4. Sensory Systems

The term 'sensory systems' applies to those parts of the nervous system concerned with the detection, transmission and analysis of information about stimuli from the internal and external environments. Sensation is the conscious perception of such stimuli; much of the sensory information that is received by the body is outside the realm of consciousness. Sensory systems include the *receptors*, the *afferent nerve fibres* of sensory neurones and the *central pathways* activated by appropriate stimuli.

4.1 Receptors

Receptors can be either specialized cells of endings, of varying complexity, of sensory neurones which are able to transform different types of energy into nerve impulses.

1. Somatic receptors

- cutaneous receptors: on the body surface and accessible mucous membranes

- proprioceptors: in muscles, tendons and joints

2. Visceral receptors

- in the walls of blood vessels, GIT, bladder and other hollow viscera

3. CNS receptors

- in the brain and spinal cord

4. Receptors of special senses

- visual receptors: in the eye

- auditory receptors: in the ear

- orientation receptors: in the vestibular apparatus

- olfactory receptors: in the nose

- gustatory receptors: in the tongue and oral mucosa.

Specificity

Receptors are, to a large extent, specific or selective in their response, being sensitive to one particular kind of energy. This energy, or change in energy, forms the *adequate stimulus* and a receptor transforms or *transduces* this particular kind of stimulus into a change in membrane potential.

Transduction Mechanism

A stimulus may act directly on the *membrane of the nerve ending,* i.e., free nerve endings in the skin, or indirectly via an *accessory structure,* i.e., a capsule or hair shaft, or via a *receptor cell,* i.e., rod and cone cells in the eye, taste buds in the tongue, hair cells in the ear.

A stimulus to a receptor cell causes a change in the conductance of the receptor membrane and this in turn causes a local change in the membrane potential, the *receptor potential.* The receptor potential evokes a local *generator potential* in the sensory nerve terminal either directly by electrotonic spread or indirectly by release of a chemical transmitter. The generator potential initiates action potentials which are propagated along the sensory nerve to the CNS.

The *receptor potential* usually arises from a change in membrane conductance to Na^+ ions. The potential change is commonly one of depolarization although there are exceptions. For example, vertebrate photoreceptors are hyperpolarized by light while vestibular hair cells are either depolarized or hyperpolarized according to the direction of hair displacement. The receptor potential is non-propagating, has no refractory period and its amplitude is graded and dependent on the strength of the stimulus. Repeated stimuli can therefore summate. The relationship between stimulus intensity and receptor potential ('transfer function') is as a rule logarithmic.

Where there is a separate receptor cell, the *generator potential* is a synaptic potential probably due to an increase in both G_{Na} and G_K. Its properties are similar to those of the receptor potential and it may provide amplification of the receptor potential signal. Both receptor and generator potentials are more resistant to local anaesthetics than are action potentials. The relationship between generator potential amplitude and the frequency of action potentials in the sensory fibre is approximately linear. The final result of this combination of transfer functions is that the frequency of action potentials is proportional to the logarithm of stimulus intensity (Weber-Fechner law).

Adaptation

This is the term applied to the decline in the receptor potential shown by most receptors during the application of a constant or maintained stimulus. Receptor potentials in *slowly adapting receptors,* i.e. muscle spindles and Golgi tendon organs, are prolonged and decay slowly while those in *rapidly adapting receptors,* i.e. hair receptors and Pacinian corpuscles, quickly fall below threshold. The mechanism is not known but in some cases adaptation is influenced by the nature of the accessory structure such as the Pacinian corpuscle. Changes in receptor potential are reflected as changes in the discharge frequency of action potentials in the afferent fibres. During a constant stimulus the impulse frequency in sensory neurones with slowly adapting receptors may remain at a relatively constant level but in sensory neurones with rapidly adapting receptors it may decline rapidly and cease altogether within seconds.

Coding of Sensory Information

A stimulus is transformed within a *sensory unit* into one or a number of stereotyped action potentials. The term sensory unit applies to the afferent nerve fibre of a single sensory neurone, all its peripheral branches and central terminals, and any non-neural transducer cells associated with it. The impulses so generated provide information to the CNS about the nature, position and intensity of the stimulus.

The nature or *modality* of sensation (i.e. the type of sensation experienced, i.e. vision, touch, etc.) depends on the specificity of the receptor for a certain form of energy. If a receptor is activated by other types of stimuli, necessarily at higher intensities, the brain still interprets the sensation as that of the adequate stimulus. Thus activity in optic nerve fibres is interpreted as the sensation of vision whether the activity was produced by light or by sharp pressure to the eye.

Information on *stimulus position* is conveyed to specific parts of the brain in a way that depends on the particular sensory unit or groups of sensory units that are activated. For example, each cutaneous sensory unit responds only to appropriate stimuli over a localized region of the body surface. This region forms the *receptive field* for that sensory unit. Its size reflects the threshold of the receptors and the degree of branching of the neurone. Certain regions of the body, i.e. hands and face, have smaller receptive fields than others, i.e. trunk. Receptive fields of individual sensory units overlap so the stimulus is usually effective in exciting a number of sensory units in the skin. In an analogous fashion visual fibres have effective visual fields and joint receptors have effective angles of movement.

A supra-threshold stimulus usually produces a burst or train of impulses rather than a single impulse. The response from tonic or phasic receptors increases as the intensity or rate of change of the stimulus increases. The number of neurones responding also increases and this is known as *'recruitment'* of sensory units. *Stimulus intensity* is therefore coded by:

(a) the frequency of impulses in individual sensory units;

(b) the number of active sensory units.

4.2 Sensory Neurones

Leaving aside the special senses, sensory nerve fibres may be classified as somatic or visceral. Their cell bodies are located outside the CNS in various ganglia. *Somatic sensory neurones* have their cell bodies either in the trigeminal or dorsal root ganglia. Their peripheral axons (somatic afferent fibres) travel in peripheral nerves carrying information from the skin, skeletal muscles, tendons, joints and bone. Their central processes travel in trigeminal or dorsal roots to the CNS. *Visceral sensory neurones* have their cell bodies in the various cranial nerve ganglia or in the dorsal root ganglia of the thoracic, lumbar and sacral regions. Their peripheral axons (visceral afferent fibres) travel with sympathetic and parasympathetic nerves and carry information from receptors in blood vessels and internal viscera, particularly the heart, lungs, bladder, rectum and genital organs. Their central axons travel in the cranial VII, IX and X nerves to the nucleus of the tractus solitarius in the brain-stem, or, in the

thoracic and sacral regions, join the dorsal roots to enter the dorsal horn of the spinal cord with the somatic afferent fibres.

The greater the diameter of the peripheral nerve fibre the greater the conduction velocity. It is common to use the alphabetical A, B and C system for cutaneous afferents and the numerical I, II, III and IV system for muscle afferents.

Associated with the differences in diameter, peripheral nerve fibres also show differences in the following functional properties:

1. *Modality.* Although there are no rigid correlations between diameter and modality, some general trends are clear.

2. *Conduction velocity.* Increases with increasing fibre diameter and with myelination.

3. *Electrical threshold.* When a nerve is stimulated by electrical pulses, the strength of the stimulus decreases with increasing fibre diameter. Consequently, unmyelinated fibres require the greatest stimulation. This is a property of the axons and does not reflect thresholds to physiologic stimuli.

4. *Refractory period.* This decreases with increasing diameter; action potentials are of shorter duration and recovery is faster in large fibres. Thus the frequency of firing in unmyelinated fibres seldom exceeds 10 per sec while short bursts of 500 per sec or more are occasionally seen in large myelinated fibres.

5. *Sensitivity to local anaesthetics.* Local anaesthetics act on excitable membranes to reduce the rate of Na^+ inflow during the action potential and hence block activity. Small fibres are the most susceptible because of their high surface area to volume ration. Thus after application of local anaesthetic to a cutaneous nerve, sensations of temperature change and pain are blocked before touch and pressure.

6. *Sensitivity to hypoxia.* Ischaemia blocks large fibres first, probably because of their low surface area to volume ration. Thus in this type of block, vibration sensitivity and position sense are lost before the ability to appreciate pain or changes in skin temperature.

4.3 Somatosensory Pathways

Afferent nerve fibres, except for those of the special sense organs, enter the CNS mainly via the spinal dorsal roots, and the trigeminal and vagal roots. The innervation areas of peripheral nerves to the skin show little overlap and hence section of a nerve gives a characteristic region of sensory loss. However, fibres from one peripheral nerve enter the spinal cord over several dorsal roots, so that a particular innervation area is represented over a number of segments. The innervation area of the skin supplied by a single dorsal root is known as a *dermatome.* Dermatomes from adjacent dorsal roots overlap considerably so that section of a single root does not produce a region of complete anaesthesia.

After entering the spinal cord, fibres usually bifurcate giving ascending and descending branches which mostly end in adjacent grey matter. Inputs giving rise to sensations usually follow one of two ascending pathways within the spinal cord - the *dorsal column pathway* and the *anterolateral pathway.*

Fibres destined for the dorsal column pathway are mainly large myelinated (Abeta) fibres which enter the spinal cord via the more medially positioned dorsal rootlets. They bifurcate, giving one branch which enters the *dorsal horn* and a second branch which enters the ipsilateral *dorsal column.*

The branches in the dorsal horn have a variety of destination. Branches of the largest fibres from the annulospiral endings of the muscle spindles make direct synaptic contact with motor neurones in the ventral horn. Branches from muscle, joint and skin mechanoreceptors synapse in the dorsal horn with the cells of origin of the *spinocerebellar tracts* which supply the cerebellum with information used in the control of posture and movement. Other branches contact dorsal horn cells and are involved in local segmental activity.

Dorsal Column Pathway

The branches of the primary afferent fibres in the dorsal column ascend without synapsing to the medulla. There they synapse with neurones in the ipsilateral *dorsal column nucleus.* These neurones send their axons to the opposite side of the medulla, forming a well-marked histological feature - the *sensory decussation* - where the fibres from the two sides cross. After crossing, the fibres ascend in a tract known as the *medial lemniscus,* which passes through the mid-brain and terminates in the *ventrobasal nuclear complex* of the thalamus. The thalamic neurones send their axons to layer IV of the six layers in the postcentral gyrus of the cerebral cortex (*somatosensory cortex*).

The dorsal column pathway carries information necessary for fine tactile discrimination, vibration sensitivity and position sense. Throughout the pathway the sensory representations are preserved. Because the dorsal column pathway provides for these rather refined sensibilities it is usually called the *discriminative* (specific) pathway. Since the medial lemniscus is a major component of this pathway it is also referred to as the *lemniscal system.*

Somatotopy. Receptive fields in this pathway remain fairly small and localized and, throughout the whole pathway from dorsal columns to the somatosensory cortex, adjacent fibres or cells correspond to adjacent areas in the periphery. Thus the body surface is represented in an orderly, topographic fashion known as *somatotropic organization.* Moreover, certain peripheral areas have higher innervation densities peripherally and therefore disproportionately larger central representations throughout the whole pathway.

Conduction properties. Activity in this pathway is relatively stable, showing little alteration with arousal and attention and a lower susceptibility to blockage by general anaesthetic and hypoxia than that in the anterolateral pathway.

Anterolateral Pathway

Fibres contributing to this pathway are the smaller myelinated (Adelta) and unmyelinated C fibres which enter the spinal cord via the more lateral rootlets, together with some branches of larger fibres. Many bifurcate, sending branches rostrally or caudally in the dorsolateral tract (tract of Lissauer) before synapsing in the dorsal horn with second-order neurones most commonly found in laminae I and V. The axons of second- or third-order neurones cross to the opposite side of the cord and ascend in the anterolateral tract.

The anterolateral tract is sometimes called the *spinothalamic tract.* However, only a small percentage of the fibres pass directly to the thalamus and it is now clear that there are at least three functional divisions of the fibres. One, often termed *neospinothalamic*, is of recent phylogenetic origin and is most marked in primates. The thalamic terminations are found adjacent to those of the medial lemniscus, i.e., in the ventrobasal part of the thalamus. The second functional division, the *palaeospinothalamic*, is slower conducting and terminates in the medial group of thalamic nuclei. This pathway may carry information interpreted as burning, poorly localized pain, for lesions in the intralaminar nuclei relieve such pain without affecting the appreciation of pricking pain. The third functional division, sometimes called the *spinoreticular tract,* is found in all vertebrates and terminates in the reticular formation of the medulla, pons and mid-brain. These cells in turn relay to the thalamus and hypothalamus.

Fibres entering the anterolateral pathway carry information about *touch, pressure, cold, warm* and *noxious stimuli.* However this pathway shows far more convergence and interaction than the dorsal column pathway. Hence modality specificity is less precise and cells may respond to several different types of stimuli; at thalamic level, some cells respond to somatic, auditory and visual inputs. This pathway is therefore often referred to as the *non-discriminative* (non-specific) pathway.

Because this is the only pathway carrying impulses resulting from noxious and thermal inputs, damage to the anterolateral tract can give rise to a dissociated sensory loss; touch of a particular skin region can still be felt (via the dorsal column path) but both types of pain (pricking and burning) and temperature changes are not perceived.

Somatotopy. Somatotopic organization in the neospinothalamic tract is similar to that in the dorsal column pathway but it is far less precise in the palaeospinothalamic and spinoreticular tracts. Receptive fields are larger and may extend over the whole hand or even limb.

Conduction properties. In contrast to the dorsal column, this pathway is, except for the neospinothalamic portion, slowly conducting. Responses, particularly in the spinoreticular portion, show marked alterations with attention and can habituate to repeated stimuli. They are also far less resistant to anaesthesia.

Function of Relay Nuclei

On any sensory pathway there are always several interruptions at synaptic regions known as *relay nuclei;* information can never travel via a single fibre from receptor to cortex.

For the somatosensory pathways the nuclei consist of cells in the dorsal horns of the spinal cord, the dorsal column nuclei, the corresponding nuclei in the trigeminal system and the ventrobasal nuclear complexes of the thalamus. These nuclei are important in the functioning of the sensory pathways as they provide for interaction and modification of the input by excitatory and inhibitory mechanisms. These mechanisms are activated by ascending and descending pathways.

Inhibition can be either presynaptic or postsynaptic. One situation in which pre- and postsynaptic inhibition are thought to contribute to the functioning of sensory pathways is surround inhibition.

Surround Inhibition

This is also called lateral or afferent inhibition. It is important in all sensory systems, particularly the visual and auditory systems, in the sharpening of contrasts, in the localization of stimuli and in spatial discriminative ability.

A sensory unit commonly has an excitatory receptive field surrounded by a region, the inhibitory surround, which when stimulated reduces the output of the unit. The inhibitory surround of a unit is located in the excitatory fields of other adjacent sensory units which, when stimulated, exert an inhibitory effect on that unit by way of interneurones. These interneurones may act either by pre- or postsynaptic inhibition. Thus the unit with the greatest afferent input imposes the greatest inhibition on its neighbours.

At each central synapse, diverging connections may result in activity becoming widespread. Surround inhibition is important because it reduces the spread of activity. It occurs at synaptic relays at all levels of the sensory system, thus ensuring that the focus of activity is kept sharply localized, with weakly excited surround connections being inhibited by the strongly active centre.

Descending Inhibition

Descending pathways originating in various regions of the brain exert control over the sensory as well as the motor functions of the spinal cord. They act at every synaptic level to reduce irrelevant activity and to sharpen contrasts to improve discriminative ability. For example, the inhibition of descending pathways by the application of a cold block to the spinal cord alters the activity of dorsal horn cells caudal to the block. Conversely, electrical stimulation in the mid-brain in the vicinity of the periaqueductal grey matter produces analgesia. This analgesia is produced by nerve fibres descending from the mid-brain to the relay nuclei in the dorsal horn where they take part in the inhibition of dorsal horn neurones.

4.4 Somatosensory Cortex

The primary or *first somatosensory cortex (SI)* lies along the central sulcus. It is classically considered to lie behind the sulcus in the postcentral gyrus, though many sensory responses occur precentrally. A *second* and smaller somatosensory area (SII) lies along the lip of the lateral fissure. Layer IV of the somatosensory cortex receives inputs from the thalamus. From there activity spreads to more superficial and deeper layers before passing to

other cortical regions. Neurones in columns perpendicular to the surface have similar receptive fields and respond to inputs from similar receptors. Thus it may be that the somatosensory cortex, like the visual cortex, is organized functionally into columns.

Somatotopy

Responses in the first somatosensory cortex result from stimulation on the opposite side of the body, except in the case of the face, and are somatotopically organized. The density of peripheral innervation determines the size of the corresponding cortical area. In man the hands and lips are disproportionately represented.

Lesions to the somatosensory cortex cause severe impairment of fine tactile discrimination in the corresponding peripheral area. Electrical stimulation of the cortex gives rise to a tingling sensation in the corresponding part of the periphery, though normal tactile sensations are not elicited.

It is not known if there is a cortical representation of nociceptive stimuli. Stimulation of the cortex is rarely painful and lesions of the first or second somatosensory areas seldom cause analgesia. Indeed such lesions are more likely to cause hyperpathia or abnormal sensitivity to stimuli. Neurones responding to tooth pulp stimulation have been found in the second somatosensory area but in very small numbers and very little is known about them.

Evoked Potentials

On stimulation at the surface of the body a mass response consisting of the IPSPs and EPSPs of many activated cells can be recorded from the surface of the somatosensory cortex, or even through the scalp if averaging techniques are used to improve the signal to noise ratio. This mass response is known as an *evoked potential.* They most commonly consist of alternating positive and negatives waves, the first wave being positive.

The *latency* of an evoked potential varies in different sensory systems and in different animals but is very consistent under similar stimulating and recording conditions. This has proved valuable in the early diagnosis of certain diseases like *multiple sclerosis,* in which the latency of the evoked potential is increased because of loss of myelin along the pathway. Evoked potentials can also be used to assess the integrity of a sensory path in infants or comatose patients.

4.5 Modalities of Sensation

Mechanoreception

The sensations usually associated with mechanical stimulation of the skin are *touch* and *pressure,* although more complex sensations such as *vibration* and *tickle* are also recognized. The figure illustrates the kinds of mechanoreceptors to be found in hairy and glabrous skin of mammals. Muscles and joints contain receptors which contribute to *position sense* as well as responding to *pressure* and *stretch.* Viscera have only a few mechanoreceptors.

Mechanoreceptors are specialized to detect particular properties of the stimulus such as its position, its intensity, its duration, its velocity or its acceleration. Receptors that respond when the stimulus is stationary are *position* or length detectors. As the stimulus is applied the frequency of nerve impulses increases with the amplitude of deformation and then remains steady or declines gradually when the displacement is static. Such slowly adapting receptors can also gauge the *intensity* and *duration* of mechanical deformation of the skin or muscle. During a change in position or length they may also provide information about the velocity of deformation. Examples of such receptors are Meckel's discs and Ruffini endings. Both are probably involved in the sensation of pressure on the skin.

Receptors detecting primarily *velocity* respond mainly during movement and cease to fire after movement has stopped. Such rapidly adapting receptors are called *'phasic'* receptors in contrast to *'tonic'* receptors that continue to respond to a constant stimulus. Phasic receptors are involved in sensation such as touch and tickle. Examples of this type of receptor are Meissner's corpuscles in glabrous skin and hair follicle receptors in hairy skin.

A third type of receptor responds to rapid transients in skin displacement, i.e. to *acceleration.* They are very rapidly adapting and may discharge only one impulse for each stimulus. Two types are known - Pacinian corpuscles and certain hair receptors. Rapidly repeated stimulation of these receptors evokes a sensation of vibration. Pacinian corpuscles are extremely sensitive to vibration and detect very small amplitudes of the order of 1 microm, particularly between 150 and 300 Hz.

Touch

Tactile sensations can be produced by indenting the skin by as little as 10 microm. Localized regions or *touch points* occur which are more sensitive to touch or pressure than surrounding areas. In the fingertips the thresholds of the receptors are significantly lower than surrounding areas. The capacity for *spatial discrimination* also varies over different parts of the body. For example, two-point discrimination assessed with the pointed arms of a pair of calipers is 1 to 3 mm over the tips of the fingers and tongue. In contrast the minimum spatial discrimination is 20 to 50 mm over the forearm and back.

Proprioception

In muscle and tendons there are mechanoreceptors providing information about muscle length and tension. These are usually associated with *muscle spindles* and *Golgi tendon organs.* In joints there are mechanoreceptors that respond to bending of the limbs. These may be Ruffini endings in joint capsules, Golgi endings in ligaments or Pacinian corpuscles often found associated with joints and along bones and ligaments. All of these receptors (and mechanoreceptors in the skin) may be involved in the subconscious control of posture and movement, also in the conscious awareness of posture and movement, which is called *proprioception.* Their roles in position sense (*kinaesthesia*) are summarized below.

The joint receptors do not, as was once thought, appear to be able to signal the position of joints with real fidelity except at the extremes of the joint range. It is found that patients with complete joint replacement by a mechanical prosthesis retain position sensation

with respect to that joint. Many of the receptors signalling joint movement with great fidelity were based on the recording signals originating in muscle spindles.

Muscle spindles and Golgi tendon organs give information about the state of joints but active and passive tension have to be distinguished to make sense of the information. One organ - the tongue - has muscle spindles but not joints and therefore no joint receptors. If the tongue is anaesthetized so that information from mucous membranes is lost, its position can still be distinguished. Moreover, vibration of muscles (a powerful stimulus to muscle spindles) can give rise to illusion of movement and inaccurate estimations of joint position. These illusions remain even if the joints and skin are anaesthetized.

The slowly adapting receptors of glabrous skin appear to signal the movement of the distal finger joints over a wide range and this ability is retained even if the muscles moving the joints are disengaged. Moreover if position sense is compared in fingers and toes after both skin and joints have been anaesthetized and after joints only have been anaesthetized, there is a deficit in the first but not in the second instance.

In conclusion then, it appears that muscle spindles and Golgi tendon organs are the principal receptors for position sense but skin receptors have an important role in fingers and toes and may well have a role elsewhere. Joint receptors presumably also have a role particularly at the extremes of movement.

Thermoreception

When parts of the body are exposed to changes in temperature within the range of approximately 20 to 40 °C there is an initial sensation of cold or warmth but this sensation gradually fades to one of thermal neutrality as adaptation occurs. Above and below this so-called 'neutral zone' permanent sensations of heat and cold are experienced. The upper and lower limits of this zone vary. The zone expands when the area of skin exposed is large and contracts when it is small. This is because *spatial summation* of the inputs occurs in the CNS.

There are two types of receptors associated with these sensations - *cold receptors* that respond to a decrease in skin temperature and *warm receptors* that respond to an increase. These *cutaneous thermoreceptors* are also involved in the regulation of body temperature, together with receptors in the hypothalamus and spinal cord. The structure of cutaneous thermoreceptors is not well defined but they are probably *free nerve endings.* They are distributed separately in discrete areas of the skin, i.e. there are cold-sensitive and warm-sensitive spots, the former being more numerous than the latter.

The afferent fibres associated with cold receptors usually show a tonic discharge at skin temperatures between 15 and 20 °C with a peak frequency at about 30 °C. They give a phasic response to a fall in temperature of less than 0.1 °C. Although normally silent above 40 °C, they may give a transient paradoxical response around 45 °C. The afferent fibres of warm receptors show a tonic discharge at skin temperatures above 35 °C and give maximum frequencies around 45 °C. At temperatures a few degrees above this their activity ceases. They also give a phasic response to a rise in temperature of less than 0.1 °C.

Pain

Pain can be described as the sensation resulting from stimuli which are intense enough to threaten or to cause injury. Such stimuli may be mechanical (i.e. scratch), chemical (i.e. acid) or thermal (i.e. burn). Neurologists commonly test pain sensitivity by a pinprick. However, pain sensations may show no simple correlation with the intensity or extent of tissue injury. Areas of apparently normal skin may show increased sensitivity (hyperpathia) while massive tissue destruction may occur without pain. Thus the location and type of injury is important. Pain sensitivity also varies in different individuals, races and cultures. Even the same injury in the same individual can cause different degrees of pain depending on the situation. For example, injuries in accident victims are often not remembered as painful at the time of the accident. It is clear that the sensation of pain is complex and that the body can alter the threshold in different situations.

It is usual to consider pain as having two components, the sensation *per se* and the emotional overtones of suffering and distress which are associated with it. While these two components usually occur together, certain procedures may leave one without the other. Thus sensation may occur without distress after frontal lobotomy operations, while abnormal activity in certain thalamic areas may lead to a sensation of pain that is particularly distressing and intractable. Certain drugs may also have different effects on the two components. Morphine for instance is especially effective on the emotional, reactive component. These considerations make studies on pain mechanism difficult.

Nociceptors

The receptors in skin, muscle, joint and viscera that respond to painful stimuli - nociceptors - are probably free nerve endings. They are supplied by either small myelinated (Adelta) fibres or unmyelinated (C) fibres. The endings with Adelta fibres signal high intensity mechanical stimuli. The endings with C fibres signal high intensity mechanical or heat stimuli or are less selective, responding to high intensity mechanical, thermal and noxious chemical stimuli (polymodal nociceptors). The response is usually a vigorous burst of activity. Sometimes the two groups of nerve fibres give rise to a 'double' sensation, the pain differing in latency and quality. There is a sharp initial pain signal which is caused by faster conducting A fibres, then later a long-lasting, aching pain due to activity in C fibres.

Many nociceptors show *sensitization,* that is, an increase in activity in response to repeated stimulation. Such sensitization probably underlies the hyperalgesia found in an injured area. Various factors, such as K+, acetylcholine, kinins and prostaglandins released by tissue damage have been implicated as mediators activating nociceptors but no single factor has yet been identified. *Itch* may be a form of pain sensation or a distinct sensation. It also requires the liberation of a chemical substance, possibly histamine.

Viscera have few receptors, including nociceptors. As a result of this paucity of receptors sensations are poorly localized. Nociceptors are located in the tooth pulp, the mesenteries and sheaths of blood vessels. They are not present at all in certain other tissues, for example brain, so brain tissue can be cut without giving rise to pain. The sensations most commonly detected from viscera are those of fullness or pain. Thus stretch in rectum and bladder gives rise to the sensation of fullness and triggers emptying reflexes, while throughout

the viscera, excessive stretch or distension commonly gives pain. This is often colicky in nature as for example in biliary colic and ureteric colic. Visceral pains are commonly poorly localized or even referred to other parts of the body.

Cramping pains may occur with excessive use of skeletal muscle as a result of stimulation of nociceptors by unknown factors. The painful condition of *angina pectoris* is due to the release of abnormal factors caused by ischaemia of heart muscle.

Referred Pain

Damage to an internal organ is commonly associated with pain or tenderness not in the organ but in some skin region sharing the same segmental innervation. A classic example of this is the referral of cardiac pain to the left shoulder and upper arm. The most likely explanation for referred pain is that some central cells receive both cutaneous and visceral inputs. Such cells have been described in lamina V of the dorsal horn. In the normal situation lamina V cells are activated by skin inputs. When the visceral organ is injured it activates the same cell in the dorsal horn and this is interpreted as injury to the skin. The skin, though uninjured, feels tender and local anaesthetics applied to the skin help to relieve pain by reducing the total sensory input from the skin.

Phantom Limb Pain

Amputation of a limb is often followed by the feeling that the limb is still present. The phantom area gradually shrinks and may completely disappear, but a small percentage (5-10%) of amputees are left with a persistent and severe pain apparently from the absent region. The pain is thought to arise centrally because sectioning of the contralateral-anterolateral tracts may give only temporary analgesia, and the pain may return and be felt at the same site as preoperatively. However in some cases the pain may be relieved for long periods by a prolonged or severe stimulus to the stump, although in others the stump may be reamputated or anaesthetized without any relief.

Opioids

Opiates, such as morphine, heroin and codeine, are amongst the most powerful analgesics known. They act centrally by combining with receptors in many regions, including those associated with pain reception, such as the periaqueductal grey matter of the brain-stem, parts of the limbic system and the substantia gelatinosa (lamina II) of the spinal cord.

An increased understanding of the way in which they are active has occurred with the discovery of the endogenous *opioid peptides,* comprising enkephalins, endorphins and dynorphins, which are powerful analgesics when administered intracranially. The *enkephalins* are pentapeptides (tyrosine-glycine-glycine-phenylalanine, then methionine or leucine) produced within the brain in regions like the limbic system and thalamus and in the substantia gelatinosa of the spinal cord. The *endorphins* and *dynorphins* are larger molecules containing a core of amino acids similar to the enkephalins. They were first found in the pituitary and later shown to be present in several regions of the brain. In the CNS opioid peptides are localized in nerve terminals and are thought to act as neurotransmitters or neuromodulators. They have both inhibitory and excitatory actions when iontophoresed on to neurones.

Although quite different in structure from the opioid peptides, the opiates appear to act by binding to the same receptors. The opioid peptides are as potent, or even more potent, in relieving pain than opiates when injected into the brain. They are not effective when injected intravenously because they do not cross the blood-brain barrier and are rapidly degraded. It is claimed that their levels are decreased in chronic pain states and increased by electrical stimulation of the periaqueductal region which results in analgesia. They may play a role in *acupuncture* as the effects of acupuncture can be blocked by the opiate antagonist naloxone.

As well as acting at higher levels of the CNS, the opioid peptides may also act at the level of the spinal cord. *Substance P,* a peptide present in the terminals of afferent fibres, has been suggested as the transmitter for nociceptive afferents in the dorsal horn. Opioid peptides may suppress pain by acting presynaptically to block release of substance P from these afferent fibres.