Neurophysiology of Pain
• Alteration in sensory function → dysfunctions of the general or special senses

• Dysfunctions of the general senses → chronic pain, abnormal temperature regulation, tactile dysfunction

**Definitions of pain**

• Pain is a complex unpleasant phenomenon composed of sensory experiences that include time, space, intensity, emotion, cognition, and motivation

• Pain is an unpleasant or emotional experience originating in real or potential damaged tissue

• Pain is an unpleasant phenomenon that is uniquely experienced by each individual; it cannot be adequately defined, identified, or measured by an observer
The experience of pain

Three systems interact to produce pain:

1. sensory - discriminative
2. motivational - affective
3. cognitive - evaluative

1. **Sensory - discriminative system** processes information about the strength, intensity, quality and temporal and spatial aspects of pain.

2. **Motivational - affective system** determines the individual’s approach-avoidance behaviours.

3. **Cognitive - evaluative system** overlies the individuals learned behaviour concerning the experience of pain. It may block, modulate, or enhance the perception of pain.
Pain categories

1. **Somatogenic pain** is pain with cause (usually known) localised in the body tissue
   a/ nociceptive pain
   b/ neuropatic pain

2. **Psychogenic pain** is pain for which there is no known physical cause but processing of sensitive information in CNS is disturbed

Acute and chronic pain

**Acute pain** is a protective mechanism that alerts the individual to a condition or experience that is immediately harmful to the body

**Onset** - usually sudden
Relief - after the chemical mediators that stimulate the nociceptors are removed

- This type of pain mobilises the individual to prompt action to relieve it

- Stimulation of autonomic nervous system can be observed during this type of pain (mydriasis, tachycardia, tachypnoe, sweating, vasoconstriction)

Responses to acute pain

- increased heart rate
- increased respiratory rate
- elevated blood pressure
- pallor or flushing, dilated pupils
- diaphoresis
- ↑ blood sugar
- ↓ gastric acid secretion
- ↓ gastric motility
- ↓ blood flow to the viscera, kidney and skin
- nausea occasionally occurs
Psychological and behavioural response to acute pain
- fear
- general sense of unpleasantness or unease
- anxiety

Chronic pain is persistent or intermittent usually defined as lasting at least 6 months

The cause is often unknown, often develops insidiously, very often is associated with a sense of hopelessness and helplessness. Depression often results
Psychological response to chronic pain

Intermittent pain produces a physiologic response similar to acute pain.

Persistent pain allows for adaptation (functions of the body are normal but the pain is not relieved)

Chronic pain produces significant behavioral and psychological changes

The main changes are:
- depression
- an attempt to keep pain-related behaviour to a minimum
- sleeping disorders
- preoccupation with the pain
- tendency to deny pain
Pain threshold and pain tolerance

The pain threshold is the point at which a stimulus is perceived as pain. It does not vary significantly among healthy people or in the same person over time.

Perceptual dominance - intense pain at one location may cause an increase in the pain threshold in another location.

The pain tolerance is expressed as duration of time or the intensity of pain that an individual will endure before initiating overt pain responses. It is influenced by - person’s cultural prescriptions - expectations - role behaviours - physical and mental health.
- Pain tolerance is generally decreased:
  - with repeated exposure to pain,
  - by fatigue, anger, boredom, apprehension,
  - sleep deprivation

- Tolerance to pain may be increased:
  - by alcohol consumption,
  - medication, hypnosis,
  - warmth, distracting activities,
  - strong beliefs or faith

Pain tolerance varies greatly among people and in the same person over time.

A decrease in pain tolerance is also evident in the elderly, and women appear to be more tolerant to pain than men.
Age and perception of pain

Children and the elderly may experience or express pain differently than adults.

Infants in the first 1 to 2 days of life are less sensitive to pain (or they simply lack the ability to verbalise the pain experience). A full behavioural response to pain is apparent at 3 to 12 month of life.

Older children, between the ages of 15 and 18 years, tend to have a lower pain threshold than do adults.

Pain threshold tends to increase with age.

This change is probably caused by peripheral neuropathies and changes in the thickness of the skin.
Neuroanatomy of pain

The portions of the nervous system responsible for the sensation and perception of pain may be divided into three areas:

1. afferent pathways
2. CNS
3. efferent pathways

The afferent portion is composed of:

a) nociceptors (pain receptors)
b) afferent nerve fibres
c) spinal cord network
• Afferent pathways terminate in the dorsal horn of the spinal cord (1st afferent neuron)

• 2nd afferent neuron creates spinal part of afferent system

• The portion of CNS involved in the interpretation of the pain signals are the limbic system, reticular formation, thalamus, hypothalamus and cortex

• The efferent pathways, composed of the fibers connecting the reticular formation, midbrain, and substantia gelatinosa, are responsible for modulating pain sensation
FIG. 13-2. Nociceptors and spinal segment. A, Nociceptive and other afferent and efferent pathways in a spinal nerve at the dorsal horn. B, Small A-delta and C fibers from synapses primarily with cells in lamina V but also with cells in laminae IV and VI.
The brain first perceives the sensation of pain

• The thalamus, sensitive cortex:
  - perceiving
  - describing
  - localising

• Parts of thalamus, brainstem and reticular formation:
  - identify dull longer-lasting, and diffuse pain

• The reticular formation and limbic system:
  - control the emotional and affective response to pain

Because the cortex, thalamus and brainstem are interconnected with the hypothalamus and autonomic nervous system, the perception of pain is associated with an autonomic response
Figure 1  Schematic diagram of some of the main anatomical components of the ‘pain matrix’, and their possible functional significance. PAG = Periaqueductal grey matter.
The role of the afferent and efferent pathways in processing of pain information

Nociceptive pain

Nociceptors: Endings of small unmyelinated and lightly myelinated afferent neurons

Stimulators: Chemical, mechanical and thermal noxae

Mild stimulation → positive, pleasurable sensation (e.g. tickling)

Strong stimulation → pain

These differences are a result of the frequency and amplitude of the afferent signal transmitted from the nerve endings to the CNS

Location: In muscles, tendons, epidermis, subcutaneous tissue, visceral organs

- they are not evenly distributed in the body (in skin more then in internal structures)
Nociceptive pain: mechanisms involved in development
Afferent pathways:

- From nociceptors → transmitted by small A-delta fibers and C-fibers to the spinal cord → form synapses with neurons in the dorsal horn (DH)

- From DH → transmitted to higher parts of the spinal cord and to the rest of the CNS by spinothalamic tracts

*The small unmyelinated C-neurons are responsible for the transmission of diffuse burning or aching sensations

*Transmission through the larger, myelinated A-delta fibers occurs much more quickly. A-fibers carry well-localized, sharp pain sensations
Efferent analgesic system

Its role: - inhibition of afferent pain signals

Mechanisms:

- pain afferents stimulates the neurons in periaqueductal gray (PAG) - gray matter surrounding the cerebral aqueduct in the midbrain results in activation of efferent (descendent) anti-nociceptive pathways

- from there the impulses are transmitted through the spinal cord to the dorsal horn

- there they inhibit or block transmission of nociceptive signals at the level of dorsal horn
Descendent antinociceptive system

Enk – enkephalinergic
PAG – paraaqueductal gray
EAA – excitatory amino acids
RVM – rostral ventro-medial medulla
The role of the spinal cord in pain processing

- Most afferent pain fibers terminate in the dorsal horn of the spinal segment that they enter. Some, however, extend toward the head or the foot for several segments before terminating.

- The A-β fibers, some large A-delta fibers and small C-fibers terminate in the laminae of dorsal horn and in the substantia gelatinosa.

- The laminae than transmit specific information (about burned or crushed skin, about gentle pressure) to 2nd afferent neuron.
2nd afferent neurons transmit the impulse from the substantia gelatinosa (SG) and laminae through the ventral and lateral horn, crossing in the same or adjacent spinal segment, to the other side of the cord. From there the impulse is carried through the spinothalamic tract to the brain. The two divisions of spinothalamic tract are known:

1. the neospinothalamic tract - it carries information to the mid brain, thalamus and post central gyrus (where pain is perceived)
2. the paleospinothalamic tract - it carries information to the reticular formation, pons, limbic system, and mid brain (more synapses to different structures of brain)
FIG. 13-3. Spinal cord and CNS pathway. Stimuli are transmitted from pain receptors through sensory nerves into the dorsal root ganglia. The impulse enters the spinal cord, forms a synapse, crosses the cord, and rises to the spinothalamic tract.
Theory of pain production and modulation

• Most rational explanation of pain production and modulation is based on gate control theory (created by Melzack and Wall)

• According to this theory, nociceptive impulses are transmitted to the spinal cord through large A- delta and small C- fibers

• The cells in the spinal cord function as a gate, regulating transmission of impulses to CNS

➢ Stimulation of larger nerve fibers (A-alfa, A-beta) causes the cells in SG to "close the gate".

• A closed gate decreases stimulation of T-cells (the 2nd afferent neuron), which decreases transmission of impulses, and diminishes pain perception
Stimulation of small fiber input inhibits cells in SG and "open the gate".

- An open gate increases the stimulation of T-cells $\rightarrow$
  $\uparrow$ transmission of impulses $\rightarrow$ enhances pain perception

- In addition to gate control through large and small fibers stimulation, the central nervous system, through efferent pathways, may close, partially close, or open gate. Cognitive functioning may thus modulate pain perception

**Action of endorphins (ED)**

All ED act by attaching to opiate receptors on the plasma membrane of the afferent neuron. The result then is inhibition of releasing of the neurotransmitter, thus blocking the transmission of the painful stimulus
Application:
After hitting one’s elbow or head, rubbing the area seems to provide some relief.

This may activate other sensory nerve fibers that are even "faster" than A-delta fibers.

These fibers send information about pressure and touch that reach the spinal cord and brain to override some of the pain messages carried by the A-delta and C-fibers.
Neuropathic pain

- It occurs as a result of injury to or dysfunction of the nervous system itself, peripheral or central

- Deafferentation pain - form of neuropathic pain: a term implying that sensory deficit in the painful area is a prominent feature (anesthesia dolorosa)

- Phantom pain - pain localizei into non-existing organ (tissue)

- Long-lasting pain after short-lasting pain stimulus
What causes neuropathic pain?

Neuropathic pain often seems to have no obvious cause; but, some common causes of neuropathic pain include:

-Alcoholism, Amputation, Back, Leg, and Hip problems, Chemotherapy, Diabetes mellitus, Facial nerve problems, HIV infection or AIDS, Multiple sclerosis, Shingles (Herpes yoster), Spine surgery

What are the symptoms of neuropathic pain?

Symptoms may include:

-Shooting and burning pain,
-Tingling and numbness
Cerebral reorganization may cause phantom limb pain

• One study of adult monkeys revealed cortical reorganization in which the mouth and chin invade cortices corresponding to arm and digits. (Dotrovsky, et al 1999)

• In humans, similar reorganization has been observed using magnetoencephalographic techniques and there was a linear relationship between pain and degree of reorganization (flor, et al 1998)
Somatosensory Strip

Understanding Phantom Limb Phenomena
Allodynia – phenomenon characterised by painful sensations provoked by non-noxious stimuli, (e.g. touch), transmitted by fast-conducting nerve fibres.

Mechanism: changes of the response characteristics of second-order spinal neurons so that normally inactive or weak synaptic contact mediating non-noxious stimuli acquire the capability to activate a neuron that normally responds only to impulses signaling pain.

- **Hypersensitivity** – increased sensitivity of the system involved in the pain processing
- **Hyperalgesia** – increased the pain sensitivity to noxious stimuli

**Allodynia** - phenomenon characterised by painful sensations provoked by non-noxious stimuli, (e.g. touch), transmitted by fast-conducting nerve fibres
Peripheral neuralgias after trauma or surgery

Common forms of neuropathic pain

- lumbosacral and cervical rhizotomy,
- peripheral neuralgia

- Most peripheral neuralgias are the result of trauma or surgery. Such a conditions does not necessary occur as a result of damageing a major nerve trunk but may be caused by an incision involving only small nerve branches (incisional pain)

Mechanism: the pain is due to neuroma formation in the scar tissue (?)
Incidence of severe pain due to spinal cord and cauda equina lesions ranges from 35 to 92% of patients.

This pain is ascribed to 3 causes:

1. Mechanically induced pain (fracture bones, myofascial pain)
2. Radicular pain (compression of nerve root)
3. Central pain (deaferentation mechanism)
Acute Pain

We can distinguish two types of acute pain:

1. Somatic
2. Visceral
   – referred

Somatic pain is superficial coming from the skin or close to the surface of the body.

Visceral pain refers to pain in internal organs, the abdomen, or chest.

Referred pain is pain that is present in an area removed or distant from its point of origin. The area of referred pain is supplied by the nerves from the same spinal segment as the actual site of pain.
Different types of chronic somatic pain

I. Nervous system intact
   1. nociceptive pain
   2. nociceptive - neurogenic pain (nerve trunk pain)

II. Permanent functional and/or morphological abnormalities of the nervous system (preganglionic, spinal - supraspinal)
   1. neurogenic pain
   2. neuropathic pain
   3. deafferentation pain
The most common chronic pain

1. Persistent low back pain
   - result of poor muscle tone, inactivity, muscle strain, sudden vigorous exercise

2. Chronic pain associated with cancer
3. Neuralgias - results from damages of peripheral nerves
   
a) Causalgia - severe burning pain appearing 1 to 2 weeks after the nerve injury associated with discoloration and changes in the texture of the skin in the affected area.
   
b) Reflex sympathetic dystrophies - occur after peripheral nerve injury and is characterised by continuous severe burning pain. Vasomotor changes are present (vasodilatation $\rightarrow$ vasoconstriction $\rightarrow$ cool cyanotic and edematous extremities).


These conditions include: myositis, fibrositis, myalgia, muscle strain, injury to the muscle and fascia

The pain is a result of muscle spasm, tenderness and stiffness
5. **Hemiagnosia**

- is a loss of ability to identify the source of pain on one side (the affected side) of the body. Application of painful stimuli to the affected side thus produces **anxiety, moaning, agitation and distress** but no attempt to withdraw from or push aside the offending stimulus. Emotional and autonomic responses to the pain may be intensified.

- **Hemiagnosia is associated with stroke that produces paralysis and hypersensitivity to painful stimuli in the affected side**

6. **Phantom limb pain** - is pain that an individual feels in amputated limb
Pathophysiology of muscle pain

- **Muscle pain** - a part of somatic deep pain (MP), it is common in rheumatology and sports medicine. It is rather diffuse and difficult to locate.

- Muscles are relatively insensitive to pain when elicited by needle prick or knife cut, but overlying fascia is very sensitive to pain.

Events, processes which may lead to muscular pain are:

- **metabolic events:**
  - metabolic depletion (↓ ATP → muscular contracture)
  - accumulation of unwanted metabolities (K⁺, bradykinin)
Pathophysiology of visceral pain

- **Visceral pain:**
  
  **Types** - angina pectoris, myocardial infarction, acute pancreatitis, cephalic pain, prostatic pain, nephrlolytiatic pain

- **Receptors:** unmyelinated C - fibres

- For human pathophysiology the kinds of stimuli apt to induce pain in the viscera are important.

It is well-known that the stimuli likely to induce cutaneous pain are not algogenic in the viscera. This explains why in the past the viscera were considered to be insensitive to pain
Adequate stimuli of inducing visceral pain:

1. abnormal distention and contraction of the hollow viscera muscle walls
2. rapid stretching of the capsule of such solid visceral organs as are the liver, spleen, pancreas...
3. abrupt anoxemia of visceral muscles
4. formation and accumulation of pain - producing substances
5. direct action of chemical stimuli (oesophagus, stomach)
6. traction or compression of ligaments and vessels
7. inflammatory processes
8. necrosis of some structures (myocardium, pancreas)
Characteristics of true visceral pain:

a) It is dull, deep, not well defined, and differently described by the patients.

b) Sometimes it is difficult to locate this type of pain because it tends to irradiate.

c) It is often accompanied by a sense of malaise.

d) It induces strong autonomic reflex phenomena (much more pronounced than in pain of somatic origin):
   - Diffuse sweating, vasomotor responses, changes of arterial pressure and heart rate, and an intense psychic alarm reaction - "angor animi" - in angina pectoris.

- There are many visceral sensations that are unpleasant but below the level of pain, e.g. feeling of disagreeable fullness or acidity of the stomach or undefined and unpleasant thoracic or abdominal sensation. These visceral sensations may precede the onset of visceral pain.
**Refered visceral pain (transferred pain)**

**Referred pain** = when an algogenic process affecting a viscus recurs frequently or becomes more intense and prolonged, the location becomes more exact and the painful sensation is progressively felt in more superficial structures.

- **Referred pain may be accompanied by allodynia and cutaneous and muscular hyperalgesia**

**Mechanisms involved in referred pain creation:**

a) convergence of impulses from viscera and from the skin in the CNS:
   - Sensory impulses from the viscera create an irritable focus in the segment at which they enter the spinal cord. Afferent impulses from the skin entering the same segment are thereby facilitated, giving rise to true cutaneous pain.

b) sensitization of neurons in dorsal horn
• Painful visceral afferent impulses activate anterior horn motor cells to produce rigidity of the muscle (visceromotor reflexes)

• A similar activation of anterolateral autonomic cells induces pyloerection, vasoconstriction, and other sympathetic phenomena

These mechanisms, which in modern terms can be defined as positive sympathetic and motor feedback loops, are fundamental in referred pain

• It is clear that painful stimulation of visceral structures evokes a visceromuscular reflex, so that some muscles contract and become a new source of pain
• It has been observed that the local anesthetic block of the sympathetic ganglia led to the disappearance, or at least to a marked decrease, of referred pain, allodynia, hyperalgesia.

• In some conditions, referred somatic pain is long-lasting, increases progressively, and is accompanied by dystrophy of somatic structures.

Possible mechanisms:

- onset of self-maintaining **vicious circle** impulses:
  
  peripheral tissue → afferent fibers

  ↑

  central nervous system

  peripheral tissue ← somatic and sympathetic efferent fibres
Intricate conditions - in some types of pain, e.g. chest pain, is difficult to distinguish the true cause of pain because such kind of pain may be related to cervical osteoarthrosis, esophageal hernia, or cholecystitis. It is difficult to ascertain whether these intricate conditions are due to a simple addition of impulses from different sources in the CNS or to somatovisceral and viscerosomatic reflex mechanisms.

It has been demonstrated that the mnemonic process is facilitated if the experience to be retained is repeated many times or is accompanied by pleasant or unpleasant emotions.

Pain is, at least in part, a learned experience - e.g. during the first renal colic, true parietal pain followed visceral pain after a variable interval. In subsequent episodes of renal colic pain, parietal pain developed promptly and was not preceded by true visceral pain. This is probably due to the activation of mnemonic traces.
Silent myocardial ischemia (SMI)

- Chest pain is only a late and inconstant marker of episodes of transient MI in vasospastic angina (30 %), in stable angina (50 %)

- Mechanisms of SMI
  a) Lack of the pain is, in part, related to the duration and severity of MI. Episodes shorter than 3 min, and those accompanied by a modest impairment of left ventricle (↑ in end-diastolic pressure inferior to 6 mm Hg) are always painless. Longer and more severe episodes are accompanied by chest pain in some instances but not in others.

  b) Patients with predominantly SMI appear to have a generalized defective perception of pain (↑ threshold and tolerance).

  Mechanism: ↑ level of circulating β-endorphin (?)
Disturbances in pain perception and nociception

Most of the disturbances are congenital

a) **Congenital analgesia** - nociceptive stimuli are not processed and/or integrated at a level of brain. Patient does not feel a pain

b) **Congenital sensoric neuropathy** - nociceptive stimuli are not transmitted by peripheral nerves or by spinal afferent tracts.

Acquired disturbances in pain perception and nociception

They may occur at **syringomyely, disturbances of parietal lobe of brain, in patients suffering from neuropathy** (e.g. chronic diabetes mellitus)
What is pain?

For humans, it is *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*

Even with humans, there is no objective way to accurately measure pain.

- Likert scales
- Clinical interviews
- MRI
Nociception and Pain

Nociception and pain are not the same thing, as the same stimulus can elicit a different pain response within the same individual. Many factors influence the perception of pain:

- Genetics
- Drug use
- Mental states
Pain and Animals

So how do we even begin to quantify the perception of pain in animals?
It’s possible that animals don’t perceive pain in an analogous way to humans.
It’s also possible that some animals do perceive pain in an analogous way to humans.
• Does that mean that researchers are responsible for “torturing” research animals?
• Researchers have ethical guidelines for (some) animals, but how do we know which ones we should be responsible for, and how do we minimize their pain if we can’t quantify it?
Pain and Animals

For non-human animals, a common definition of pain: *An aversive sensory experience caused by actual or potential injury that elicits protective motor and vegetative reactions, results in learned avoidance and may modify species-specific behaviour, including social behaviour*². Note that we have now taken away mention of emotional states. We also assume that an animal must have nociceptive pathways that are in someway analogous to humans.
Do Fish Experience Pain?

• Fish have nociceptive receptors that are “identical to human receptors.”
• There is still some debate as to whether fish brains are capable of processing “pain” in an analogous way to humans, as fish lack a developed cerebral cortex.
Do Fish Experience Pain?

Fish do show avoidance-learning behavior.

Experiment:
- Room 1 gives an electric shock
- Room 2 does not.
- Fish will choose Room 2 consistently after a small number of trials.
- Fish that were given morphine did not show a preference for a room.
Do Fish Experience Pain?

One experiment found that fish show protective motor reactions.

Experiment: Rainbow trout had their lips injected with bee-venom. For several hours, they rubbed their lips on the floor and walls of their tank.
Do Fish Experience Pain?

One experiment found that fish show protective motor reactions.

When other researchers tried to replicate the experiment, it was found that the original study used a local anesthetic before the injection. Without the anesthetic, the fish did not show the rubbing behavior.
Do Fish Experience Pain?

There is still active debate over how much a fish’s behavior is influenced by potentially painful stimuli. There appear to be few, if any, long-term behavioral changes following intense trauma (such as surgery) in most fish.
Do Fish Experience Pain?

New research suggests that, while fish have receptors that are analogous to human nociceptors, the nerve fibers that carry the information to the spine and brain are completely different.
Do Fish Experience Pain?

- A normal human nociceptive nerve contains 83% C-type fibers.
- People with genetic diseases which cause insensitivity to pain have considerably lower percentages of C-type fibers (24-28%)
- Teleost fish have approximately 5% C-type fibers, and elasmobranchs have no C-type fibers.
- Thus, most of the signals are carried on nerve fibers that we typically associate with reflexive actions, not pain.
Conclusions?

There are no clear answers as to whether fish experience pain in an analogous way to humans.

Rhetoric from both sides of the debate makes scientific discussion difficult.

A new definition of “pain” is probably necessary to help shape the discussion.