REVIEW OF LITERATURE
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'Pain is perfect misery, the worst of all evils and excessive overturns all patience.'

(John Milton: Paradise Lost)

Historical review:

The same was realized by the primitive man also, who used massage and herbs to relieve it. The use of analgesics goes back to 2250 B.C., in the maiden record of the Babylonian clay tablet from Nippur. The analgesic pills were first referred by Celsus in his De Medicine (first century A.D.). The importance of the central nervous system for pain was realized by Galen (second century A.D.), who performed experimental cordotomy. William Harvey, overwhelmed by his circulation discovery, announced heart to be the sole culprit for pain. A step forward was the concept of "delicate threads" for the transmission of sensation, reproduced by Descartes in 1644. Contrary to all beliefs, Chinese consider the evil of pain as recent guest, easy to expell out by acupuncture through 365 suitable points.

With the dawn of nineteenth century, the actual strategy of pain control grew up from its
childhood. Charles Bell (1811) laid his emphasis on dorsal roots of the spinal nerves, being distinct from ventral roots in function. Johannes Muller expounded the theory of specific nerve energies which was later disproved.

By the sunset of nineteenth century, pain perception was explained by three different ways in the form of emotional experience, intensive theory and specific sensory theory. Schiff (1848) ruled out the importance of touch and found pain a distinct entity. Hix (1894) separated pain and pressure spots over skin. Vonfrey (1894) histologically identified end organs for each sensation. Thus the concept of pain as a sensation got speed, further emphasized by Strong in 1895.

The hallmark of pain control was the first demonstration of surgical anaesthesia at the Massachusetts General Hospital in October 1846 by William T.G. Morton. The isolation of morphine by Seetaner in 1806, marked the onset of systemic analgesia. Bennett (1873) and Anrep (1878) demonstrated analgesic properties of cocaine to advance regional anaesthesia. Abbe performed posterior rhizotomy to introduce neuro-surgical technique for halt of pain,
PATHWAYS OF PAIN

Pain is one of man's most compelling experiences. It is an unpleasant sensation, which only the individual can appraise and as such is incapable of a satisfactory objective definition. (Merskey and Spear, 1967). Sherrington (1906), has described pain as "the psychical adjunct to an imperative protective reflex." This concept certainly draws attention to the protective aspect of pain.

Although the nature of pain was recognised by the great Greek philosophers, the theory that the pain can be produced by intensive stimulation of any sensory organ, has been frequently discussed. The neuro-anatomical basis of pain sensibility has been unfolded in the past, following the discovery of sensory functions of the posterior spinal nerve roots and the existence of medullary pathways comparatively specialized for pain.

The receptor organs for pain are distributed throughout the body, but it is convenient from the clinical aspect to consider pain under the following headings.

A. Superficial or cutaneous pain.
B. Deep pain (Muscles, Bones, Ligaments, Joints and fascia).
C. Visceral pain.
D. Referred pain.
E. Psychogenic or functional pain.

The physiological mechanism and the neural pathway for reception, conduction and appreciation of painful stimuli, irrespective of the site of its origin, are same, and therefore the description that follows is common to all types of pain.

The neurophysiological mechanism can best be understood under the following headings. (1) Reception of pain: The superficial, deep and visceral tissues are studded with the network of non-myelinated or poorly myelinated nerve fibres, responsible for the transmission of pain. These fibres respond to a variety of excessive stimuli e.g. thermal, mechanical, electrical or chemical.

The exact nature of the response whether by direct excitation of bare nerve endings or by tissue damage with secondary release of pain producing substances, is not clearly understood. Although Hardy and others (1951), by working with thermal energy, concluded, that the onset of pain coincided with the temperature at which alterations in tissue protein
started taking place. As a result they anticipated release of pain producing substance. But, Beecher (1956) rejected this theory and pointed out that extensive tissue damage can be produced without pain being experienced. He blames the level of anxiety as being responsible for the occurrence of pain. Wolf and Wolf (1958) consider that in such extensive injuries, coagulated serum, oedema and devitalized tissue may shield the pain endings from noxious stimuli. Moreover, damage to nerve terminals and fibres may desensitize traumatized tissue.

A pain producing substance, probably a polypeptide, has been detected by Armstrong and his co-workers (1957) in inflammatory exudates. They have also held several other substances, like histamine, acetylcholine, angiotensin, bradykinin, adenosine triphosphate, serotonin, hydrogen and potassium ions and 5-hydroxytryptamine, responsible for producing pain (Armstrong et al., 1953). Recent evidence (Ferreira, 1972), suggests that prostaglandin E, sensitizes the pain receptor to stimuli such as pressure and also the action of chemical mediators.

(ii) Conduction of pain:— Pain is conducted from the receptor site to the spinal cord, and thenceforth,
through various ascending pathways to the sensory cortex for its perception, by means of mixed nerves which act as transmitting cables.

These mixed nerves are collection of various types of fibres both myelinated and non-myelinated, and Gasser (1943), has classified these fibres into three broad groups depending upon the diameter and the conduction velocity of nerve impulses. The classification is as follows:

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Fibre</th>
<th>Diameter (in μm)</th>
<th>Conduction speed (in meters/sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelinated</td>
<td>Alpha</td>
<td>20</td>
<td>120</td>
</tr>
<tr>
<td>Somatic fibres A</td>
<td>Beta</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gamma</td>
<td>(3-4 μm)</td>
<td>(6-30), pain fibres</td>
</tr>
<tr>
<td></td>
<td>Delta</td>
<td>2 μm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epsilon</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Myelinated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral fibres B</td>
<td></td>
<td>&lt;3 μm</td>
<td>3-15</td>
</tr>
<tr>
<td>(Pre-ganglionic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-myelinated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic fibres C</td>
<td></td>
<td>&lt;2 μm</td>
<td>52, pain fibres</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Two groups of fibres are responsible for the transmission of pain. These are —
(a) the myelinated A delta fibres which have the diameter of 3-4 um and conduct at the speed of about 35 meters per second.

(b) the more slowly conducting C fibres which are unmyelinated, have a diameter of less than 2 um, with a conduction velocity of .5-2 meters per second.

The existence of both fast and slow neural pathway for conducting pain impulse to the central nervous system, is suggested by the occurrence of a double pain sensation, so called the 'echo pain'. The term applies to the twin peaks of pain which may follow the brief pain stimulus to the skin. Landau and Bishop (1953), concluded from their experimental study that C fibres-pain had a delayed, burning and persistent character, while the one transmitted through delta fibres is sharp and pricking in nature.

(iii) Central nervous system :=

(a) Transmision in spinal cord:= All the primary sensory afferents have their cell bodies in the dorsal root ganglion of the spinal cord. Pain fibres enter the spinal cord via the dorsal root, and then ascend or descend for one or two segments in the medial portion of Lissauer's tract to enter the more ventrally placed dorsal horn. Medial portion of Lissauer's tract carries excitatory fibres from adjacent roots, while lateral
portion carries inhibitory fibres.

The second synapse is formed in the substantia gelatinosa at the tip of dorsal horn, after the fibres have traversed 1-3 segments. The axons of the second neuron cross the mid line in the anterior commissure to form the lateral spinothalamic tract, which ascends and terminates in the lateral nucleus of the thalamus.

The spinothalamic tract is characteristically divided into two-
(a) The neospinothalamic tract—which arises from the dorsal horn, occupies the antero-lateral quadrant of the spinal cord. The axons terminate in the ventrobasal complex of the thalamus. This tract perceives the intensity of pain and localises it.

(b) The paleospinothalamic tract—which originates from the dorsal horn, receives C fibres input, crosses the anterior commissure and ascends in the spinal cord closely applied to, but more ventral than the neospinothalamic tract.

The fibres, after giving collaterals to the reticular formation of the brain-stem, terminate in the central, lateral and the intra-laminar nuclei of the thalamus. This pathway transmits the arousal and emotional component of pain.
A third spinal ascending pathway which may play some role in the nociception, is the spino-recticular pathway which consists of projections from small myelinated and unmyelinated fibres in the dorsal horn, mostly ipsilaterally and to a lesser extent contralaterally. The fibres terminate in the brain stem reticular formation, particularly in pons and medulla.

The grey matter in the spinal cord is arranged in the form of 10 laminae. Lamina 10 is around the central canal, lamina 9 is the motor neurons while 7 and 8 are the interneurons. The dorsal horn, as it is classically known as, is laminae 1-6. Laminae 1, 2 and 3 form the substantia gelatinosa; 4, 5 and 6 form the nucleus proprius with clarkes column in 6. Laminae 1-6 receive the primary afferent neurons and the cells in each layer converge on the layers below. Each lamina is activated by its own afferent neurons and a particular level of activity is achieved in this fashion (Sampson Lipton, 1976).

(b) **Reticular system** - The fibres originating in the brain stem reticular formation, receive input from several sources, including almost certainly, the paleospinothalamic and spino-recticular pathways;
essend in polysynaptic projections to the wide area of thalamus. This provides an alternative route for pain impulses to bombard a large area of the cerebral cortex. It is believed that stimuli following this pathway activate the cortex and help to maintain consciousness; this is probably a non-specific arousal mechanism.

(iv) Thalamus and the sensory cortex - Consciousness of pain is experienced at the level of thalamus, which contains a series of nuclei; a number of these are known to be involved in the appreciation of pain. Ascending reticular fibres form two groups, one of which is distributed to the intralaminar nuclei of thalamus while the other passing to the hypothalamus. Spinothalamic tracts terminate in the posterolateral ventral nuclei of thalamus before relaying onwards and the posterior column fibres also terminate in the thalamus. Thus it can be appreciated that all sensory fibres converge on the thalamus.

After relay in the thalamus the sensory fibres project onto the post-central gyrus in the cerebral cortex, maintaining the dermatomal arrangement of the fibres. It is possible to map out a distorted image of the body in the cortex itself.
The relative importance of thalamus and cortex, in the perception of pain, is still disputed. Head (1920) believed that pain is experienced when nerve impulses arrive in appropriate part of thalamus and regarded it as the centre of consciousness for pain. Thalamic sensation is crude and poorly localised, while cortex is essential for localising and detecting variations in the intensity of pain. To ascribe sensation to the thalamus and perception to the cortex, is to take too narrow a view of a complex functional inter-relationship. The conscious appreciation of pain appears to depend upon the widespread activity of intact cortex. It thus enables the individual to interpret and formulate his own personal reaction to a particular painful experience.

The intensity of pain, suffered, varies enormously with the personality, intelligence and culture of the individual. Emotional stress and anxiety adversely affect the pain response as also debility and fatigue.

(v) **Descending pathways** - Descending pathways comprise of fibres which originate in the orbital frontal cortex and probably descend via cortico-spinal tracts. The fibres which originate in the mid brain reticular
formation and raphe nucleus of the medulla and
descend via polysynaptic pathways, reach the dorsal
horn to modulate input to all laminae of dorsal
horn particularly lamina 5. These descending fibres
may influence activity at the dorsal horn level
via either pre or post synaptic contacts and may
be either facilitatory or inhibitory.

Theories of pain –

For pain transmission, perception and
appreciation, three theories were put forward.

First was the 'specific pain theory'
in which it was postulated that there were specific
pain receptors in the skin and specialized nerves
and pathways transmitted painful stimulation from
periphery to spinal cord and from spinal cord to
brain. It was believed that pain was perceived on
a one-for-one basis.

Second was the 'pattern theory' in
which it was postulated that pain sensation was coded
in same fashion at the periphery as in brain and that
it was the patterns of frequency and strength of the
electrical stimulation passing through nerve fibres
and nerve cells which ultimately were interpreted as
pain.
Most recent and still accepted is the third 'Gate-control theory' proposed by Melzack and Wall (1965), expanded in the form of a model by Casey and Melzack (1967) schematically represented in the diagram.

In this theory, it is suggested that the sensory input from the skin is modulated by a gate control system before its eventual perception as pain. The sensory impulses from the skin are distributed to three systems in the spinal cord, the tracts of the dorsal columns for onwards transmission to the brain, the cells of the substantia gelatinosa and the first central transmission (T) cells in the dorsal horn which transmit sensory information to high centres.

The substantia gelatinosa acts as a gate control mechanism. As it has been shown (Wall 1962; Mendell and Wall, 1964) that although the large fibres are at first very potent in activating the T cells, their effect is later diminished by an inhibitory process. Small fibres have excitatory effect. Continuous nerve impulses transmitting primarily by small fibres, keep the gate comparatively open. Skin stimulation evokes the volley of impulses in which large fibres activity predominates. The T cells are activated, but due to a inhibitory process
GATE CONTROL THEORY OF PAIN

L - Large diameter fibre
S - Small diameter fibre
T - First Central Transmission cells
the gate is partly closed. Sustained stimulation activates small fibre system, while adaptation occurs in large fibres. Thus the gate is opened and the outflow of impulses from T cells is increased.

Central efferent fibres influence the gate control mechanism through emotion or previous experience in the form of 'central control trigger' mediated by dorsal column (Hagbarth and Kerr, 1954; Wall, 1967).

Management of pain:

The management of pain is still a partially solved problem. The planning of treatment depends upon the cause of pain, nature of the cause, age and psychosomatic behaviour of the patient. Various techniques are practised, each one having its own limitations.

1. Drug therapy - parenteral analgesics require repeated dosage, needing multiple pricks. The selection can be made from Dicinal, Levophenol, Methadone, Bezitramide, Phanazocine and Pentazocine.

2. Nerve blocks - are ineffective in generalized pain. They can be either chemical or electrical.

3. Electrical stimulation - procedure is difficult, giving only temporary relief. External electrical stimulation and dorsal column stimulation are two
important ways.

4. Acupuncture - a new introduction requires much knowledge and skill, less effective for chronic pain.

5. Radiotherapy - has selected implication, requiring costly technology.

6. Hypothermia, hyperthermia and psychotherapeutics - have limited scope.

7. Destructive methods - like percutaneous cervical cordotomy, rhizotomy, transnasal pituitary injections and other neurosurgical techniques are drastic and difficult.


9. Intrathecal methods - intrathecal phenol, chlorocresol, alcohol and cold saline or barbetalase has disadvantage of introducing infection directly to central nervous system.

10. Epidural analgesia - which practically has no disadvantage and therefore is emerging like a boon to mankind.

**Epidural Space** -

The epidural space is the space between the periosteum lining the vertebral canal and the dura mater surrounding the canal. Its cephalad extension is till foramen magnum where dura attaches
to entire circumference of foramen, caudally it continues with the sacral canal, anteriorly lies the posterior longitudinal ligament, while posteriorly are laminae and ligamenta flava, lateral limits are marked by the pedicles and forty eight inter-vertebral foramina. what makes the epidural injection safe for the therapeutic and diagnostic administration of drugs, is the anatomy of the space (Pages, 1921; Dogliotti, 1933; Odom, 1940; Cousins, 1945).

The epidural space is not uniform in size and shape throughout. It is triangular and widest in the lumbar region (4-6 mm), (Bromage, 1954; Cheng, 1963; Macintosh, 1957). Attempts to pin point the capacity of extradural space were pioneered by Sicard and Forestier (1921). Lipiodol was injected and the volume was co-related with roentgenographic appearance. Total capacity of 118 ml for extradural space was calculated by Farr (1925) by injecting sodium iodide in fresh Cadavers.

The contents of epidural space are fat and loose areolar tissue, through which run the internal vertebral plexus, lymphatics and the dural projections, which surround the spinal nerve roots (Bromage, 1954; Cheng, 1963). In third trimester of
pregnancy and in cases of large intra-abdominal tumours, the vertebral venous plexus is engorged reducing the size of space vis a vis the dose (Bromage, 1963-64). The epidural space is a potential space with a negative pressure (Bromage, 1954; Cheng, 1963; Dogliotti, 1933; Haldt, 1928; Janzen, 1926). Only 80% of the patients have this negative pressure (Dawkins, 1971).

**Identification of the epidural space**

The following points suggest that the needle is in the extradural space.

1. Sudden lack of resistance to advancing needle as it pierces the dense ligamentum flavum.

2. Sudden ease of injection of a little air or liquid from a freely running syringe attached to a needle. If the point is in ligamentum flavum, plunger rebounds, if it is in the space, plunger can be pushed in easily (Sicard and Forestier, 1922; Dogliotti, 1931).

3. Movement of the bubble on Odom's indicator (Odom, 1936), which can be attached to hub of spinal needle.


5. Withdrawal of hanging drop of saline on hub of needle (Gutierrez's sign), (Gutierrez, 1932).

7. The Ikle syringe (Ikle, 1950).

8. The drip indicator (Dawkins, 1961).

9. Ultrasonic localisation of lumbar epidural space (Cork et al., 1979).

Occasionally small amount of clear fluid may continue to drip slowly from the needle hub, and usual physical tests such as temperature estimation, attempts at aspiration and observation of flow rate still leave doubt in the mind. The chemical properties of spinal fluid, saline solution and local anaesthetic drugs in various concentrations were compared utilizing a urine test strip (Reisner, 1976).

<table>
<thead>
<tr>
<th>Solution</th>
<th>pH</th>
<th>Glucose</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.S.F.</td>
<td>7</td>
<td>0</td>
<td>1+</td>
</tr>
<tr>
<td>Saline soln. 0.9%</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bupivacaine .25%</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>.5%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>.75%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Lidocaine 1%</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1.5%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Napivacaine 1%</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Tuohy (1945) discovered his special needle which he claimed could direct a catheter in the desired direction. Henkin et al. (1970) have described a disposable epidural-anesthesia-system which incorporates an external Teflon catheter with a precurved tip. The needle tip can be hidden inside the soft catheter tip giving a blunt tipped combination which greatly reduces the chance of accidental dural puncture. Since the catheter is of larger bore than the needle, it allows for reliable aspiration of cerebro spinal fluid and blood and offers no resistance to drug injection. Use of various type of epidural catheters and their methods of sterilization have been described by Davidson et al. (1951). Teflon and Vinyl tubing may be autoclaved, while polythene tubing should be sterilized with tincture of zephran.

Technical hazards -

1. Accidental puncture of dura - This may occur with the epidural needle or the polythene catheter (Hehre 1960, and Sanchez, 1967). Massey-Dawkins (1969) reports an incidence of 0.6% of perforation of dura by polythene catheter even though the needle had been correctly placed in the epidural space. Hehre and Saying (1960) advise that massive subarachnoid block can be avoided by injecting 2 ml. of analgesic
solution through the catheter as test dose.
Epidual block should be performed under strict
aseptic conditions, because of the possibility of
dural puncture (Bromage, 1954).

Incidence of spinal tap is lower
when visual methods are used rather than when the
loss of resistance test is employed for identifi-
cation of epidural space (Massey-Dawkins, 1969).

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Incidence of spinal tap</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chaplin and Ramwick (1958)</td>
<td>1.1%</td>
</tr>
<tr>
<td>2. Lund and Quinn</td>
<td>2.0%</td>
</tr>
<tr>
<td>3. Carr and Metre</td>
<td>2.3%</td>
</tr>
<tr>
<td>4. Moir and Willocks</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

2. Errors in camula placement -

Sanchez et al. (1967) found that an
epidural catheter passed through Tuohy needle
could move in the desired direction only in 47% of
cases. It passed out into para vertebral space in
6.6% cases. Munevuki et al. (1970) found that a
catheter in epidural space tends to curl upon
itself after 4-5 cm. Hehre and Saying (1960)
reported a case, where a catheter introduced into
epidural space tied itself into a true knot after
more than 4 cm. of it had been introduced.
Massey- Dawkins, (1969) advises that more than 5 cm. of catheter should not be introduced.

Catheter tip was cut off in 3 cases, inside the epidural space in attempting to pull it out through Tuohy needle (Bonica et al., 1957).

3. Haematoma - It may be caused by the introduction of any needle whether or not an analgesic drug has been injected. The resulting pressure effect of haematoma within the vertebral canal, particularly in the extradural space, may compress the cord causing paraplegia.

**Historical review of epidural block**

Approach to the epidural space through sacral hiatus was introduced by Corning, and then used in dogs by French investigators Sicard and Cathelin in 1901. In 1920 Zweifel analysed the incidence of fatalities in caudal epidural blocks. The space was studied by Sicard and Forestier (1921) by injecting coloured solution. Practical lumbar epidural anaesthesia owes its birth to Pages (1921). Later Dogliotti (1931-33), Hess (1934), Odom (1935), Gutierrez, (1939) and Harger et al. (1941), popularised the epidural technique. Heile (1913) tried to reach the epidural space by the intervertebral foramina.
Sicard and Casten (1904) have shown that the epidural space did not communicate with the subarachnoid space, by injecting india ink suspension into the epidural space of dogs. Same was emphasized by Sanford and Dobb (1941). Bertochi (1932) found dura almost impermeable to local anaesthetics. On the contrary now it is clear that the local anaesthetics cross the dura and enter the subarachnoid space (Flumin et al., 1953 and Usubiaga, 1961-64).

Sensitive radio assay technique using C\textsuperscript{14} labelled lignocaine or mepivacaine showed that the concentration of local anaesthetic in subarachnoid space was nearly as high in case of intradural route as with extradural route (Bromage et al., 1963; Bromage and Burfoot, 1964). Usubiaga (1961-64) reported recovery of 7.3% of epidural procaine in the subarachnoid space. The concentration of epidural procaine was directly proportional to the recovery amount in cerebro-spinal fluid. In many cases procaine level exceeded the amount necessary to block the myelinated fibres in spinal nerve roots (Flumin et al., 1953). Thus 3-10 percent of epidurally injected substance may enter the subarachnoid space.

Moore et al., (1958) studied the spread of contrast media in the epidural space of 19 human
cadavers, 1-3 hrs. after death by injecting solutions through L2-3 space. With 40 ml. he could trace it from the C7 to S2 vertebrae. The solutions tracked out of each intervertebral foramina through the entire length of the visible shadows, irrespective of age. Kishimura et al., (1959) reported a tendency of cephalad spread of the solutions in 56.7% of cases, irrespective of the position of the patient and the direction of the needle. The contrast medium when injected through second lumbar interspace, was rarely seen beyond first sacral vertebra. Similar findings were reported by Usukiage et al., (1964).

Yates (1965) reported visualisation of epidural space upto second lumbar vertebra without any tilt of the table by injecting 20 ml. of contrast medium through caudal route. Dutta et al., (1972) studied injected radio-opaque solutions at the third lumbar interspace before administering epidural anaesthesia and reported a tendency for cephalad spread in 66.7% of cases, with the absence of leakage through intervertebral foramina in 42.4%. They could visualise the epidural space from T2-3 vertebrae with 20 ml. of injection. They further concluded that the dispersion was cephalad, even when tip of the needle was directed caudally.
The longitudinal spread of the epidural solution is dependent on the volume injected. Sharrock (1978) pointed out that the height affected the extent of epidural anaesthesia in the elderly but had no influence in the younger individuals, because in elderly patient the intervertebral foramina are not patent as is shown by radiographs taken after the injection of radio-opaque dye into the paravertebral space. No method exists for the pre-determination of the size of intervertebral foramina and consequently the amount of solution which will leak along side of the nerves.

Bonica (1957) pointed out that the site of epidural injection should be nearest to the mid-point of the segments to be blocked, dosage being 1 - 1.5 ml. of solution per segment with a total of 12-15 ml. of solution. Caudal epidural requires 20 ml. of solution.

Fate of drug in epidural space -

The fate of an epidural injection meets primarily diffusion through dura and leakage through intervertebral foramina (mainly in young individuals). Vascular and lymphatic absorption, diffusion through villi and perivascular spaces and uptake in extradural fat mark the other ways of spread (Bromage, 1963).
Sicard and Foresteir (1921) injected India ink and lipoidal suspension in an attempt to study the study the site of action of analgesic solution and noted that these solutions tracked along with the intervertebral foramina and could be traced in the regional lymph glands 10 days after the injection. Odom, (1936) also confirmed that the leakage of solutions through each intervertebral foramen was constant and felt that analgesic solution acted at the paravertebral level. Bromage (1957) has produced a following working hypothesis reconciling all the clinical and experimental evidences available for the mode of action of epidural anaesthesia, as shown in the coming chart.

Lund (1961) observed greater dispersion of radio-opaque solutions in the older age group, with less leakage of solution through intervertebral foramina. He attributed this to lesser patency of the foramina. Erdemir et al., (1965) observed that even the weakest correlation does not exist between the height of the patient and the dispersion of solution.

The factors controlling the height of epidural analgesia may be summarised as the site of injection, volume of solution, position of patient
The fate of an extradural injection

Longitudinal spread in Extradural space (Volume dependent)

Leakage by vascular absorption

Leakage through intervertebral foramina (mainly in young subjects)

Systemic effects

Paravertebral block of nerve trunks

Centripetal sub-perineural spread

Subpial spread and uptake in pia mater

Diffusion through dural root sleeves via arachnoid villi and peri-vascular spaces

Subdural spread

Spinal root block

Spinal block

Uptake in extradural fat

Diffusion through spinal cord dura

Diffusion in extradural fat

Spinal Sub-dural space

Cerebrospinal fluid

Peripheral cord block
after injection, concentration of solution, pregnancy and intra-abdominal tumours. There is an exaggerated spread of epidural anaesthesia in arteriosclerotic patients. (Bromage, 1962).

The cephalad border of analgesia was determined by Urban (1973), 0.75 to 4 hours following induction of spinal or lumbar epidural anaesthesia. Levels thus obtained followed a straight line best described by the skin intercept of a transverse section through the trunk. There was no difference between spinal and epidural anaesthesia in this regard.

Site of Action -

As regards the site of action of extra durally injected solution, it acts in three ways. Firstly, by passing through the dura mater, secondly, by affecting the nerves in the paravertebral spaces and thirdly, at the ink-suff zones, where dura thins out to become perineurium, permitting the passage of crystalloid molecules and Colloidal carbon (Woollam and Millen, 1953). Frumin et al., (1953) have demonstrated extradural local analgesic in the cerebro-spinal fluid at a different level. Whether this concentration is sufficient for analgesia or not is questionable (Sarnoff and Arrowood, 1946).
**Opiates as epidural analgesics**

Post operative pain following abdominal and thoracic operations was relieved by lignocaines, with the disadvantage of tachyphylaxis. Later long acting drug Bupivacaine was used to give analgesia for 8-12 hours (Moore, 1975; Cronin and Davies 1975). Later opiates were used as epidural analgesics for chronic as well as acute pain of post operative period. The drugs used are Morphine 2-3 mg. (Behar, 1979; Bapat, 1979); Pethidine 100 mg. (Cousins et al., 1979) and Fentanyl 0.1 mg. (Wolfe et al., 1979). Behar et al., (1979) injected 2 mg. of morphine for acute or chronic pain, onset of action was 2-3 minutes and effect lasted from 6-24 hours. Bapat (1979) found the onset to be 5 minutes in acute cases and 1\(\frac{1}{4}\) - 2 minutes in chronic cases. The duration of action was 20-40 hours to 15 days in chronic cases. Husemeyer et al., (1979) found that 2 mg. of epidural morphine was ineffective to provide adequate analgesia in labour. Chayan et al., (1980) tried epidural morphine after caesarean section. They reported that relief of pain was sufficient to substitute surgical anaesthesia.

In the experiment of Gupta et al., (1980) onset remained the same, as in Behar series but the duration was found to be 6 hours to 7 days,
while amputees got permanent relief, with the same dosage of epidural morphine. In the series of Joan et al., (1980) pain relief lasted for 390 to 1205 minutes after 2 mg. of morphine. Johnston et al., (1980) pointed out the duration to be 3-50 hours in the cases of multiple fractured ribs. McClure et al., (1980) compared the results of 2-5 mg. morphine with a placebo injection in post operative period. After 20 minutes of injection, the placebo group, as a whole, had a satisfactorily significant reduction in the mean pain score. Few of the placebo group patients asked for further injections of dmsm, as they felt pain after 20 minutes. Scott and McClure, (1979) found 2 mg. morphine in 10 ml. saline to be inadequate to provide analgesia in the immediate post operative period, but usually gave good results on the day following surgery.

Repet et al., 2 mg. morphine epidurally.

<table>
<thead>
<tr>
<th>Type of pain</th>
<th>No. of cases</th>
<th>Pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Onset</td>
</tr>
<tr>
<td>Chronic</td>
<td>7</td>
<td>1 1/2 - 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute on chronic (gangrene)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Acute (Post-operative)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Acute (Obstetric)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Observer</td>
<td>Onset (mts.)</td>
<td>Peak (mts.)</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Morphine - 2 mg.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behar et al.</td>
<td>2-3</td>
<td>10-15</td>
</tr>
<tr>
<td>Bapat et al. acute</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>chronic-1/4</td>
<td></td>
<td>1-15 days.</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>2-3</td>
<td>-</td>
</tr>
<tr>
<td>Joan et al.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Johnston et al.</td>
<td>2-3</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pethidine 10 mg.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cousins et al.</td>
<td>5</td>
<td>10-20</td>
</tr>
<tr>
<td><strong>Fentanyl 1 mg.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolfe et al.</td>
<td>4-10</td>
<td>20</td>
</tr>
</tbody>
</table>

Extradural morphine has been reported to produce analgesia within 5 minutes (Behar et al., 1979; Magora et al., 1980). The effect of morphine sulphate on single unit activities of various dorsal Rexed laminae was studied by Luke et al., (1974) using an extracellular micro-electrode recording technique in decerebrate spinal cats. Intravenous morphine sulphate, 0.5, 1 and 2 mg./kg. body weight suppressed, in a dose related manner, spontaneous single unit activities in Rexed laminae 1 & 5, known to respond principally to noxious stimuli. It however did not effect spontaneous activities in lamina 4 and 5, known to respond to non-noxious
stimuli. Morphine and related compounds have significant effects on the spinal cord.

Animal experiments on cats by Kasaka et al., (1974) suggested that morphine causes selective suppression of Rexed laminae 1 and 5. Wang (1979) demonstrated that the response to nociceptive stimuli (flexor and crossed extensor reflex) was markedly depressed while the response to stretch (Knee and ankle jerks) was either not affected or slightly augmented by morphine sulphate.

Plasma concentrations of morphine, after intramuscular, extradural and intrathecal injections were studied by Chauvin et al., (1981). They concluded that morphine given extradurally has a higher rate of vascular absorption than morphine given intrathecally, the former being similar to that observed after intramuscular administration.

The radio-immune assay test showed that the opiate was present in the cerebro-spinal fluid after the epidural injection of morphine and it reached the peak value after about 35 minutes. Here the systemic concentration of morphine was negligible whereas its concentration in cerebro-spinal fluid was relatively high (Behar et al., 1979).
Chambers et al., (1981) introduced 10 mg. morphine in epidural space, before the onset of pain, by mixing it in 20 ml. of 0.5% bupivacaine and found better results when the morphine was given before the pain was present.

The commonly used preparations of morphine contain preservatives like chlorocresol, chlorobutanol and methyl hydroxy benzoate, giving an additional level of analgesia. Preparations containing preservative for epidural and intrathecal injections may cause paralysis (Craig, 1977).

Cousins et al., (1979), injected 100 mg. of pethidine hydrochloride, in 10 ml. of saline, epidurally. The pain relief started at 5th minute, with mean duration of action 6 hours, range 4.5-20 hours. Etherer (1975) studied the blood concentration of pethidine after epidural injection which was similar to that following intramuscular injection.

Rutter et al., (1961) compared the results of morphine, pethidine and fentanyl using them in 2 mg., 50 mg. and 1 mg. dosage respectively. They concluded the results, using a visual linear analogue; pethidine was found to be least effective, morphine longest acting and fentanyl had a relatively shorter duration of action. In all
patients there was a decrease in respiratory rate, but there was no depression of ventilation as judged by changes in PaCO₂.

Epidural fentanyl was first used by Wolfe et al., (1979) in the form of 0.1 mg. in 8 ml. 0.9% normal saline. Pain relief started in 4-10 minutes and lasted for 200-400 minutes, with a peak action in 20 minutes. No significant alteration in heart rate, blood pressure, respiratory rate or consciousness level was detectable. Daily and Smith (1980) used fentanyl with excellent results. Rutter et al., (1981) found poor results with 0.1 mg. fentanyl, with a duration of action of 2 hours. Nalda et al., (1981) used .25 mg. fentanyl with good results.

No literature is available on Fortwin given epidurally for post operative period.

**Side effects - Morphine -** In Bapat series, all the patients received 2 mg. morphine epidurally. Three patients of chronic pain did not pass urine for 12 hours. Reiz et al., (1980) reported the side effects of morphine chloride out of their experience of 1200 patients. They used 2 mg. morphine in 10 ml. normal saline. In the first 242 patients a commercial preparation containing sodium pyrosulphite 0.1 mg.
and sodium EDTA 0.1 mg. per 10 mg. morphine chloride was used. The remaining 958 patients were treated with a preservative free filtered solution.

The side effects as related to epidural morphine were:

<table>
<thead>
<tr>
<th>Side effects</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea &amp; vomiting</td>
<td>204</td>
<td>17%</td>
</tr>
<tr>
<td>B.P. drop 20 mm of Hg.</td>
<td>24</td>
<td>2%</td>
</tr>
<tr>
<td>Itching (first 242 pts.)</td>
<td>35</td>
<td>15%</td>
</tr>
<tr>
<td>Itching (Next 958 pts.)</td>
<td>9</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>181</td>
<td>15%</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1</td>
<td>.09%</td>
</tr>
</tbody>
</table>

Hales, (1980) reported pruritis in case of fractured rib, with 5 mg. morphine in 10 ml. normal saline. Pruritis was from nipple to knee and it disappeared with the disappearance of analgesia.

In the series of Andrews and Surendran, (1981), one patient developed respiratory depression. The patient was having obstructive jaundice. The respiratory rate was reduced to around 6-8 per minute, reversed by lethidron. One patient developed itching all over the body. Two patients had vomiting. Four patients complained urinary retention upto 18-24 hours following surgery. None of them needed
catheterization.

There are reports of respiratory depression and coma following epidural opioids, time of onset is from 45 minutes (Glynn, et al., 1979; Scott and McClure, 1979; Beas, 1980; Velch, 1981), to 4–6 hours (Christensen, 1980; Reiz and Westberg, 1980).

Glynn et al., (1979) administered 100 mg. of pethidine in two old patients, the onset of sedation and respiratory depression was approximately after 30 minutes. Scott and McClure, (1979) found respiratory depression with 100 mg. of pethidine in two old patients, and required naloxone intravenously.

Wolfe and Nicholas, (1979) found complete absence of side-effects in their series. Lisander and Stanquist, (1981) have shown experimentally in cats that fentanyl .01–.05 mg. given extradurally abolished or substantially reduced the inhibitory reflex with a latent period of 5 minutes or less, thus producing paralytic ileus.

Mode of Action - Opiates act as agonists interacting with stereospecific saturable binding sites or receptors in the brain and other tissues. These
binding sites are widely and unevenly distributed throughout the central nervous system, with maximum concentration in limbic system, thalamus, striatus, hypothalamus, mid brain and spinal cord (Synder et al., 1974; Simon and Hiller, 1978). Affinity for the binding sites marks their potency. Met-enkephalin and leucine-enkephalin and other larger polypeptides isolated from brain and other tissues interact with opioid receptors producing similar but not identical pattern. Opioids decrease the release of acetylcholine from some peripheral and central cholinergic neurons, elevate brain acetylcholine level and antagonise the acetylcholine depleting effects of hexamethonium (Domino and Wilson, 1973). In some preparations, morphine blocks the effect of 5 hydroxy-tryptamine but can also stimulate its release from gut. Chronic administration increases the turnover of 5 hydroxy-tryptamine in brain.

Specialized cell cultures are needed for the study of mode of action. Opiates decrease the activity of adenylate cyclase in such cultures. But whether the changes of cyclic AMP in neurons are related with actions of opiates is not established. Opiates can alter the release of a
member of neuro-transmitters. Transmembrane transport of Ca\(^{++}\) is affected leading to its depletion in brain, thereby relating the antagonising effect of Ca\(^{++}\) (Way, 1978). Furthermore opiates suppress the activation of membrane-bound protein-kinase needed for phosphorylation of other membrane proteins, by calcium (Clouet et al., 1978; Schulman and Greengard, 1978). Any plus ion also affects the affinity of opiates for receptors. Its elevation reduces the affinity of binding of agonists while increasing that of antagonists (Synder, 1978).

Pharmacology of drugs -

MORPHINE - morphine is the principal alkaloid contained in opium, the dried powder derived from the milky exudate of the capsule of poppy (Papaver somniferum). The poppy juice being first referred by Theophrastus in 300 B.C. and Duoscorides in 60 A.D.. In 1807, Serturier, named morphine after Morpheus, the Greek God of dreams.

Morphine produces its major effects on the central nervous system and bowel. The therapeutic dose of morphine produces analgesia, drowsiness, changes in mood and mental clouding.
There is no loss of consciousness with selective
relief of pain; other sensory modalities like touch,
vibration, vision, hearing etc., are not affected.
Continuous dull pain is relieved more than sharp
intermittent pain. Morphine administration leads to
central nervous system depression, causing
analgesia, sleep, respiratory depression,
depression of cough reflex. Central nervous system
stimulation, produced by it, leads to vomiting,
menisus, hyperactive spinal cord reflexes, rarely
convulsions. Changes of mood like euphoria and
dysphoria are known to occur. Moreover morphine
produces smooth muscle stimulation, causing gastro-
intestinal muscle spasm (constipation), biliary tract
spasm and renal tract spasm. The respiratory centre
is depressed, leading to a reduction in the
respiratory rate and minute volume. Respiratory
depression is progressive with increasing dosage and
is the principal toxic effect of overdose, after
which the respiratory rate may fall to three per
minute, the patient may become comatose,
hypotensive and cyanosed. The respiratory depression,
coupled with pin-point pupils, is usually diagnostic
of narcotic over-dose, though in extremes the pupils
may dilate.
Morphine is poorly absorbed from the gastrointestinal tract because it is conjugated in the gut wall (Brunk and Delle, 1974). After given by injection, it is quite extensively taken up in the tissues, readily crosses the blood brain barrier and placenta to the foetus, producing respiratory depression. Having free OH groups, morphine is conjugated in the liver and the conjugated metabolites are rapidly excreted by the kidneys. The usual dose of morphine is 0.1-0.2 mg. per Kg. body weight, though more than this may be required in resistant individuals.

PETHIDINE— Pethidine was first synthesized in 1939 by Schaumann and Eisleb at the Hoechst Farbwerke in Germany in a search for an atropine substitute.

The structure of pethidine does not resemble that of morphine but its molecule conforms to the steric configuration of the opioid receptor, thereby having same mode of action as that of morphine. The principal difference being that both analgesia and side effects are of brief duration. The sedative and tranquilising effects are almost as good, and though the incidence of nausea, vomiting, dry mouth, hypotension and
dizziness is transiently higher than after morphine, the duration of these side-effects is brief (Dundee et al., 1965). Pethidine does not cause gastrointestinal tract spasm and meiosis. It causes dangerous interaction with monoamine oxidase inhibitors.

Pethidine raises the cerebro-spinal fluid pressure. It often relieves bronchial spasm. It causes spasm of the sphincter of Oddi, an effect counteracted by amyl nitrite, nitroglycerine, adrenaline, and aminophylline. It reduces tone and amplitude of contraction of ureters.

It may release histamine from tissues, producing a typical triple response. It has a quinidine-like effect on myocardium and has been used to reduce the incidence of arrhythmias associated with cyclopropane anaesthesia. It may increase the incidence of post operative nausea and vomiting, an effect reduced by its combination with atropine or hyoscine (Dundee et al., 1964).

Pethidine is fairly rapidly broken down by liver, disease of which may retard its destruction. The principal product is nor-pethidine, excreted by kidney. Renal excretion can be increased
by forcing fluids and by making the urine more acid.

It is one tenth as potent as morphine and the dose is 1.5-2.0 mg./Kg. body weight.

**PENTAZOCINE** - was first described by Archer in 1962 and by Keats and Telford in 1964. Analgesic potency of 30 mg. equals to that of morphine 10 mg. and pethidine 75-100 mg. (Conaghan et al., 1966). Respiratory depression occurs equal to that of morphine and pethidine in equipotent doses. Hypertension may be produced (Keats and Telford, 1965).

The depression of pentazocine is not reversed by specific narotic antagonists, but by nikethamide, and by methylphenidate (Doran and Burt, 1970) and by naloxone (Churchill, 1979). It raises the blood pressure. It is a very weak narcotic antagonist, being one fiftieth of the activity of nalorphine. It crosses the placenta less. It is of briefer duration of action than pethidine and less cumulative. Dose is 30-60 mg.

**PENTANYL** - It is a synthetic derivative of pethidine. It displays the typical spectrum of activity of the narcotic analgesics with the exception of having little hypnotic and sedative effects. The analgesic
action of a single intravenous dose of fentanyl will last for about 30 minutes, while the amount of fentanyl which is equianalgesic with 10 mg. morphine, is of the order of 0.2 mg. (Morrison Loan and Dundee, 1971). While lee and Atkinson (1977) mention that 0.05 mg. fentanyl has the analgesic potency of morphine 10 mg. or pethidine 100 mg.

Respiratory depression is marked, apnoea being common with doses in excess of 0.009 mg./Kg. body weight, can be antagonized by nalorphine and its congeners. Fentanyl has little effect on haemodynamic stability (Frys Roberts and Kelman, 1967; Tammisto et al., 1970) and it reduces both cerebral blood flow and cerebral oxygen consumption (Michenfelder and Theye, 1971). It is also a potent stimulator of vomiting centre.

Rigidity of the thoracic and abdominal muscles to an extent which makes inflation of the lungs difficult, has been reported after rapid intravenous injection of fentanyl (Corssen et al., 1964). This is presumably a manifestation of stimulation of spinal reflexes and, if it occurs, it can be abolished by the use of a muscle relaxant.
Fentanyl 0.1-0.6 mg. with droperidol

5 mg. produces neurolept anaesthesia. The combination of fentanyl 0.05 mg. and droperidol 2.5 mg. is available as thalamonal. Usual dose is 2 ml.