Pain: Pain is a protective mechanism for the body, it is an unpleasant sensory and emotional experience associated with actual and potential tissue damage, or described in terms of such damage. It is important that pain perception and reaction to pain is separated, this is particularly important for clinical pain because suffering is more heavily influenced by the reaction to pain than by actual pain intensity. Attention, motivation, past experience, and the meaning of the situation can influence the individual’s reaction to pain. Thus pain involves anatomic structures, physiologic behaviors, and psychological, social, cultural, and cognitive factors. Some individuals are born insensitive to pain (congenital analgesia).

Peripheral receptors The pain and temperature system does not have specialized receptor organs. Instead, it uses free nerve endings throughout skin, muscle, bone, and connective tissue to perceive changes in temperature and pain peptides. Although pain will result from damage to a free nerve ending, in reality most pain is a result of substances released by damaged tissues: prostaglandins, histamine, and substance P. The free nerve ending has receptors for these substances and lets you know when tissue has been damaged.

Axon diameters: Pain (and temperature) includes the third and fourth axon groups, Aδ and C fibers. There are two subtypes of pain. "Fast pain", carried by the Aδ fibers, is the instantaneous pain that makes your arm jerk back before you even realized you were burned. It is sharp and piercing and over quickly. "Slow pain" is carried by C fibers. C fibers are not only small, they are unmyelinated (the only sensory axons without myelin), so their
conduction velocity is quite slow. Slow pain is primarily mediated by those tissue-damage peptides listed above, and can go on indefinitely. It is distressing, it can be dull and aching, and it does not trigger withdrawal reflexes like the fast pain. A perfect example of slow pain is when you stub your toe on the coffee table. You feel the jolt of impact (proprioception and Pacinian corpuscles), and you have approximately a heartbeat to think, "This is really going to hurt." That heartbeat is the C-fiber travel time from your toe to your brain. When the signal hits, the pain is severe and lasts for quite a while. It is, however, a nice demonstration of the relative conduction velocities of Aδ and C fibers.

**Types of Pain:**

1. **Fast pain:** felt within 0.1 sec. after pain stimulus is applied. It's described as sharp, pricking, acute, electrical...etc it is localized to skin & not felt in most of the deeper structures. Receptors involved in fast pain are **Free nerve endings**. Stimulus type is either Mechanical or thermal. Transmitted in the peripheral nerves to the spinal cord by type Aδ fibers at velocities of 6 - 30 m / sec. Fast pain can be localized better than slow pain & when tactile receptors that excite the DC-ML system are also stimulated the localization can be nearly exact. NT involved in fast pain pathway is **Glutamate**.

2. **Slow Pain:** Felt after 1 sec. & increase slowly over many seconds or minutes. It is described as slow, burning, aching, throbbing, nauseous, chronic pain.......It is localized to the skin & almost any deeper tissue or organ. Receptors involved in slow pain are **Free nerve endings**. Stimulus types are mechanical, thermal & chemical (like Bradykinin, Serotonin, Histamine, K⁺, acids, Acetylcholine & proteolytic enzymes). Slow pain is transmitted via **type C** fibers to SC at velocities between 0.5 - 2 m / sec.

1 / 10 to 1 / 4 of the fibers terminate in Thalamus, other fibers will go to reticular nuclei of Pons, Medulla, & mesencephalon, tectal area of mesencephalon, & periaqueductal gray region then from here fibers will go to intralaminar & ventrolateral nuclei of Thalamus & Hypothalamus then to Somatic sensory cortex. Reticular nuclei & intralaminar nuclei are part of the "Arousal system" that is why person cannot sleep if he is in severe pain. The localization in this pathway is poor because of the multi-synaptic & diffuse connectivity of this pathway.

Pain is perceived at sub-cortical level. Reticular formation & Thalamus can cause conscious perception of pain. Cortex plays an important role in interpreting the quality of pain. NT involved in slow pain is **Substance P**. In general **tissue ischemia** can lead to pain due to...
accumulation of lactic acid from anaerobic metabolism & may be due to bradykinin & proteolytic enzyme accumulation too.

**Muscle spasm** is the base for many clinical pain syndromes. Pain occurs in muscle spasm due to the direct effect of mechano-sensitive pain receptors & also due to indirect effect through compressing blood vessels leading to ischemia & accumulation of metabolites.

**Pain & Temperature Pathway:** As the dorsal root enters the cord (all sensory information comes in via the dorsal root, and all sensory cell bodies are in the dorsal root ganglion), the fibers sort themselves out by diameter. The largest fibers enter the cord most medially, and the smallest fibers enter most laterally. Pain afferents (all of the following applies to temperature as well) enter the cord laterally, due to their small size, and synapse more or less immediately. "More or less", because they actually can travel one or two segments up or down the cord before synapsing. **Lissauers tract** is the tract carrying these migrating axons, but they are only in the tract for a short time. Within one or two levels, they enter the dorsal horn and synapse. The dorsal horn is a multi-layered structure. The thin outermost layer is called the **posterior marginalis** layer. The wide pale second layer is called the **substantia gelatinosa**, and the layer deep to that is called the **nucleus proprius**. The layers continue into the ventral horn, but the two types of pain fibers enter different layers of the dorsal horn. Aδ fibers enter the posterior marginalis and (the nucleus proprius?), and synapse on a second set of neurons. These are the secondary afferents which will carry the signal to the thalamus. The secondary afferents from both layers cross to the opposite side of the spinal cord through the anterior commissure and ascend in a tract called the **spinothalamic tract** (Tracts are always labeled from beginning to end).

The C fibers enter the substantia gelatinosa and synapse, but they do not synapse on secondary afferents. Instead they synapse on **interneurons** (neurons which do not project out of the immediate area).most of the signals then pass through one or more interneurons before entering mainly lamina V, also in the dorsal horn. Here the last neurons in the series give rise to long axons that mostly join fast pain fibers passing through the anterior commissure to the opposite side of the cord. The spinothalamic tract ascends the entire length of the cord, and the entire brainstem, staying in about the same location all the way up. By midbrain the spinothalamic tract appears to be continuous with the medial lemniscus. They will enter the VPL of the thalamus together. The spinothalamic system enters the VPL, synapses, and is finally carried to cortex by the thalamocortical neurons. Here is a schematic diagrams of the dorsal horn, the synapses and the entire pathway:
Clinical correlate:
Because the pain and temperature information crosses almost as soon as it enters the spinal cord, any unilateral lesion of the spinothalamic tract in the spinal cord or brainstem will result in contralateral loss of pain and temperature. This is an extremely useful clinical sign because it means that if a patient presents with analgesia on one side of the trunk or limbs, the location of the lesion must be on the contralateral side of the spinal cord or brain stem. The analgesia begins 1-2 segments below the lesion and includes everything below that level.

A note about generalizations: There is actually a fair amount of mixing that goes on between the tracts. Some light touch information travels in the spinothalamic tract, so that lesioning the dorsal columns will not completely knock out touch and pressure sensation. Some proprioception also travels in the dorsal columns, and follows the medial lemniscus all the way to the cortex, so there is conscious awareness of body position and movement. The pain
and temperature system, although it does ascend to somatosensory cortex, also has multiple targets in the brainstem and other areas.

**Pain control:** Pain Analgesia System (Pain suppression system): It has been recognized for centuries that opium and related compounds (such as morphine) are powerful analgesics. Several decades ago scientists hunted down the opiate receptor which was responsible for the potent effects. They then reasoned that if there was such a receptor in the body, maybe the body used its own endogenous form of opium to control pain. (It has also been recognized for centuries that under certain circumstances, i.e. the heat of battle, a serious wound may not cause pain.) This hypothetical compound was named "endorphin", from endogenous-morphine. Soon after, an entire class of peptide neurotransmitters was discovered that interacted with the opiate receptor, and now includes endorphins, enkephalins, and dynorphins. Synthetic, exogenous forms of these compounds continue to be discovered, prescribed, and abused, and are classed under the general term, "narcotics". There are opiate receptors throughout the central nervous system. In the dorsal horn, they are located on the terminals of the primary afferents, as well as on the cell bodies of the secondary afferents. Opiate interneurons in the spinal cord can be activated by descending projections from the brainstem (especially the raphe nuclei and periaqueductal grey), and can block pain transmission at two sites. 1) They can prevent the primary afferent from passing on its signal by blocking neurotransmitter release, and 2) they can inhibit the secondary afferent so it does not send the signal up the spinothalamic tract.

The reaction toward painful stimuli varies in different individuals. This results from the capability of brain itself to suppress the pain signals reaching it via pain control system (pain analgesia system), which include periaquiductal gray& periventricular areas of the mesencephalon & upper pons. Their neurons send signals to the Raphe magnus nucleus & nucleus reticularis paragigantocellularis then signals send through the dorsolateral column to a pain inhibitory complex located in the dorsal horns of the SC. NT's involved in the analgesia system are Enkephalins from periaqueductal & periventricular neurons & also from local SC neurons & Serotonin from Raphe magnus neurons (It has been shown that tricyclic antidepressant drugs, such as amitriptyline, which enhance the effects of serotonin by blocking its presynaptic uptake, have been found to be effective in the management of certain types of chronic pain).
Enkephalins cause pre-synaptic & post-synaptic inhibition to C & Aδ pain fibers where they synapse in dorsal horn. Pre-synaptic inhibition may be via blocking Ca $^{+2}$ channels. Multiple areas in the brain especially the areas of analgesia system have shown to have opiate receptors. Around 12 different naturally occurring opiate substances have now been found in nervous system, the most important are β - Endorphines in Hypothalamus & pituitary gland & met - Enkephalins, Leu - Enkephalines & Dynorphin (in much lower quantities) in brainstem & SC (analgesia system). The opiate receptors are the site for action of morphine like drugs.

Stimulation of type Aβ fibers from the peripheral tactile receptors can depress the transmission of pain signals e.g. rubbing the skin near painful area, or applying liniments is always helpful in relieving pain.
The same mechanism & the psychogenic excitation of the analgesia system are probably the basis of pain relief by (Acupuncture).
The Gate control Theory: Large & small fibers excite lamina V neurons that projects to the CNS. Neurons in the substantia gelatinosa inhibit transmission between large fibers & lamina 5 cells & those from small fibers & lamina 5 cells. Activation of large fibers excites substantia gelatinosa cells & therefore increases their inhibitory effect on the lamina 5 cells & closes the gate. Activation of small fibers inhibits substantia gelatinosa neurons & removes their inhibitory effect on lamina 5 neurons & therefore opens the gate.

Pain & temperature sensation from the face: The small diameter fibers carrying pain and temperature enter at mid pons, and then do something unusual - they turn down the brainstem. They travel down the pons and medulla until they reach the caudal medulla, which is where they finally synapse and cross. The tract that the descending axons travel in is called the spinal tract of V, and the long tail of a nucleus that they finally synapse in is called the spinal nucleus of V. These names come from the fact that they actually reach as far down as the upper cervical spinal cord. The spinal nucleus of V can be divided into three regions along its length; the region closest to the mouth is called subnucleus oralis, the middle region is called subnucleus interpolaris, and the region closest to the tail is called subnucleus caudalis. The pain fibers actually synapse in subnucleus caudalis, so you may hear that term used instead of the spinal nucleus of V.
The secondary afferents from subnucleus caudalis cross to the opposite side, and join the spinothalamic tract on its way to the thalamus.

**On to the thalamus:** The somatosensory information from the face joins that from the body and enters the thalamus with it. Information from the face actually enters the ventroposterior medial nucleus (VPM). The thalamocortical afferents take all of the signals, whether from VPL or VPM, to primary somatosensory cortex. Once there, it is distributed in a somatotopic (body-mapped) fashion, with the legs represented medially, at the top of the head, and the face represented laterally.