NERVOUS SYSTEM BLOCK

Lecture 30

Pain Modulation

PHYSIOLOGY TEAM – 430

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– What is pain?

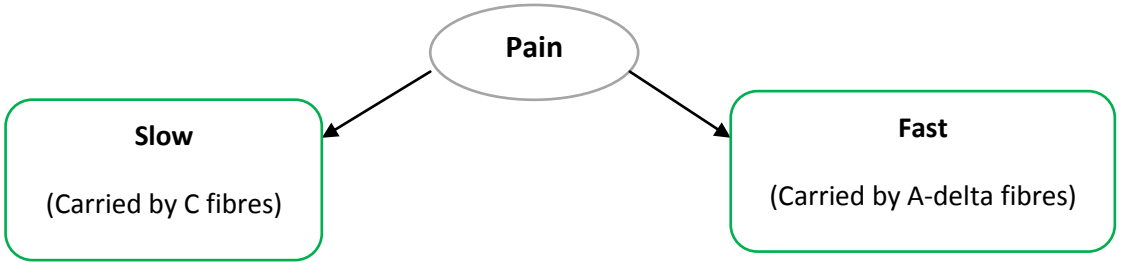
Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

(Do not confuse it with nociception which is an unconscious activity induced by a harmful stimulus; the neural processes of encoding and processing noxious stimuli)

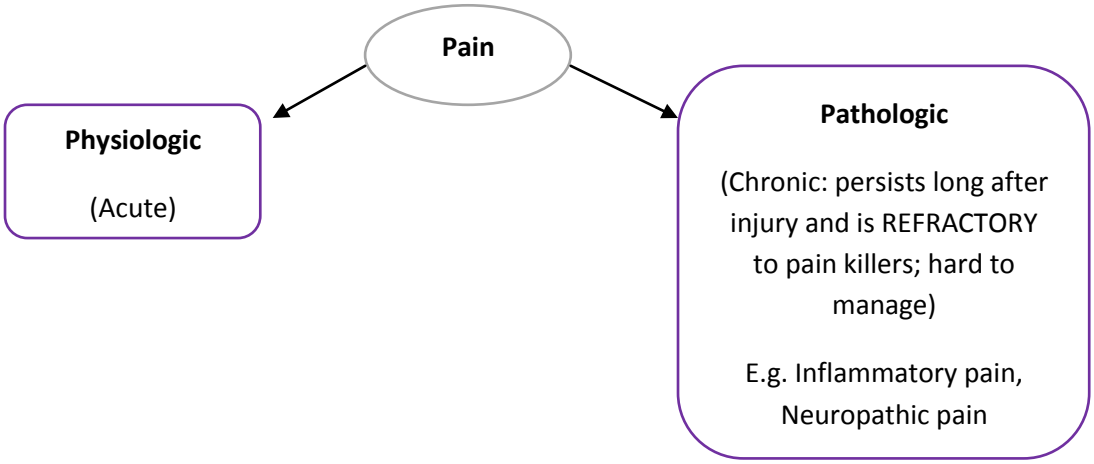
So now that we know the difference, **what is pain modulation?**

Pain modulation means regulation/adjusting pain to a lower level; toning the pain down. It is naturally done in the body by 2 mechanisms: gate-theory (spinal modulation; at the spinal level) and the pain control analgesic system (at a supraspinal level)

– Classification of Pain :



It could also be



- ## What is Neuropathic pain?

  Neuropathic pain may result from nerve injury, occurs in various forms and is commonly difficult to treat. For example, **causalgia,** which is a condition characterised by spontaneous burning pain occurring long after unimportant injuries. This pain is often accompanied by hyperalgesia and allodynia. Also, nerve injury leads to sprouting and eventual overgrowth of noradrenergic sympathetic nerve fibres in the dorsal root ganglion of sensory nerves from the injured area. Sympathetic discharge of norepinephrine/adrenaline is what brings on the pain. The nerve's distal cut end develops a scar tissue forming rounded ball, called a neuroma, which is sensitive to pressure; pain.
  Examples: post herpetic neuralgia, diabetic neuropathy.

- ## What is hyperalgesia?

  It is an exaggerated response to a noxious/dangerous stimulus.

- ## What is allodynia?

  It is a pain sensation in response to an innocuous/harmless stimulus. Example: pain felt when taking a shower after sunburn.

- ## Other types of pain:

- **Phantom limb pain :**
  This type of pain is felt in the region of an amputated limb, long after it has been amputated, and may also occur after the removal of other body parts such as teeth, eyes and breasts. Many theories explain this and the current one is based on the evidence that the brain can reorganise if sensory input is cut off.
- **Stress-induced analgesia:**
  When you are really engrossed in doing something interesting or having to face a situation which demands all your attention, little awareness of pain occurs, if pain exists. This is most clearly illustrated in the example of wounded soldiers in battle fields, who despite being greatly injured, will feel pain only after danger has passed.

- **Muscular pain :**
  When blood flow to muscles has been occluded, contraction of the muscle will cause pain, and will persist after contraction until blood flow is back to normal.

- **Visceral pain:**
  Travelling with autonomic fibres, it reaches spinal cord via dorsal horn and joins the lateral spinothalamic projecting to the thalamus and somatosensory cortex.

It is poorly localised, unpleasant and associated with nausea and autonomic symptoms. Also, most importantly, it RADIATES to other areas.

- What may cause visceral pain?

  Distension, ischemia and inflammation.

- When applying actions such as cutting or crushing the affected viscera, would there be any pain?

  No

- **So what is referred pain?**

Pain felt at a somatic area which is at a considerable distance away from the actual injured viscera. This pain is thought to be explained by two hypotheses. Firstly, the **dermatomal rule**, saying that the two structures (the origin of pain & the referred site) have developed from the same embryonic segment or dermatome, e.g. heart and arm. Second hypothesis, **the convergence-projection theory,** states that the basis for referred pain may be convergence of somatic and visceral pain fibres on the same 2nd-order neurons in the dorsal horn that project to the thalamus and then to somatosensory cortex.

Examples of referred pain:

Affected Organ	Site of Referred Pain
Meninges	Back of head and neck
Heart	Central chest, left arm
Trachea	Behind sternum
Oesophagus	Behind sternum
Diaphragm	Shoulder tip
Stomach	Upper abdomen, epigastrium
Appendix	Umbilicus
Small bowel	Around umbilicus
Duodenum	Upper abdomen, epigastrium
Large bowel	Lower abdomen, above pubic bone
Kidney	Loin
Ureter	Testicles
Trigone of bladder	Tip of penis
Uterus	Low back
Hip	Knee

Pain syndromes:

- **Thalamic syndrome:**

  A rare neurological disorder where the body becomes *hypersensitive* to pain due to damage of the thalamus; obstruction of the thalmogeniculate branch of posterior cerebral artery which affects **posterior thalamic nuclei.** Primary symptoms include pain and loss of sensation (in face arms and/or legs).

- **Trigeminal neuralgia**

  A neuropathic disorder characterised by episodes of **intense pain** in the face when stimulated by simple triggers such as a blast of air, washing and even combing the hair. It is caused by compression of trigeminal nerve root by an enlarged blood vessel, or may be due to aneurysm (outpouching of blood vessel) by a tumour, an arachnoid cyst in the cerebellopontine angle, trauma or even by tongue piercing!

Now, let's turn our attention to the main topic in this lecture: **Pain modulation**.

Pain is ***naturally*** modulated in the human body by:

A. Gate Control Theory:

Having learnt this from practical experience, shaking/rubbing an injured area results in a decreased amount of pain, have you ever wondered why?

The theory behind this is the gate control of pain which states: Pain is a function of the balance between the information travelling into the spinal cord through large (touch, pressure, vibration) nerve fibres [carrying non-nociceptive information] and information travelling into the spinal cord through thin (pain) nerve fibres [carrying nociceptive information]. If the relative amount of activity is greater in large nerve fibres, there should be little or no pain. However, if there is more activity in small nerve fibres, then there will be pain.

Let's go through this theory in steps:

1) Both thin (pain) and large (touch, pressure, vibration) nerve fibres carry information from site of injury to 2 destinations.
2) The 2 destinations are (a) dorsal horn of spinal cord; transmission cells that carry pain signals up to the brain and (b) inhibitory interneurons that impede transmission cells' activity.
3) When both nerve fibres are active → transmission cells are *excited*
4) Activity in thin fibres → inhibitory cells are *impeded;* allowing transmission cells to fire
5) Activity in large fibres → inhibitory cells *excited;* inhibiting transmission cell activity
6) Hence, the more large nerve fibres activated in comparison to thin ones, the less pain is felt.
7) So, WITHOUT any stimulation: both large and thin nerve fibres are quite and the inhibitory interneurons BLOCKS the signal in the projection neuron (that connects to the brain); gate is CLOSED; NO PAIN
8) With NON-PAINFUL stimulation: large nerve fibres are activated; activating the projecting neuron AND activating the inhibitory interneurons (which now blocks the signal in the projection neuron that connects to the brain); gate is CLOSED; NO PAIN
9) With PAINFUL stimulation: thin nerve fibres become more active, activating the projection neuron AND BLOCKING the inhibitory interneurons; pain signal is NOT BLOCKED; gate is OPEN; **PAIN!**
10) So this is the explanation behind skin rubbing, shaking the painful part, transcutaneous electrical stimulation & acupuncture; to STIMULATE mechanoreceptors that ACTIVATE neurons of dorsal column large fibres, allowing them to TAKE OVER the thin fibres' activity.

PAIN!

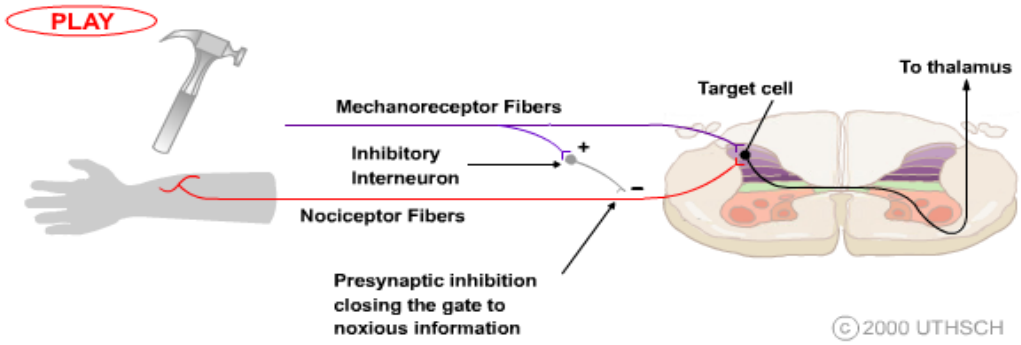
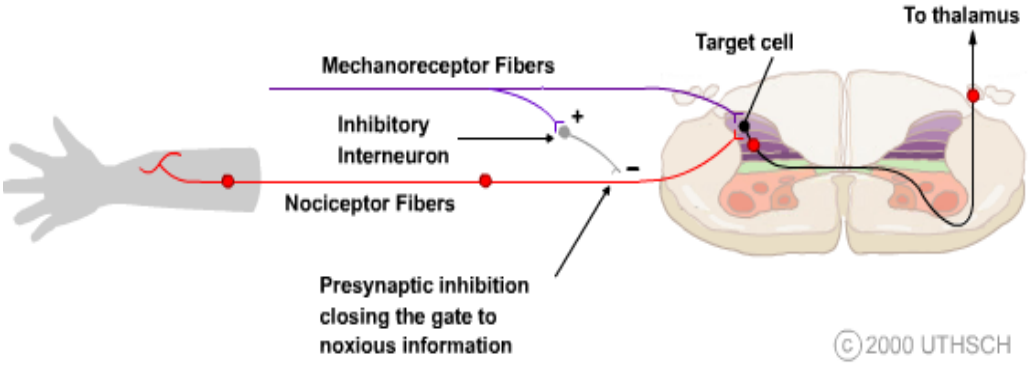


Figure 8.1
The gate control theory of pain modulation. The gate control theory is based on presynaptic inhibition of pain information produced by mechanical stimulation, and provides the basic rationale for the TENS.



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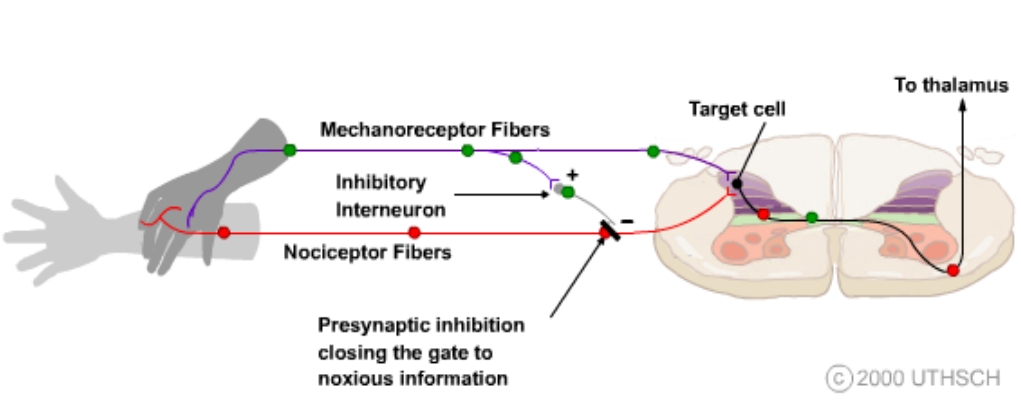

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- **What are the types of thin (pain) nerve fibres?**
  - A-delta fibres [FAST pain]
  - C fibres [SLOW pain]

- **And what about large fibres?**
  - A-beta fibres

In summary:

- **What are the 3 factors that control the gate?**

1. Activity in pain fibres → OPEN gate
2. Activity in other sensory nerves → CLOSES gate
3. ***Messages from brain*** **(thinking/paying attention about/to the pain, being focused in something which in turn distracts the awareness of pain)**

For more clarification:

- Substance P is a neurotransmitter from type C fibres
- Impulses carried by Type C pain fibres cause release of substance P; OPEN gate
- Impulses carried by A-beta fibres cause *presynaptic* inhibition of C fibres AND *postsynaptic* inhibition of 2nd-order neurons in dorsal horn
- From the spinal cord, the messages go directly to several places in the brain including the thalamus, midbrain and reticular formation

- **So is that what controls the gate only?**

No, there is also control by HIGHER CENTRES called **control triggers**

- **How do these centres control the gate?**

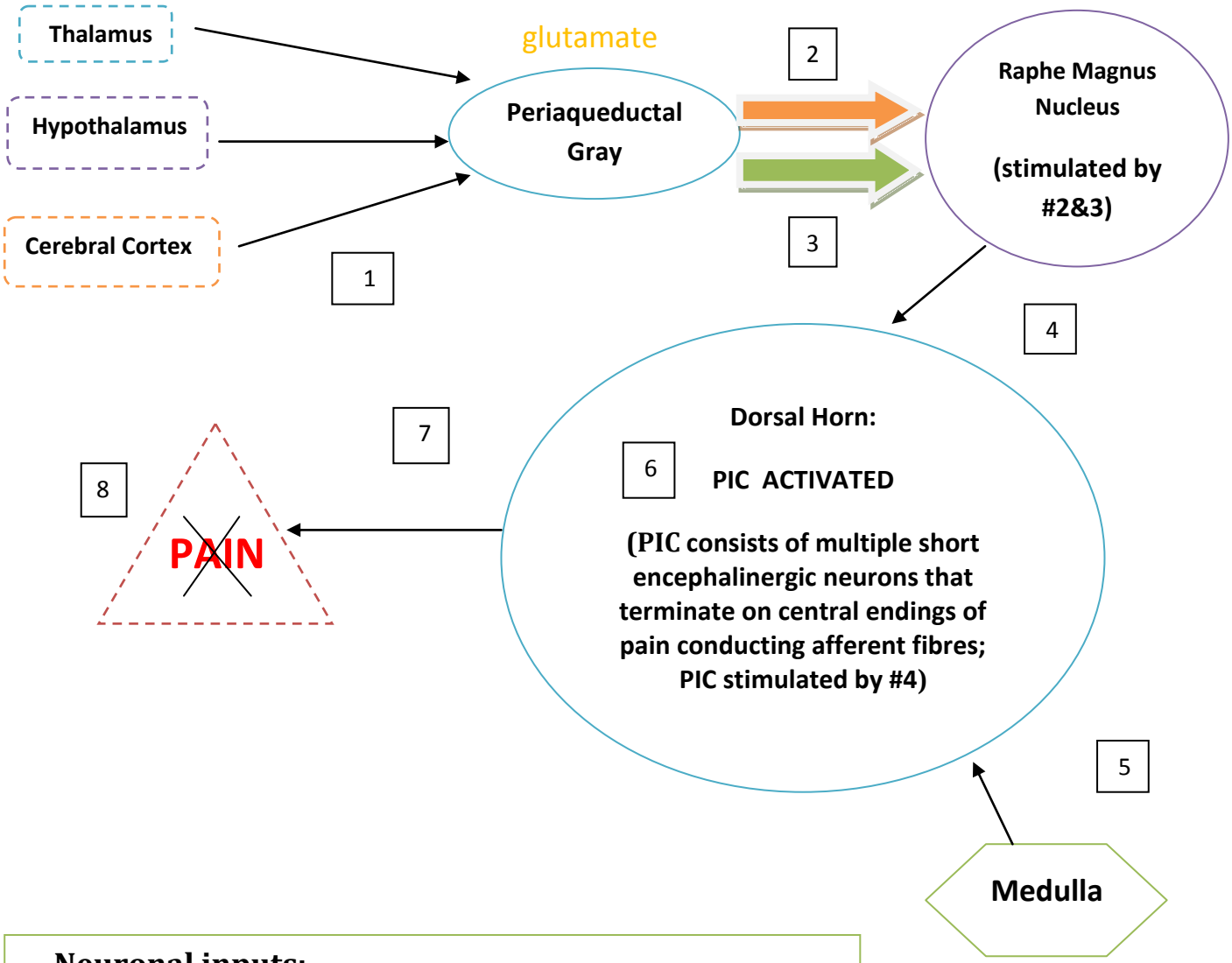
Via specialised nerve impulses that arise in the brain, inhibitory and excitatory nerve signals travel down and influence the gate.

- **What areas of the brain are responsible for pain REDUCTION?**

- Periaqueductal Gray (PAG) – in midbrain
- Nucleus raphe magnus (NRM) – in upper medulla
- Periventricular nucleus – in hypothalamus, near 3rd ventricle
- Pain inhibitory complex (PIC) – in dorsal horn of spinal cord

B. Pain Control Analgesic System (supraspinal modulation)/(descending pathway)

The following happens:



Neuronal inputs:

1. **Asparate**
2. **Glutamate**
3. **Serotoninergic neurons**
4. **Noradrenergic neurons**
5. **PIC activated; pain signals blocked**
6. **Encephalin released**
7. **Encephalin PREVENTS release of substance P from pain nerve endings; pre & postsynaptic INHIBITION of pain transmission**

- Opioid Peptides

What are opioid peptides?

OPs are short sequences of amino acids that bind to opioid receptors in the brain, they may be produced by the body or present in food. Apart from responding to stress and **pain**, they play an important role in motivation, emotion, control of food intake and attachment behaviour.

➔ They are called opioids because they are similar to morphine; which is derived from a plant called "opium".

What are the classes of opioid peptides?

1- B-endorphin (ENDOGENOUS; derived from proopiomelanocortin POMC) – in basal hypothalamus
   [MOA: neurons producing it are present in PAG → inhibit GABAnergic interneurons (which usually SUPPRESS ANTI-nociceptor neurons)]
2- Enkephalins – in dorsal horn, raphe magnus, golbus pallidus
   [MOA: interneurons producing them are found in lamina II, responsible for producing lamina I-nociceptor-specific spinothalamic neurons]
3- Dynorphins – hypothalamus, PAG, dorsal horn, reticular formation
4- Endogenous morphine - It has been identified in terminals forming synapses with neurons having μ-opioid receptors in pain modulating pathways

Enkephalin is an endogenous opiate that regulates nociception in the body, by blocking substance P; CLOSING gate.

How do opioid peptides work?

They bind to opiate receptors in analgesic system and in dorsal horn of spinal cord on central endings of pain conducting nerve fibres

Where are they most highly concentrated?

1- The spinal dorsal horn

2- Medulla

3- Hypothalamus

4- Peripherally

Opioid antagonist: it is a receptor antagonist that acts on opioid receptors. **Naloxone** is a commonly used opioid antagonist drug.

Uses:

- It has no partial agonist effects, in fact it is a **partial inverse agonist** at mu opioid receptors, and so is used for treating opioid overdose.
- Also, this aspect makes it a good treatment for opioid addiction by reversing the altered homeostasis and other long-term effects know as post acute withdrawal symptoms, such as respiratory and cardiovascular depression.
- Displace receptor bound opioids

Pain relief

Agent/Procedure	Site	Mechanism
Aspirin, NSAIDs	PNS	Block production of inflammatory mediators
	Peripheral nerves	Sectioning of peripheral nerves
Sympathectomy	Skull, CNS, PNS	Removal of a sensory or autonomic ganglion
Exogenous opioid-like drugs	CNS, PNS, Gastrointestinal tract	Manipulation of endogenous opioid network
Electrical stimulation	Dorsal column	Will alleviate pain *below* site of stimulation
Transcutaneous electrical nerve stimulation	Large diameter afferents	Neuromodulation
Antidepressant drugs	Brainstem	Stimulation/administration of drugs that modify serotonergic/noradrenergic synapses

Test your knowledge – Multiple Choice Questions:

1- Pain is:

a) Unconscious activity caused by a harmful stimulus
b) Any unpleasant sensation with/without tissue damage
c) Neural process of processing noxious stimuli
d) Any unpleasant sensation associated with tissue damage whether or not individual is aware of

2- Natural mechanisms of pain relief are:

a) Gate control and electrical stimulation
b) Gate control
c) Gate control and pain analgesic system
d) No natural mechanism

3- Radiating pain is usually in origin:

a) Visceral
b) Muscular
c) Facial
d) Neuropathic

4- 46 y/o female presenting with severe facial pain upon strange stimuli such as applying her everyday make-up, what is the most probable diagnosis and what's its explanation?

a) Thalamic syndrome; damage of thalamus
b) Trigeminal neuralgia; congenital defect in cranial nerve 5
c) Trigeminal neuralgia; compression of cranial nerve 5
d) Herpes zoster

5- All are true except:

a) Activity in thin fibres lead to impedance of inhibitory cells
b) Activity in large fibres lead to impedance of inhibitory cells
c) Thin fibres carry pain impulses
d) Activity in both fibres cause excitement in transmission cells

6- All are responsible for pain reduction except:

a) Post thalamic nuclei
b) Periaqueductal gray
c) Nucleus raphe magnus
d) Periventricular nucleus

7- All are true regarding encephalin except:

a) Prevents release of substance P
b) Pre and postsynaptic inhibition of pain transmission
c) Stimulated by noradrenergic neurons
d) Released from ventral horn

8- NSAIDs ' analgesic effect is conducted by:

a) Blocking nerve endings
b) Inhibit release of inflammatory mediators
c) A placebo effect only
d) Block transfer of signals at spinal level

9- Regarding referred pain:

a) Appendicitis pain is referred to umbilical area
b) Kidney stone pain is referred to suprapubic area
c) Fractured radius pain is referred to finger tips
d) Angina pain is referred to umbilical area

10- Neuralgia is:

a) Pain following nerve damage
b) Shrinkage of acute nerve endings
c) Cannot be treated surgically
d) Only seen in amputees

11- Phantom limb phenomenon is:

a) Only seen in amputees
b) May be encountered in post cancer breast surgery
c) Done due to inability of brain to reorganise the surgical event
d) Cannot be treated

Answers:

1) D
2) C
3) A
4) C
5) A
6) A
7) D
8) B
9) A
10) A
11) B