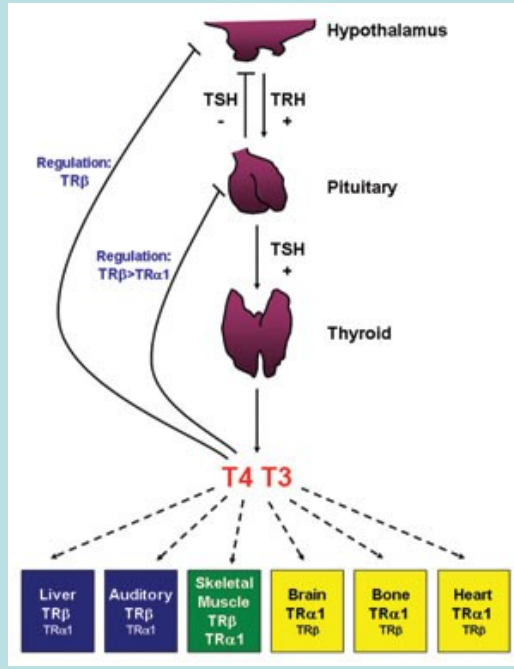

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Body Temperature Regulation - Heat Loss

- Mechanism involved in regulation:
  - Dilatation of the superficial blood vessels - delivers blood containing core heat to the periphery where it is dissipated through radiation, conduction, and convection;
    - There are numerous *arteriovenous (AV) shunts* under the skin surface that allow blood to move directly from the arterial to the venous system.
    - When the shunts are open, body heat is freely dissipated to the skin and surrounding environment;
    - When the shunts are closed, heat is retained in the body.
    - The blood flow in the AV shunts is controlled almost exclusively by the sympathetic nervous system in response to changes in core temperature and environmental temperature environment.
  - Sweating - increases heat loss through evaporation.

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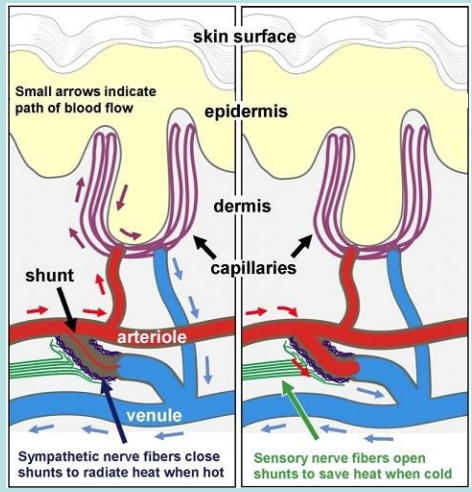
Mechanism of action of the arteriovenous shunt



In the extremities there are specialized shunts (think valves), which can redirect blood flow towards or away from the capillary beds in the palms and soles

"**The AV shunts create a bypass of the capillary bed for the major purpose of regulating body temperature…**

Under warm conditions, the shunts close down to force blood into the capillaries at the surface of the skin in order to radiate heat from the body, and our hands get sweaty. Under cold conditions, the shunts open wide allowing blood to bypass the capillaries in order to conserve heat, and our hands get cold."

The shunts are controlled by nerve fibres that open and close as needed.

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Causes of fever

- Central type fever= ***neurogenic fever***
- Non – central type fever:
  - Infectious disorders
  - Noninfectious disorders:
    - Myocardial infarction
    - Pulmonary emboli
    - Neoplasms (e.g. malignant cells in leukemia, Hodgkin's disease produce pyrogens)
    - Trauma
    - Surgery

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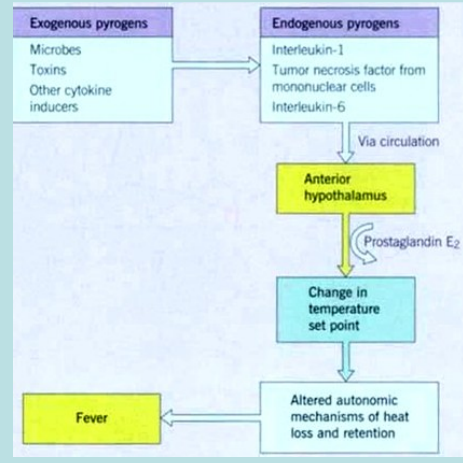
Mechanism of Fever

- Fever can be caused by a number of microorganisms and substances that are collectively called **exogenous *pyrogens*** **(**many proteins, breakdown products of proteins, lipopolysaccharide toxins released from bacterial cell membranes, etc.).
  - *exogenous pyrogens,* act indirectly and may require several hours to produce their effect. **these exogenous pyrogens induce host cells to produce fever-producing mediators such as interleukins and prostaglandin**
  - Some pyrogens can act directly and immediately on the hypothalamic thermoregulatory center to increase its set point.



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Mechanisms of fever

- Exogenous pyrogens induce host cells, such as blood leukocytes and tissue macrophages, to produce fever-producing mediators called *endogenous pyrogens* (*e.g.,* interleukin-1).
  - The endogenous pyrogens mediate a number of other responses. For example, interleukin-1 is an inflammatory mediator that produces other signs of inflammation, such as leukocytosis, anorexia, and malaise.
- The phagocytosis of bacteria and breakdown products of bacteria that are present in the blood lead to the release of endogenous pyrogens into the circulation.
- The endogenous pyrogens increase the set point of the hypothalamic thermoregulatory center through the action of prostaglandin E2.
- In response to the sudden increase in set point, the hypothalamus initiates heat production behaviors (shivering and vasoconstriction) that increase the core body temperature to the new set point, and fever is established.

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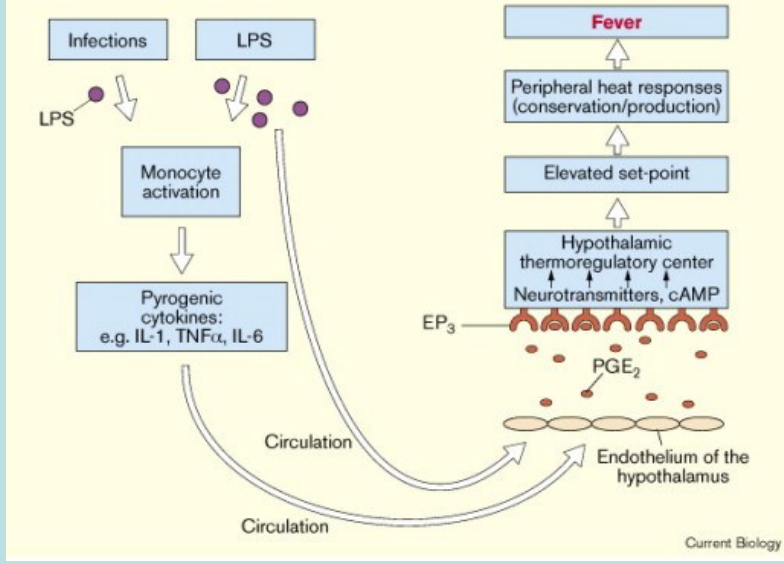

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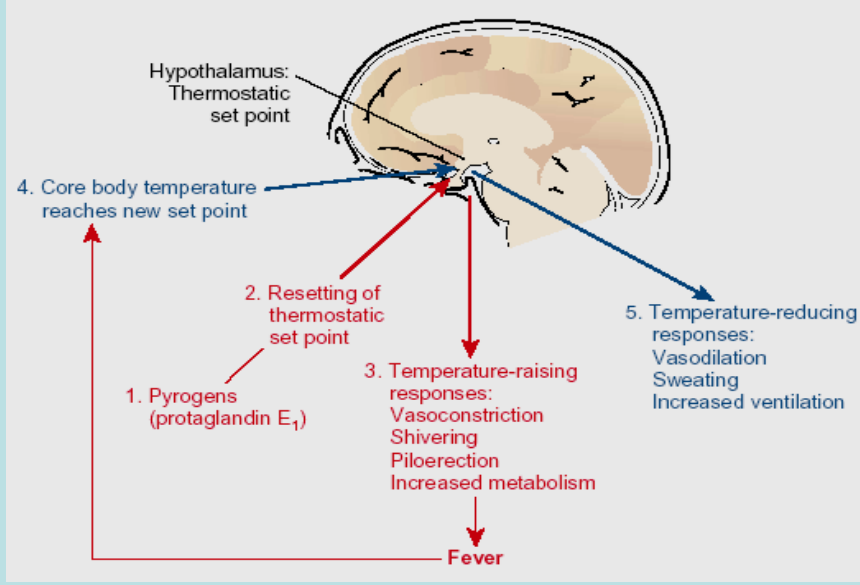
Mechanisms of fever



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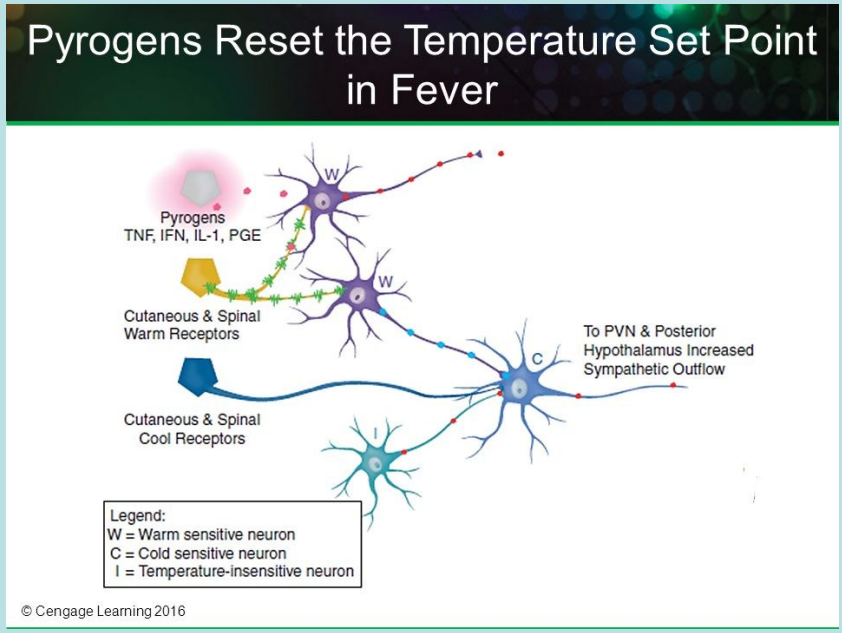

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Mechanisms of fever

- (1) release of endogenous pyrogen from inflammatory cells;
- (2) resetting of hypothalamus thermostatic set point to a higher level (prodrome);
- (3) generation of hypothalamic mediated responses that raise body temperature (chill);
- (4) development of fever with elevation of body to new thermostatic set point;
- (5) production of temperature lowering responses (flush and defervescence) and return of body temperature to a lower level.

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Hypothalamus :

– releases TSH to increase production of T3 & T4

– releases ACTH which increases release of glucocorticoids

– Causes increased release of epinephrine (adrenalin)

– Decreases production of ADH

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Manifestations of fever

- There are 4 successive stages - not all persons proceed through the four stages of fever development:
  - 1. Prodrome
    - nonspecific complaints, such as mild headache and fatigue, general malaise, and fleeting aches and pains;
  - 2. Temperature rises
    - generalized shaking with chills and feeling of being cold;
    - vasoconstriction and piloerection usually precede the onset of shivering;
    - skin is pale;
    - when the shivering has caused the body temperature to reach the new set point of the temperature control center, the shivering ceases, and a sensation of warmth develops.
  - 3. Flush
    - cutaneous vasodilation occurs and the skin becomes warm and flushed;
  - 4. Defervescence
    - the initiation of sweating.

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Types of fever

- Intermittent
  - Temperature returns to normal at least once every 24 hours;
  - It is commonly associated with conditions such as gram - negative / positive sepsis, abscesses, and acute bacterial endocarditis;
- Remittent
  - Temperature does not return to normal and varies a few degrees in either direction;
  - It is associated with viral upper respiratory tract, legionella, and mycoplasma infections;
- Sustained or continuous
  - Temperature remains above normal with minimal variations;
  - It is seen in persons with drug fever;
- Relapsing
  - There is one or more episodes of fever, each as long as several days, with one or more days of normal temperature between episodes;
  - It may be caused by a variety of infectious diseases, including tuberculosis, fungal infections, Lyme disease, and malaria.

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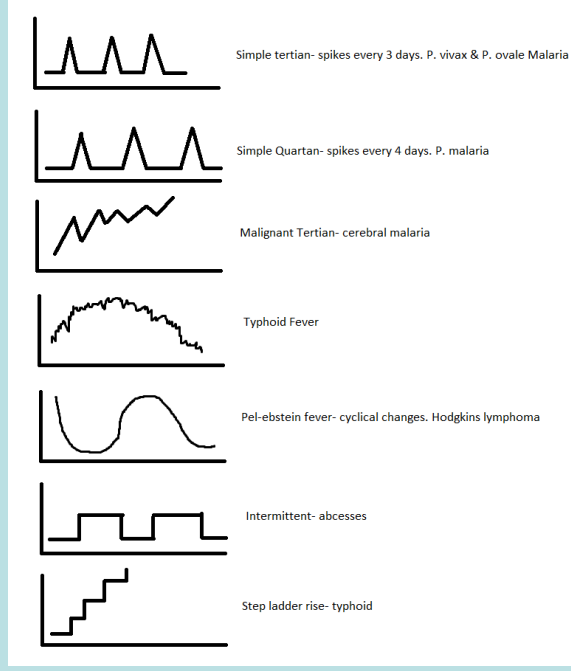

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Fever of unknown origin

- It is defined as a temperature elevation of 38.3°C or higher that is present for 3 weeks or longer.
- Among the causes are:
  - malignancies (lymphomas, metastases to the liver and central nervous system);
  - infections such as human immunodeficiency virus or tuberculosis, or abscessed infections;
  - drug fever;
  - cirrhosis of the liver.

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The effects of fever

- Dehydration (sweating) and loss of salts and minerals
- Metabolic effects:
  - Increased need for oxygen;
    - Increases the heart rate
    - Increases the respiration rate
  - During fever the body switches from using glucose to metabolism based on protein and fat breakdown;
  - Increased use of body proteins as an energy source;
  - With prolonged fever, there is increased breakdown of endogenous fat stores;

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The effects of fever

If fat breakdown is rapid, metabolic acidosis may result.

CNS effects: headache, convulsion, illusion

Digestive: loss of appetite, bad digestion – decrease in glucose intake

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Benefits of fever- why fever is good?

Increased temperature kills microorganisms and adversely affects their growth and reproduction

Decrease serum levels of iron, copper and zinc – needed for bacterial reproduction

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Benefits of fever- why fever is good? II

- Causes lysosomal breakdown and autodestruction of cells, preventing viral replication in infected cells
- Increased leukocyte motility
- Facilitates the immune response – activation of T cells
- Enhances phagocytosis
- Production of interferon increased

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But fever is bad when:

- too high – impairs neurological and respiratory functions
  increased work load of heart in patients with heart disease or stroke
- damage to hypothalamus can cause temp. to become dangerously high
- Can cause complications in pregnancy
- Fever over 106°F (41 °C) requires emergency care

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CAUTION **Problems with body temperature regulation**

Certain individuals may not be able to mount a full-blown fever response - we have to be careful in our evaluations of temperature elevations in these people:

- Infants under 3 months of age have difficulty regulating temperature
- immunosuppressed people
- Body temperature is lowered in the elderly, so fevers are not as high

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Principles of treatment

- Because fever is a disease symptom, its manifestation suggests the need for ***treatment of the primary cause.***
- Actions:
  - modifications of the external environment intended to increase heat transfer from the internal to the external environment;
  - support of the hypermetabolic state that accompanies fever;
  - protection of vulnerable body organs and systems;
  - treatment of the infection or condition causing the fever.

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Antipyretic drugs

- Antipyretic drugs, such as aspirin and acetaminophen, often are used to alleviate the discomforts of fever and protect vulnerable organs, such as the brain, from extreme elevations in body temperature.
- These drugs act by resetting the hypothalamic temperature control center to a lower level, presumably by blocking the activity of cyclooxygenase, an enzyme that is required for the conversion of arachidonic acid to prostaglandin E2.

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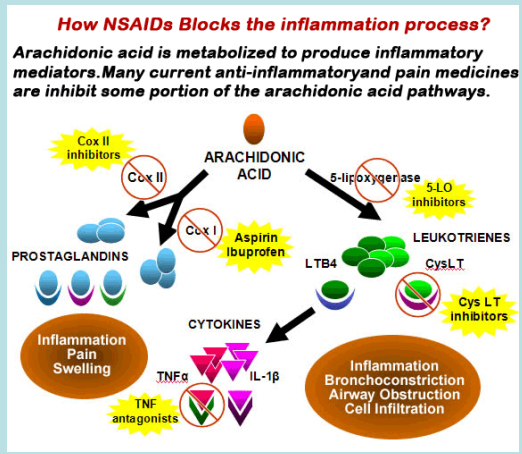
Prostaglandins are inhibited by non-steroidal anti-inflammatory drugs (aspirin, tylenol, motrin etc.)

(although overdose of aspirin raises body temp.)



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Fever in children

- The mechanisms for controlling temperature are not well developed in the infant.
- In infants younger than 3 months, a **mild elevation in temperature (*i.e.,* rectal temperature of 38°C) can indicate serious infection.**
- Both minor and life-threatening infections are common in the infant to 3-year age group.
- The most common causes of fever in children are minor or more serious infections of the respiratory system, urinary system, gastrointestinal tract, or central nervous system. Occult bacteremia and meningitis also occur in this age group and should be excluded as diagnoses.

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Manifestations

- Fever in infants and children can be classified as low risk or high risk, depending on the probability of the infection progressing to bacteremia or meningitis.
- Signs of toxicity (and high risk) include lethargy, poor feeding, hypoventilation, poor tissue oxygenation, and cyanosis.
- Blood and urine cultures, chest radiographs, and lumbar puncture usually are done in high-risk infants and children to determine the cause of fever.
- Febrile seizures can occur in some children.

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Fever in the elderly

- In the elderly, even slight elevations in temperature may indicate serious infection or disease. This is because the elderly often have a lower baseline temperature.
- Normal body temperature and the circadian pattern of temperature variation often are altered in the elderly.
- The absence of fever may delay diagnosis.
- Unexplained changes in functional capacity, worsening of mental status, weakness and fatigue, and weight loss are signs of infection in the elderly.
- Confusion and delirium may follow moderate elevations in temperature.

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Mechanisms

- Disturbance in sensing of temperature by the thermoregulatory center in the hypothalamus;
- Alterations in release of endogenous pyrogens;
- The failure to elicit responses such as vasoconstriction of skin vessels, increased heat production, and shivering that increase body temperature during a febrile response.
- Because of the increasingly poor oxygen uptake by the aging lung, pulmonary function may prove to be a limiting factor in the hypermetabolism that accompanies fever in older persons.
  - Confusion, incoordination, and agitation commonly reflect cerebral hypoxemia.

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