8: Alterations in Cognitive Systems, Cerebral Hemodynamics and Motor Function

Consciousness

- State of awareness of oneself and the surrounding environment

Clinical assessment:

- **Simple procedure**:
  - Checking ability to move and react to physical stimuli
  - Response in a meaningful way to questions and commands
  - Orientation to person, place, time
    - Identify name, current location, and current day and time
  - Check Level of consciousness (LOC)
- **Complex procedure**:
  - Glasgow Coma Scale, based on:
    - Eye response
    - Verbal response
    - Motor response
  - Gives cumulative score ranging from 3-15 with 3 being unconscious and 15 normal cognitive function

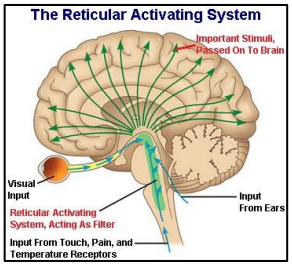

Figure 31: Reticular activating system (RAS)

Alterations in Cognitive Systems - Arousal & Awareness

Arousal: being awake or reactive to stimuli

Awareness: encompasses all cognitive functions

Clinical assessment & impairment

- Five categories for assessment:
  1. Level of consciousness
     - Awake = intact respiration, endocrine, RAS (The reticular activating system) which works with the limbic system (emotions) to coordinate the brain with the environment
  2. Pattern of breathing
  3. Pupillary changes & eye responses
  4. Oculomotor responses
  5. Motor responses
     - Vomiting, yawning, hiccups

Acute Confusional States (ACS) - *Delirium*

- Transient disorder of awareness that result from cerebral dysfunction

Causes:

- Secondary to drug intoxication, metabolic disorder, or nervous system disease
- Common in post-op patients
- Increased in elderly population

Types

- Hyperkinetic – They pull IV lines, get out of their hospital bed
- Hypokinetic – Flaccid, no response to anything

Brain Death

- Brain can no longer maintain internal homeostasis
    - Absence of functioning in brain including the brainstem and cerebellum
    - Condition observed for an extended period of time

Brain death criteria:

- Established etiology capable of causing neurological death in the absence of reversible conditions capable of mimicking neurological death
- Unresponsive coma with bilateral absence of motor responses, excluding spinal reflexes
- No brainstem function
- No spontaneous respiration (apnea)
- Absence confounding factors
    - Occurs because of known structural defect or metabolic disease

Cerebral Death

- Cerebral death (irreversible coma) is death of the cerebral hemispheres **exclusive of the brainstem and cerebellum**
- No behavioural or environmental responses
- The brain can continue to maintain internal homeostasis
- Survivors of cerebral death:
    - Remain in coma
    - Emerge into a persistent vegetative state
    - Progress into a minimally conscious state (MCS)
    - *The patient will never regain behavioural responses to stimuli*

Seizures

- Sudden (definitive feature), transient, excessive electric activity within the brain (neuron firing)
- Can be motor, sensory, autonomic, or psychic in nature
- Can be partial (focal) or generalized

Etiology

- Etiologic factors are wide and diverse in range
- *Epilepsy*:
    - A specific chronic CNS disease of abnormal brain activities characterized by ≥ 2 unprovoked seizures to make a diagnosis
    - Seizure activity with no underlying, diagnosable cause
    - Affects both males and females of all races, ethnic backgrounds and ages.
    - Symptoms can vary widely from simply stare blankly for a few seconds during a seizure, repeated twitches of arms or legs or severe lasting ones
- **CNS lesions, including:**
    - Meningitis
    - Multiple sclerosis (MS)
    - Tetanus
    - Trauma
- **Biochemical disorders including:**
    - Elevated bilirubin in children
    - Fever
    - Encephalitis
    - Electrolyte imbalance
    - Hypoglycemia
    - Lead poisoning

Manifestations

- Loss of consciousness
- Sudden loss of autonomic control
    - Incontinence is common and can be embarrassing for the person when they recover
- *Convulsions*: Jerky (rapid and repeated) contract-relax body movements
    - Also called *tonic-clonic* seizures

- *Aura*: Perceptions experienced a few seconds-hours before seizure (or migraine) begins
  - **Examples**: strange light, unpleasant smell or confusing thoughts
- A seizure is **NOT** a disease, it is a manifestation within a larger disorder

Data Processing Deficits

- The brain is responsible for receiving, processing, and interpreting data from sensors throughout the body
  - Brodmann's cytoarchitectural map identifies, generally, specialized areas of the brain used for receiving and processing this data

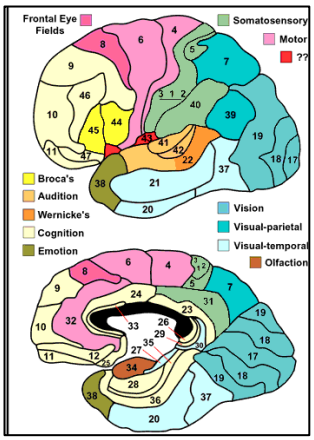

Figure 32: Brodmann's cytoarchitectural map

- *Agnosia*: Inability to process sensory information and recognize form and nature of objects
  - Poor recognition
  - May be tactile, visual, auditory, etc., or a combination depending on the areas of the brain impacted
- *Dysphasia*: Impairment of production or comprehension of language
  - Reduced ability to speak, read, or write
  - Classified both anatomically and functionally including:
    - Expressive dysphasia
    - Receptive dysphasia
    - Transcortical dysphasia
      - Person is able to repeat (echolalia) and recite with fluent speech, however comprehension is impaired, and speech makes no sense
      - They are unable to read or write in their own language
  - *Aphasia:* Severe form of dysphasia whereby the person is unable to communicate
    - Example: A person can see the glass in their hands, they know what it is, but they cannot verbally tell you they are holding a glass

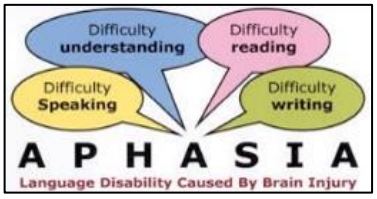

Figure 33: Types of aphasia

Dementia

- **Progressive** failure of cerebral functions that is not caused by an impaired level of consciousness
- Often includes decreased functioning and losses in:
  - Orientation
  - Memory
  - Language

  - Judgment
  - Decision making
- As intellectual function declines, the person will exhibit behaviour changes becoming more repetitive, obsessive, and decline in social functioning

Causes:

- Alzheimer disease
  - Most famous (see below)
- Vascular dementia
- Dementia with Lewy bodies (DLB)

Mechanisms:

- Neuron degeneration
- Brain tissue compression
- Atherosclerosis
- Brain trauma
- CNS infections
  - Such as HIV and slow-growing viruses associated with Creutzfeldt-Jakob disease
- Genetic predisposition associated with neurodegenerative diseases

Alzheimer Disease (AD)

- Structural changes in the brain leading to dramatic decline in intellectual functions.

Etiology

- Unknown, however there is a genetic link to Chromosome 21 in those with early onset AD and chromosome 19 in those with late onset

Pathophysiology

- Premature neuron death and cellular changes, characterized by:
  - *Amyloid plaques* accumulates in extracellular spaces
  - *Neurofibrillary tangles* (twisted bundles of filaments) intracellularly
  - Intracellular vacuoles leading cellular swelling and death with shrinkage of brain matter

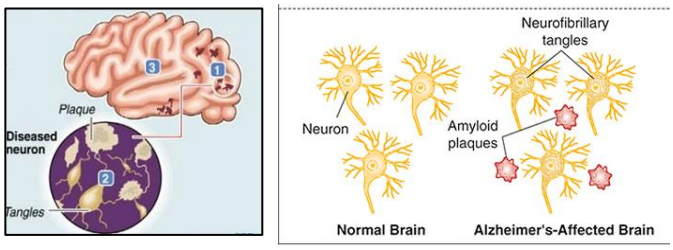

Figure 34: Plaques and tangles implicated in Alzheimer's disease

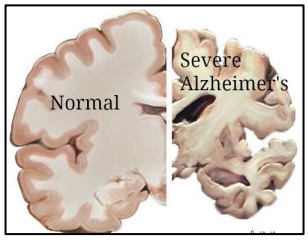

Figure 35: Comparison of normal brain to that of person with severe Alzheimer's

Theories

- Mutation in genes coding amyloid precursor protein
- Alteration in apolipoprotein E (ApoE)
- Impairment in choline acetyltransferase

Clinical manifestations:

- Forgetfulness
- Emotional upset
- Disorientation
- Confusion
- Lack of concentration
- Decline in abstraction, problem solving, and judgment
- Rule-out diagnosis
    - Diagnosis is made by ruling out other causes of dementia
    - The only definitive diagnosis can be made on autopsy

Cerebral Hemodynamics

Basics

- *Cerebral blood flow* (CBF): Amount of blood flow to the brain
    - Maintained at a rate required to meet metabolic needs
    - Constitutes 15% of cardiac output
    - Calculated by the formula CBF = CPP/CVR
- *Cerebral perfusion pressure* (CPP): Pressure required to perfuse cells of brain
    - Calculated by the formula **CPP =MAP-ICP**
- *Intracranial pressure* (ICP)
    - Normally 5 to 15 mmHg

Increased Intracranial Pressure (IICP)

- Caused by increase in intracranial content
    - For example, tumor, edema, excessive CSF, or hemorrhage

Stages:

- **Stage 1**
    - Minimal increase in ICP
    - Usually compensated
- **Stage 2**

- Systemic arteriolar vasoconstriction to increase MAP and CPP and maintain neuronal oxygenation

- **Stage 3**
  - Sustained increased ICP approaching MAP

Cerebral Edema

- Increase in the fluid (intracellular or extracellular) within the brain

Causes:

- Brain trauma
- Non traumatic causes
  - Ischemic stroke
  - Cancer
  - Inflammation (meningitis/encephalitis)

Pathophysiology and Types:

Vasogenic:

- Disruption of blood brain barrier (BBB)
- Intravascular proteins and fluid escape to brain parenchyma

Cytotoxic:

- BBB remains intact, toxins impair cellular metabolism

Interstitial:

- Disruption of Blood-CSF barrier
- CSF flows to interstitial space

Hydrocephalus

- Abnormal accumulation of CSF in the ventricles, subarachnoid space within the brain

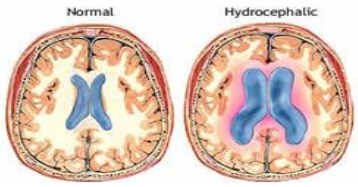

Figure 36: Comparison normal brain (right) to brain with hydrocephalus (left)

Pathophysiology and features:

- Interference in CSF flow
- Increased intracranial pressure
- Head enlargement
- Impairment of cognitive functions
  - Related to increased compression on neuronal axons and decreased oxygen perfusion and ICP increases

Treatment

- Shunt inserted to drain fluid

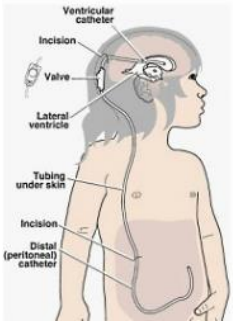

Figure 37: Shunt used to drain fluid in hydrocephalus

8: Alterations in Movement

Alterations in Movement - Terminology

Upper motor neuron syndromes:

- *Hemiparesis* or *hemiplegia*
- *Diplegia*
- *Paraparesis* or *paraplegia*
- *Quadriparesis* or *quadriplegia*

Lower motor neuron syndromes:

- *Flaccid paresis* or *flaccid paralysis*
- *Hypertonia* and *hypotonia*
- *Hyperkinesia*
    - Excessive, purposeless movement
- *Paroxysmal dyskinesias*
    - Abnormal, involuntary movements that occur as spasms

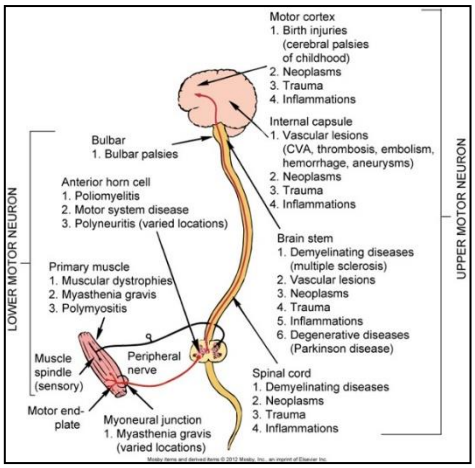

Figure 38: Motor function syndromes

- *Tardive dyskinesia*
    - Involuntary movement of face, lip, tongue, trunk, and extremities
    - Usually a side effect of antipsychotic medication
- *Hypokinesia*, *Akinesia*, Bradykinesia
    - Slowed or absent movement

Huntington Disease

- Autosomal dominant degenerative disorder

Pathophysiology:

- CAG repeats in *Huntington gene* located on chromosome 4
- There is depletion of gamma-aminobutyric acid (GABA) (an inhibitory transmitter)
    - Leads to increase in involuntary movement
- Severe degeneration of the basal ganglia (caudate nucleus) and cerebral cortex

Clinical manifestations:

- ***Chorea*** **(characteristic manifestation)**
    - Non-repetitive muscular contractions, usually in the extremities of the face
    - Random, irregular pattern of rapid, involuntary muscular contractions
    - Decreases with sleep and rest
    - Increases with emotional stress and attempted voluntary movement

- Related to changes occurring at the level of the basal ganglia

- General restlessness, lack of coordination, involuntary eye movements
- Subtle changes in personality, emotion, cognition abilities

Parkinson Disease

- A common chronic and progressive neurodegenerative disorder

Pathophysiology:

- Severe degeneration of the basal ganglia
- Diminished dopamine released by substantia nigra
- Thalamus and globus palladium become overactive resulting in motor impairments

Clinical Manifestations:

- Parkinsonian tremors, rigidity, bradykinesia
- Postural disturbances
- Autonomic and neuroendocrine symptoms
- Cognitive-affective symptoms

Disorders of Posture, Gait & Expression - Terminology

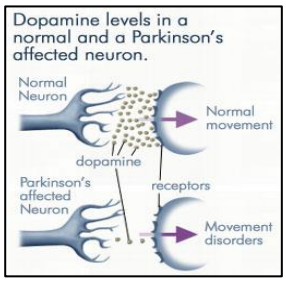

Figure 39: Dopamine levels in normal neurons versus those of one with Parkinson's disease

Figure 40: Classic Parkinsonian gait and stance

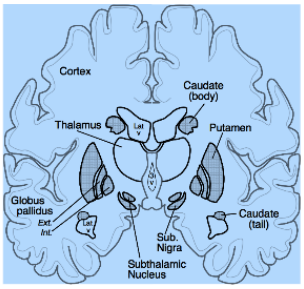

Figure 41: Brain structures impacted in Parkinson Disease

Disorders of Posture (Stance):

- *Dystonia*:
  - Maintenance of abnormal postures through muscular contractions
  - Dystonic and associated movements
    - Dystonic movements last seconds while dystonic postures are held for longer periods
- *Decorticate*:
  - Flexion inwards towards 'core' of body
- *Decerebrate*:
  - Extension outwards from body

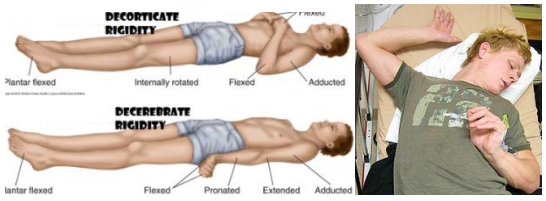

Figure 42: Decorticate and decerebrate posturing

- *Basal ganglion*
- *Senile*:
    - Increased flexed posture similar to basal ganglion

Disorders of Gait

- *Spastic gait*:
    - Shuffling gait with one leg extended and the other held stiff, which can often lead to it being dragged
    - Associated with unilateral injury
- *Scissors gait*:
    - Legs adducted so they touch and then swing around each other
    - Associated with bilateral injury and spasticity
- *Cerebellar gait*:
    - Wide base with feet often turned inward or outward for stability
- *Basal ganglion gait*:
    - Stooped, hyperflexed posture with narrow base and short-stepped gait with decreased arm swing
- *Senile gait*:
    - Similar to the basal ganglion gait

Figure 43: Disorders of gait (spastic, scissors)

Disorders of Expression:

- *Hypermimesis:*
    - Pathologic laughter or crying
- *Hypomimesis:*
    - Loss of emotion in language (arhapsody)
    - Also, receptive arhapsody where the person is unable to understand emotional speech and facial expressions
- *Dyspraxias and apraxias:*
    - Difficulty planning and executing coordinated motor movements
        - Examples of tasks include speaking, writing, using tools/utensils, playing sports, following instructions, and the ability to focus
    - May be developmental or associated with vascular disorders (common in stroke), trauma, infection, tumors, degenerative disorders

8: Pain, Temperature, Sleep, and Sensory Function

Pain

- *An an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

Neuroanatomy of Pain

- ***Nociceptors***
  - Receptors for pain
  - Free nerve endings in skin, muscle, joints, arteries, viscera
  - Can also detect chemical, mechanical, thermal stimuli
- **Pathways of nociception**:
  - Located in the spinothalamic tract
  - **Processes required for nociception**:
    - *Transduction*: Activation of nociceptors
    - *Transmission*: Conduction to dorsal horn and up via spinal cord
    - *Perception*: Awareness of pain
    - *Modulation*: Facilitation or inhibition of transmission before during, or after perception
      - **Excitatory neuromodulators**
        - Substance P, glutamate
      - **Inhibitory neuromodulators**
        - GABA, glycine, serotonin, norepinephrine, *endorphin*

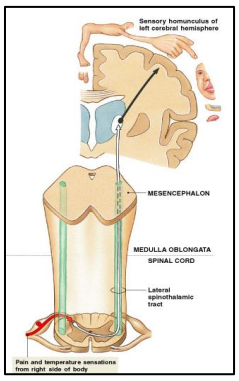

Figure 44: Pathways of nociception in the spinothalamic tract

Neuromodulation of Pain- *Endogenous Opioids*

- Short sequences of amino acids that bind to opioid receptors
  - Produce similar effect to opiates such as morphine
- **Types**:
  - *Endorphins*:
    - Block transmission of pain signals
    - Produce a feeling of euphoria
  - Enkephalins
  - Dynorphins
  - Endomorphins

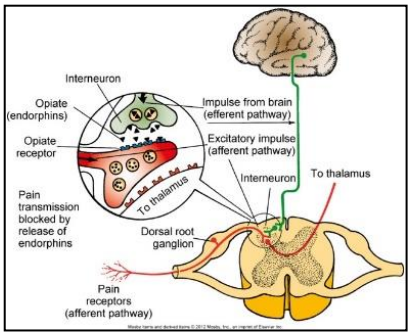

Figure 45: Endogenous opioids in the brain

Clinical Description of Pain

- *Pain threshold*:
  - Point at which a stimulus is perceived as pain
- *Perceptual dominance*:
  - Pain at one location may cause an increase in the threshold in another location
- *Pain tolerance*:
  - Duration of time or the intensity of pain that a person will endure before initiation of pain responses

Types/ Categories of Pain

Psychogenic pain

- Physical pain that is caused, increased, or prolonged by mental, emotional, or behavioral factors

Referred pain:

- Pain in an area distant from its point of origin
- Area of referred pain is supplied by the same spinal segment as the actual site eg myocardial infarction pain

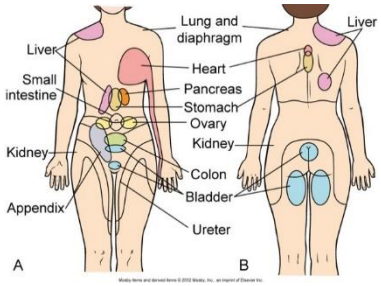

Figure 46: Referred pain locations

Acute Pain:

- Protective mechanism
- Alerts an individual to a condition or experience that is harmful to the body
- **Acute somatic**
  - Arises from skin, joints, and muscles
  - Pain is transmitted along A-delta and C-fibres
    - *A delta fibres*: pain is sharp and well localized
    - *C fibres*: dull, aching, and poorly localized
- **Acute visceral**
  - Pain in the internal organs and lining of body cavities
  - Transmitted by C fibres:
    - Poorly localized with an aching, gnawing, throbbing, or intermittent cramping quality
  - Often radiates or is referred

Chronic Pain

- May be persistent or intermittent
- Usually defined as lasting at least 3 to 6 months

- Response patterns vary
- Produces significant behavior and psychologic changes
- Usually no physiological signs as in acute
- **Common types**:
    - *Myofascial pain syndromes*:
        - Injury to the muscle and fascia with spasm, tenderness, and stiffness
    - *Chronic postoperative pain*:
        - Pain persisting beyond expected recovery time
    - *Cancer pain*:
        - Pain occurring from the tumor, procedure, treatment, infection
        - Requires different treatment approach than other types of chronic pain
        - Opioids were initially designed for treatment of cancer pain
    - *Neuropathic pain*: resulting from trauma or nerve disease (non-nociceptors)
        - **Peripheral**: e.g. diabetic neuropathy
        - **Central**: e.g. phantom limb (following amputation)

Temperature Regulation

- *Homeostasis*: Maintenance of a 'steady state' within the body
    - The body regulates temperature to maintain homeostasis (review these mechanisms from previous lectures)
- Age is a key factor affecting temperature regulation, particularly in the very young and old
    - **Pediatrics**:
        - Children produce sufficient body heat, but are unable to conserve heat produced due to:
            - Small body size and high body surface to weight ratio
            - Thin subcutaneous layer
        - Brown-fat contributes in increased heat production in cold temperatures
    - **Aging**
        - Slow blood circulation, vasoconstrictive response, and decreased metabolic rate
        - Decreased sweating, shivering, and perception of heat and cold

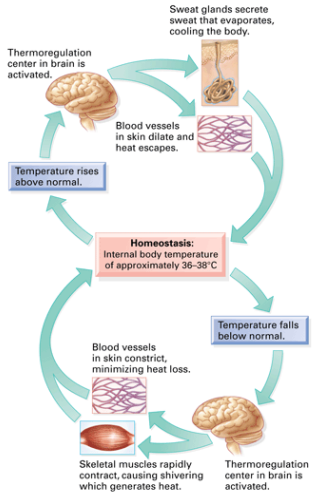

Figure 47: Homeostatic processes in temperature regulation

Mechanisms of Temperature Regulation

- **Heat Production and Conservation**
  - Processes regulated by the hypothalamus and include:
    - Chemical reactions of metabolism
    - Skeletal muscle contraction
    - Chemical thermogenesis
    - Vasoconstriction
    - Voluntary mechanisms
- **Mechanisms of Heat Loss:**
  - Radiation
  - Conduction
  - Convection
  - Vasodilation
  - Decreased muscle tone
  - Evaporation
  - Increased respirations
  - Voluntary measures
  - Adaptation to warmer climates

TABLE 13-5 MECHANISMS OF HEAT PRODUCTION AND HEAT LOSS

CONDITION	DESCRIPTION
Heat Production	
Chemical reactions of metabolism	Occur during ingestion and metabolism of food and while maintaining body at rest (basal metabolism); occur in body core (e.g., liver)
Skeletal muscle contraction	Gradual increase in muscle tone or rapid muscle oscillations (shivering)
Chemical thermogenesis	Epinephrine is released and produces rapid, transient increase in heat production by raising basal metabolic rate; quick, brief effect that counters heat lost through conduction and convection; involves brown adipose tissue, which decreases markedly in older adults; thyroid hormone increases metabolism
Heat Loss	
Radiation	Heat loss through electromagnetic waves emanating from surfaces with temperature higher than surrounding air
Conduction	Heat loss by direct molecule-to-molecule transfer from one surface to another, so that warmer surface loses heat to cooler surface
Convection	Transfer of heat through currents of gases or liquids; exchanges warmer air at body's surface with cooler air in surrounding space
Vasodilation	Diverts core-warmed blood to surface of body, with heat transferred by conduction to skin surface and from there to surrounding environment; occurs in response to autonomic stimulation under control of hypothalamus
Evaporation	Body water evaporates from surface of skin and linings of mucous membranes; major source of heat reduction connected with increased sweating in warmer surroundings
Decreased muscle tone	Exhausted feeling caused by moderately reduced muscle tone and curtailed voluntary muscle activity
Increased respiration	Air is exchanged with environment through normal process; minimal effect
Voluntary mechanisms	"Stretching out" and "slowing down" in response to high body temperatures; increasing body surface area available for heat loss; dressing in light-colored, loose-fitting garments
Adaptation to warmer climates	Gradual process beginning with lassitude, weakness, and faintness; proceeding through increased sweating, lowered sodium content, decreased heart rate, and increased stroke volume and extracellular fluid volume; and terminating in improved warm weather functioning and decreased symptoms of heat intolerance (work output, endurance, and coordination increase; subjective feelings of discomfort decrease)

Figure 48: Mechanisms of heat loss and production

Fever

- Resetting of the hypothalamic thermostat
  - Elevation occurs in response to exogenous/ endogenous *pyrogens*
- *Fever of unknown origin* (FUO)
  - Temperature >38.3C that remains undiagnosed after 3 days in hospital or ≥ 2 outpatient visits
- **Benefits of Fever**:
  - Kills many microorganisms
  - Promotes lysosomal breakdown and auto-destruction of cells
  - Increases lymphocytic transformation and phagocyte motility
  - Augments antiviral interferon production and phagocytosis

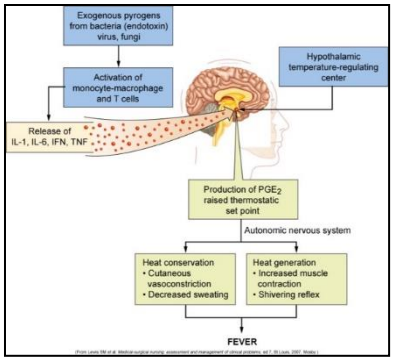

Figure 49: Pathophysiology of fever

Hyperthermia

- Not mediated by pyrogens & no resetting of hypothalamic set point. MORE serious than fever.
    - **41º C (105.8º F):** nerve damage produces convulsions
    - **43º C (109.4º F):** death results
- **Forms of hyperthermia include:**
    - Heat cramps
    - Heat exhaustion
    - Heatstroke

Malignant hyperthermia:

- Complication of inherited muscular disorders
- Can happen after surgery
- Precipitated by inhaled anesthetics, neuromuscular blocking agents

Pathophysiology:

- Impaired calcium release/uptake during muscle contraction
- Increased oxygen consumption and lactic acid production

Clinical features:

- Sustained muscle contractions
- Absent reflexes, fixed pupils, apnea, **flat ECG**

Heat Cramps

- Severe spasmodic cramps in abdomen and extremities following exercise in hot weather
- *Causes:*
    - Common in individuals not accustomed to heat
    - Performing strenuous work in warm climates
- *Pathophysiology:*
    - Prolonged sweating and associated sodium loss
- *Clinical manifestations:*
    - Fever
    - Rapid pulse
    - Increased blood pressure often accompanies the cramps

Heat Exhaustion

- A result of prolonged high core or environmental temperatures
- *Pathophysiology:*
    - Prolonged vasodilation and profuse sweating

- *Clinical manifestations:*
  - Dehydration, depressed plasma volumes, hypotension, decreased cardiac output, tachycardia
  - Dizziness, weakness, nausea, confusion, and syncope

Heatstroke ("Sun stroke")

- Potentially lethal condition, results of an overstressed thermoregulatory center
- Children are more susceptible:
  - They produce more metabolic heat when exercising
  - There is a greater surface area to mass ratio
  - Sweating capacity is less than in adults
- *Pathophysiology:*
  - Cardiovascular and thermoregulatory centers may cease functioning
  - Brain cannot tolerate temperatures >40.5º C (104.9º F)
- *Clinical manifestations:*
  - Cerebral edema
  - Degeneration of the CNS
  - Swollen dendrites
  - Renal tubular necrosis
  - Death

Hypothermia

- Body temperature less than 35º C. Can do this on purpose (operations to decrease BF)

Pathophysiology:

- CNS and respiratory depression
- Vasoconstriction & slow flow in the microcirculation
- Ice crystals form inside the cells, causing them to rupture and die
- Slow rate of cellular metabolism
- Increased blood viscosity
- Coagulation, and ischemic tissue damage

Types:

- **Accidental hypothermia**
  - Commonly the result of sudden immersion in cold water or prolonged exposure to cold
- **Therapeutic hypothermia**

- Used to slow metabolism and preserve ischemic tissue during surgery or limb re-implantation
- May lead to ventricular fibrillation and cardiac arrest

Trauma and Temperature Change

- CNS trauma leads to central fever
- Inflammation, increased ICP, intracranial bleeding
- **Examples**:
  - Accidental injuries
  - Major surgery
  - Thermal burns
- Temp monitoring is part of routine vital sign assessments

Sleep

- Active, multiphase process
- Hypothalamus is the major sleep center
- **Sleep occurs in two phases**:
  1. *Rapid eye movement (REM) sleep*:
     - 20% to 25% of sleep time
     - Also known as paradoxic sleep
     - Occurs every 90 minutes beginning after 1 to 2 hours of sleep
  2. *Non-rapid eye movement (NREM) sleep*:
     - 75% to 80% of sleep time
     - *Four stages evaluated by EEG*:
       - Stage I
       - Stage II
       - Stage III
       - Stage IV

Sleep Disorders

Primary sleep disorders

- *Dyssomnias*:
  - *Insomnia*: inability to fall asleep
  - *Primary and secondary hypersomnia*:
    - Primary: occurs with no other medical conditions present. The only symptom is excessive fatigue.

        - Secondary hypersomnia is due to other medical conditions. Examples include:
            - Parkinson's disease, kidney failure, and chronic fatigue syndrome

- *Parasomnias*:
    - *Somnambulism* (sleep walking)
    - *Night terrors* (child is asleep and has extreme fear, once awakened they forget the terror).
    - Restless legs syndrome:
        - Uncontrollable urge to move your legs, usually because of an uncomfortable sensation
        - Runs in families
        - No known cause. likely an imbalance of the brain chemical dopamine

Secondary sleep disorders

- **Alterations in the quality and/or quantity of sleep caused by primary diseases**
    - Depression
    - Pain
    - *Obstructive sleep apnea*: Most common sleep disorder with complex pathology including hypoxia and oxidative stress
    - Alterations in thyroid hormone secretion
- **Sleep-provoked disorders**
    - Sleep stage alterations produced in certain disease states