Textbook of Pain

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and this is not always possible (Hamano et al 1978). Recently, Golgi afferents have been matched with afferents stained with dorsal root HRP loading in an attempt to overcome this problem (Beal & Bicknell 1981).

Dorsal root terminals apparently vary, not only in their degenerative changes but also in the time period within which these changes occur. While this has been used to differentiate large and small terminals (Lamotte 1977, Ralston & Daly Ralston 1979) it can lead to problems. In the past, some laboratories found no degenerating afferents in substantia gelatinosa (Ralston 1968) presumably because they did not appreciate the differing time course. Other laboratories, looking at different times, did see degeneration (Heimer & Wall 1968). A further problem is that by the time a terminal is frankly degenerating, the subtle characteristics of different terminal types cannot be determined.

Transganglionic degeneration has advantages over Wallerian degeneration because single peripheral nerves can be cut, or even only small pieces of skin, and the central terminations mapped (Arvidsson & Grant 1979b). But this approach has limitations in that it is difficult to demonstrate fine-calibred fibres and therefore the projection to substantia gelatinosa looks rather small (Grant et al 1981).

In all cases where degeneration studies are used, the possibility of trans-synaptic degeneration must be borne in mind (Cowan 1970). Thus a pathway may appear to be larger than it really is and what is considered to be afferent fibre degeneration may actually be postsynaptic axon degeneration.

A thorough analysis of the results of autoradiography is necessary because of the high and variable background labelling that always occurs with this technique. Some authors have found that axons label more intensively than terminals (Ralston & Daly Ralston 1979), giving biassed results. Furthermore, some amino acids are transported transynaptically (Heacock & Agranoff 1977).

Horseradish peroxidase techniques have revolutionised our knowledge of afferent terminations, but even so they are not without problems. The distance which HRP can travel into the terminals and still be observed is limited. A comparison with Golgi staining has indicated that terminals filled with HRP from dorsal roots is better for delineating preterminal fibres, but that Golgi staining is preferable for showing terminal arborizations and boutons (Beal & Bicknell 1981).

Transganglionic transport from individual nerves and end organs has been especially useful but there are suggestions of differential uptake with small fibres taking HRP up more readily than large ones (Brushart & Mesulam 1980).

The combination of intracellular recording and HRP injection of single fibres has been tremendously productive. As yet the technique is limited to A fibres, C fibres being too small to penetrate. The question of complete filling of terminals, of course, also applies here (Brown 1981b). However, it is the only method that combines both physiology and anatomy.

Neurochemical markers are limited by their own inherent distribution in the central nervous system. FRAP is contained in a subpopulation of small DRG neurons which is separate from those that contain SOM and SP (Nagy & Hunt 1982). SOM & SP are also in two separate populations (Hökfelt et al 1976). Maps of the distribution of SOM, SP & FRAP terminals in the CNS will therefore only inform about a small, and as yet physiologically unidentified, proportion of small fibre terminations. A further problem is that it is still not entirely clear if these chemical markers are only confined to C fibres or whether they are also found in fine myelinated afferents.

Electrophysiological techniques have the great advantage that functional characterisation of the afferents studied can be carried out. They are also crucial for evaluating the importance and effectiveness of groups of terminations in passing information to the CNS. Naturally, there are limitations. Precise electrode location is often difficult to establish. Stimuli applied to a group of terminals also activate surrounding structures. Unequivocal monosynaptic connections are hard to demonstrate.

Despite these problems, these different techniques largely complement and support each other and have led to a considerable amount of information on primary afferent terminations in the CNS.

THE COURSE AND TERMINATION OF DORSAL ROOT AFFERENTS

Dorsal root ganglion and dorsal roots

The cell bodies of primary afferents in the dorsal root ganglia (DRG) can be divided into large cells (60–120 μm) giving rise to large myelinated (A beta) fibres and small 'B' type cells (14–30 μm) giving rise to perhaps small myelinated (A delta) and certainly unmyelinated (C) fibres. The ganglion cell axon is often highly convoluted forming a glomerulus. It then bifurcates to form a central and peripheral branch although recent evidence suggests that there are in fact two or more processes per DRG cell, both peripherally and centrally (Langford & Coggeshall 1981). The central processes enter the spinal cord through the dorsal roots and some travel in the ventral roots also (see p. 000). 60–70% of dorsal root ganglion cells are of the small 'B' type. (See Lieberman 1976 for more details). In man and monkeys, as the roots enter the cord at the dorsal root entry zone, A and C fibres separate into bundles. The majority of C fibres collect into a ventrolateral bundle, although there is also a small dorsomedial C fibre bundle (Sindou et al 1974, Snyder 1977). This is not so in cats where there is no organisation according to fibre diameter.

General points on entry and course of dorsal root afferents

Shortly after entering the spinal cord many dorsal root fibres bifurcate in a Y-shaped fashion, although this is not always the case. If so, one branch ascends and the other descends in the spinal cord (Rethelyi & Szentagothai 1973). Generally speaking C fibres appear to travel in the most lateral part of the dorsal white matter, including Lissauer's tract, and A fibres more medially. Primary afferents entering the grey matter are almost always collaterals and they enter along its entire border with the dorsal white matter.

Segmental distribution

Dorsal root afferents issue most collaterals in their segment of entry but the rostrocaudal spread is very large. Upper cervical roots spread six segments and lower ones fourteen (six above and seven below segment of entry) in the cat (Sterling & Kuypers, 1967; Imai & Kusama, 1969) and L3–S2 roots all show some projection in all of those segments, the most intense being in their own segment (Wall & Werman 1976, Brown & Culberson 1981). There is generally very little contralateral projection of dorsal roots. Culberson et al (1979) report that it is present below S1 in cats and that there is also some crossing at cervical levels, but none at lumber levels.

The rostrocaudal extent of projection of C fibres is less than A fibres. Szentagothai (1964) observed degeneration of small afferents following root section in kittens in one or possibly two segments above and below the level of entry, and this is agreed by other authors in monkey cervical cord (Lamotte 1977, Kerr 1975). Sprague and Ha (1964) report a spread 3 segments above and below in cat lumbosacral cord, the projection being very much less outside the segment of entry and similar results were found in cat and monkey sacrococcygeal cord (Rethelyi et al 1979). In the rat, the spread is less than one segment at midthoracic levels but several segments at lumbosacral levels. (Chung 1979).

Lissauer's tract

Lissauer's tract is the bundle of fine fibres situated just lateral to the entering dorsal rootlets with a poorly defined border towards the dorsolateral funiculus. Originally, it was proposed to consist largely of dorsal root fibres for pain conduction (Ranson 1913, 1914) but later degeneration studies showed that at most only 25% of the fibres were afferents and then probably only the most medial ones (Szentagothai 1964, Sprague & Ha 1968, Kerr 1975). Furthermore, stimulation of Lissauer's tract produced a fine beam of activated C fibres down the tract, but no primary afferent volley on adjacent dorsal roots (Merrill et al 1978). The majority of Lissauer's tract fibres therefore appeared to be propriospinal. However, more recent studies using unilateral root sections and counts of Lissauer's tract fibres on the treated and untreated sides seriously challenge this concept (Chung & Coggeshall 1979, Chung et al 1979). These studies show that more than two thirds of axons in the rat Lissauer's tract at thoracic, and lumbosacral levels are primary afferents (Chung et al 1979). The majority are unmyelinated. In the cat, the value is nearer half (Chung & Coggeshall 1979). There is a tendency for more primary afferents to be in the medial Lissauer's tract.

Somatotopy

The classical story of dorsal root termination is that as root fibres ascend the cord they move laterally and as they descend they move medially (Imai & Kusama 1969, Lamotte 1977). Superimposed on this is a true somatotopic map whereby the ventral parts of the body or distal parts of limbs terminate medially in the dorsal horn and dorsal or proximal parts laterally (Szentagothai & Kiss 1949, Grant et al 1981, Koerber & Brown 1980, Mesulam & Brushart 1979). Careful studies by P B Brown et al show that the latter pattern really determines the former. Thus L3–L5 have no medial or lateral shift in their rostral projections and nor do S1 and S2 in their caudal projections. This is probably the general pattern in areas away from the enlarged limb representations. Lateral shifts occur when projections of roots with relatively proximal dermatomes are displaced laterally because of the enlarged medial representation of distal skin in some segments; for the L5 root afferents this is a lateral displacement as they course caudally; for S1 afferents this is a lateral displacement as they course rostrally (Koerber & Brown 1980, Brown et al 1981, Brown & Culberson 1981).

The degree of orderliness of projections of afferents to dorsal horn is a subject of some controversy. Neurones in the dorsal horn of the spinal cord are arranged such that their receptive fields form a map of the body surface (Brown & Fuchs 1979) and this must be largely due to the somatotopically organized primary afferent input (Koerber & Brown 1980, Ygge & Grant 1983). The question is whether this second order map arises entirely out of the fields of terminations of primary afferent fibres. Wall and colleagues (Merrill & Wall 1972, Wall and Werman 1976, Mendell et al 1978) have found that there are some 'inappropriate' projections of afferents to the dorsal horn. Cells have been found in L7 of the cat which respond to electrical stimulation of the L4 root whereas natural stimulation of the L4 dermatome has no effect (Merrill & Wall 1972) and filaments in L2 roots terminate in S1 segments (Wall & Werman, 1976). In some cases these responses appear monosynaptic. Intracellular recordings have revealed EPSPs and IPSPs produced by the distant inputs (Mendell et al 1978). Removal of the main afferent input to a cell by denervation may increase the effectiveness of these distant inputs (Basbaum & Wall 1976, Devor & Wall 1981). The possible existence, then, of these 'inappropriate' connections has very important implications for CNS responses to injury in the periphery.

Evidence against ineffective synapses is provided by A G Brown & Noble, who have recorded intracellularly from pairs of single hair-follicle afferent fibres and single second-order spinocervical tract cells. Only when the cell's field contained the hair afferent's field did they see any synaptic contacts between the two elements, i.e. there was no evidence of non-functioning connections in this particular model system (see Brown 1981b). Nevertheless loading peripheral nerves with HRP does show the occasional inappropriate projection (Brown et al 1981).

The somatotopy of C fibre afferents may differ somewhat from the whole dorsal root. Depletion of FRAP from rodent cord following peripheral nerve sections revealed a normal mediolateral somatotopy, but there was no distribution of afferents caudal to the site of entry (Devor & Claman 1980).

Terminations of collaterals from large myelinated (A beta) fibres

Collaterals from large myelinated afferents were first described by Ramon y Cajal (1909). They originate from the lateral dorsal white matter and either penetrate through the medial part of substantia gelatinosa or curve around the

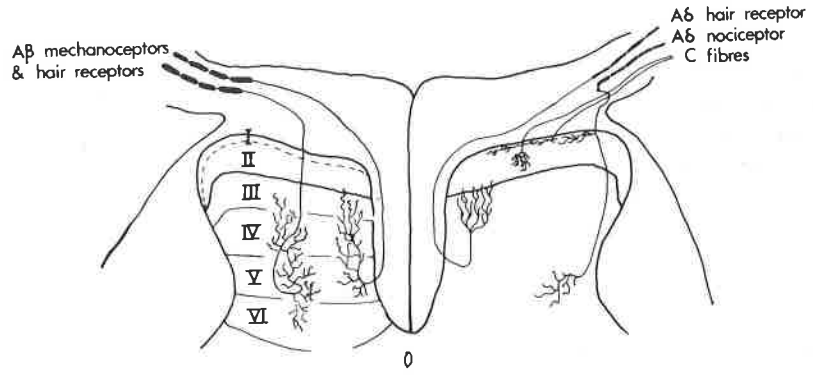

Fig. 13 A schematic diagram of the different types of cutaneous afferent terminations in the dorsal horn of the spinal cord. On the left side Rexed's lamination of the dorsal horn is shown along with terminal arbors of large myelinated afferent fibres. The terminations of the medial afferent is a typical 'flame-shaped' arbor. On the right are the terminal arbors of small myelinated and unmyelinated afferents. Although not shown here, lamina II is often divided into inner (IIi) and outer (IIo) zones.

medial side of the dorsal horn and enter ventrally (Fig. 13). According to Cajal, on reaching lamina IV they turn back and enter laminae III and II from below. In lamina III they break up into flame-shaped arborisations that in transverse sections appear to separate the neuropil into lobuli, cutting radially through the superficial dorsal horn (Fig. 13). This was confirmed in later Golgi studies by Szentagothai (1964), Sprague & Ha (1964) and Scheibel & Scheibel (1968). More recently, the superficial level to which these flame-shaped arbors reach has become a subject of some controversy. Degeneration studies have shown large fibres terminating no more superficially than lamina III (Lamotte 1977, Kerr 1975, Ralston & Daly Ralston 1979). HRP labelling of dorsal roots methods have also shown this (Light & Perl 1979). However, Proshanky & Egger (1977) on labelling cat lumbosacral roots with HRP, observed the classical 'reversing' collaterals from large diameter fibres (2–3 μm) terminating mainly in lamina III but also definitely in inner lamina II (IIi). The many elegant studies of A G Brown and his colleagues on physiologically-identified single HRP-filled A fibres reveal that they virtually never terminate above lamina III in the cat (Brown 1981a) and therefore it is suspected that the early Golgi studies reflected a more superficial termination in young animals that is not present in the adult. The Golgi studies of Beal (1979) in the adult monkey cord dispute this. This author reports flame-shaped arborisations from large parent fibres terminating in laminae III and IIi although not so abundant as has been previously claimed.

Whatever the superficial level of termination of large A fibres, the large part of their arborisations are in lamina III, IV and V (Fig. 13). Golgi studies have shown that these arbors are fairly restricted in the mediolateral plane, being about 20–100 μm wide, but they form narrow, sagittally-oriented sheets (or discs) of neuropil, about 200 μm long (Scheibel & Scheibel 1968, Beal 1979).

The existence of these longitudinal sheets along the rostrocaudal axis of the cord has been confirmed in single afferent HRP studies of Brown and his colleagues Snow, Rose and Fyffe (see Brown 1981a, b for details). A major contribution made by these authors has been to show that different types of cutaneous mechanoreceptors have different types of central terminations. Fig. 14 summarises the organisation of main types of cutaneous afferent fibres conducting at greater than 30 m/sec^{-1}.

Electrophysiological studies have also shown large A fibre afferent terminals predominantly in laminae III to V. Cells in this area respond with short latency and time locked responses to light mechanical stimulation or hair stimulation (Wall 1967, Brown et al 1973, Fitzgerald & Merrill 1979). The N wave produced by stimulation of A beta fibres is maximal in laminae IV and V (Beall et at 1977) and antidromic activation of large afferents from their terminals is most effective from stimulating this region of the dorsal horn (Wall 1958).

Many large myelinated afferents terminate also in the dorsal column nuclei, which is outside the scope of this chapter. For a review of these terminations see Willis & Coggeshall 1978.

Terminations of collaterals from small myelinated (Aδ) fibres

Beall et al (1977), recording potentials or N waves produced by peripheral nerve stimulation in the monkey lumbosacral cord, described an N_3 wave resulting from the incoming Aδ afferent volley. It had two negative foci, one in the most superficial part of the dorsal horn and one in laminae IV to VI. These proposed termination sites have been supported by anatomical studies. In Golgi stains of cat cord Hamano et al (1978) describe small fibres coming from the dorsal roots. Some, but not all, bifurcate and they run rostrocaudally for 250–950 μm. Fine collaterals were sent out and terminated at two sites: superficially in laminae I and a little in III, and in deeper layers IV–VI.

In the coccygeal and sacral cord of cats, Light and Perl (1979) have physiologically identified single Aδ afferents and filled them with HRP. High threshold nociceptors (HTMs) were found sometimes, but not always, to bifurcate, but all travelled rostrally just medial to Lissauer's tract. Collaterals were given off at two sites as described previously: to lamina I via a tortuous path and ending in terminal arbors that sometimes also penetrated outer lamina II (IIo) and also deeper in lamina V (Fig. 13). Some bran-

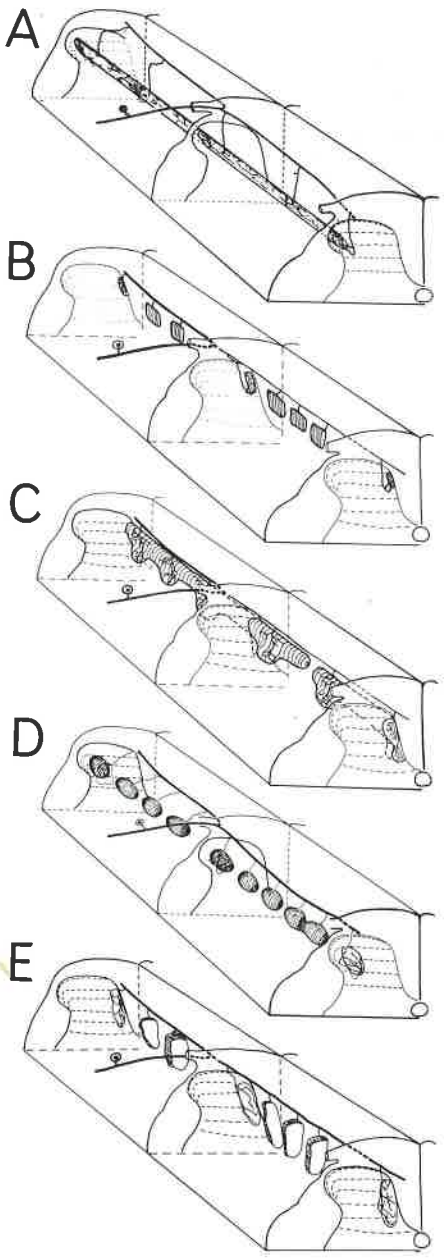

Fig. 14 Summary diagrams of the three-dimensional organisation of the collaterals from single identified sensitive mechanoreceptive afferent fibres in the cat's lumbosacral cord **A.** Hair follice afferent **B.** Rapidly adapting (Krause) mechanoreceptor axon from glabrous skin **C.** Pacinian corpuscle afferent **D.** Slowly adapting Type 1 afferent **E.** Slowly adapting Type II afferent (from Brown 1981b)

ches were also seen on the contralateral side of the cord. Delta hair afferents, however, ran in the dorsal columns, and sent collaterals through lamina I and IIo to arborise and terminate in IIi and laminae III–V.

Aδ fibres travel extensively in Lissauer's tract (about 700 μm) (Gobel et al 1981) and their terminals form a transverse plexus of fibres that run across the surface of the dorsal horn (Beal & Bicknell 1981). In deeper parts of lamina I they are longitudinally oriented and have collaterals in lamina IIo. The afferent collaterals run parallel with the dendrites of lamina I cells, and give off round to oval boutons 1.5–2.0 μm in diameter (Beal & Bicknell 1981).

These endings lie in complex glomeruli similar to those described for C fibres in the next section (Gobel et al 1981).

Terminations of collaterals from C fibres

C fibre collaterals penetrate the dorsal grey matter from the medial Lissauer's tract and appear to terminate exclusively in the superficial layers of the dorsal horn. This has been demonstrated repeatedly using many different methods: Golgi staining (Rethelyi 1977) degeneration methods (Lamotte 1977, Ralston & Daly Ralston 1979, Gobel 1981 and HRP labelling of dorsal roots in the cat (Proshansky & Egger 1977) or of exclusively lateral rootlets containing largely C fibres (see p. 000) (Light & Perl 1979). Substance P known to be localised in small afferent terminals is concentrated in laminae I and II of the dorsal horn, as well as Lissauer's tract and the dorsolateral funiculus (Hökfelt 1975). These areas are all depleted following dorsal rhizotomy (Barber et al 1979). Somatostatin is also concentrated in this area, although there is more in lamina II and I (Hökfelt 1975). The FRAP distribution, illustrated in Figure 15, overlaps with that of SOM (Nagy & Hunt 1982) and also disappears on root section (Knyihar et al 1974). Electrophysiological data also supports the superficial termination of C fibres. They can only be antidromically activated from terminal stimulation in SG (Fitzgerald & Woolf 1981), and there are a few cells in lamina I & II that respond exclusively to C fibre input (Kumazawa & Perl 1978, Fitzgerald 1981).

Thin afferent fibres appear to terminate in two ways: a capping tangential plexus of fibres over the marginal layer, oriented longitudinally (Szentagothai 1964, Kerr 1975) and bushy terminal arbors in substantia gelatinosa forming thin saggitally oriented slabs (Rethelyi 1977). This illustrated in Fig. 13. The mediolateral dimension of a C fibre arbor is only 17 μm, compared to over 100 μm for an A fibre D hair (Rethelyi 1981). Nagy et al (1981) observed numerous SP-containing rostrocaudally oriented fibres in both lamina I and II and a heavy web of fibres capping lamina I. Interestingly these authors also observed, in sagittal sections, dorsoventrally-oriented bundles of SP-containing fibres, emerging from lamina II, and descending into laminae III and IV at regular intervals of 100–200 μm. All these fibres disappeared following neonatal capsaicin treatment (Nagy 1981).

The terminal arbors of C fibres cluster together to make foci, curving and recurving in their side branches (Rethelyi 1977) which Rethelyi suggested might allow synchronous discharge of all the presynaptic terminals in a given cluster. In fact SG cells do respond to C fibre stimulation with remarkable, time-locked regularity (Fitzgerald & Wall 1980).

The exact area termination of C fibres within the superficial layers of the dorsal horn is still a subject of some controversy. Some degeneration studies show the C fibres only in lamina II, and possible III, with later degeneration of larger A fibres in lamina I and IIo (Lamotte 1977, Ralston & Daly Ralston 1979). Using degeneration studies in the

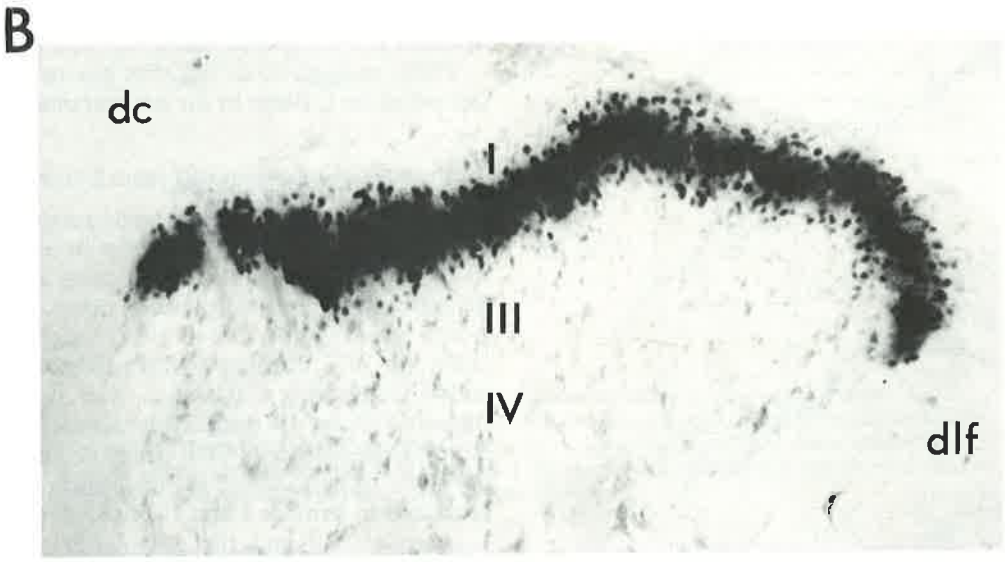

Fig. 15 A transverse section of rat spinal cord stained for FRAP. Note how the staining is restricted to substantia gelatinosa (lamina II) of the dorsal horn. Note also the large bundles of myelinated fibres passing through medial lamina II, making 'gaps' in the band of FRAP. dc = dorsal columns; dlf = dorsolateral funiculus. I, III and IV represent the laminae of the dorsal horn (courtesy of A. Ainsworth).

trigeminal system (see p. 000) and the spinal cord however Gobel (1979) describes small C fibre terminals terminating in lamina I and larger Aδ fibres in lamina II. This was confirmed using HRP to label cervical roots in cats. In lamina I, terminals came from very small <0.3 μm parent fibres, whereas from layers IIo–IIi, the terminals came from parent fibres 1.0–1.5 μm (Aδ) in size (Gobel & Falls 1979).

The controversy continues, for in a more recent study Gobel et al (1981) report the presence of both C *and* Aδ fibre terminations in lamina I. Beal et al (1981) do not find C fibres and report that the transverse plexus of fibres on the top of lamina I and the longitudinally oriented afferent collaterals within lamina I originate from finely myelinated Aδ fibres (see p. 000), thus supporting earlier degeneration HRP studies.

The synaptic endings in laminae I and II have long shaped scalloped contours, dark axoplasm and synapse on dendritic spines (Gobel 1979). Terminals are sometimes postsynaptic to axoaxonal synapses (Ralston & Daly Ralson 1979). A typical feature of the neuropil of substantia gelatinosa is the presence of glomeruli (Rethelyi & Szentagothai 1973, Kerr 1975, Coimbra et al 1974). This consists of a central afferent terminal surrounded by processes to which it is pre- and postsynaptic. Up to nine processes have been described in a glomerulus (Gobel et al 1981). However, because of their peculiar morphology, some authors claim that glomeruli have been over-emphasized and represent only 5% of synaptic profiles in the dorsal horn (Duncan & Morales 1978, Ralston & Daly Ralston 1979).

Termination of fine muscle afferents in the spinal cord

Apart from large proprioceptive afferents (not dealt with here) there are also small-diameter afferents from muscles as well as from skin terminating in the dorsal horn. Cells in the deeper laminae have been reported which respond to this kind of muscle input (Pomeranz et al 1968). Of course many of these terminations will have been included in the studies discussed in previous sections but a few selective studies have been performed.

Mense et al (1980) recorded from high-threshold myelinated mechanoreceptors from tail muscles, fascia and joint capsules and filled them with HRP. These fibres sent collaterals to lateral lamina I and longer branches to the region dorsal to the central canal. They also often sent projections to lamina I and V of the contralateral dorsal horn. No terminals were found in laminae III and IV. Mesulam & Brushart (1979) injected individual muscle groups with HRP and looked at the label transganglionically in the rat dorsal horn. HRP-filled terminals were concentrated in laminae I and II. In the rat neck region a comparison has been made, also using HRP, between the central terminations of a purely muscle nerve (the sternomastoid nerve) and a purely cutaneous one (cutaneous R. dorsalis). The muscle nerve had strong terminations in IV–VIII (presumably large afferents) and some discrete labelling in I-III. Skin afferents, however, had strong terminations in I and III with less in IV and V (Zenker et al 1980). HRP nerve labelling in the cat hindlimb also shows that the superficial dorsal horn, while receiving dense cutaneous input, receives virtually no muscle input (Swett 1983).

Termination of visceral afferents in the spinal cord

Studies involving terminations of dorsal root afferents naturally include visceral afferents. The total number of visceral fibres in the roots is small and their entry at dorsal root levels is very widespread, although they do, of course, have powerful reflexogenic effects. 50% of the splanchnic nerve consists of afferents and 80% of these are unmyelinated. A generous estimate would be that 10% of all dorsal root afferents are visceral.

The dual innervation of much of the viscera is apparent. The afferent information carried by the sympathetic nerves enters from T1 to L2 of the spinal cord, via the white rami and sympathetic chain. Afferents from the large intestine, bladder and genitalia enter the spinal cord via the parasympathetic pelvic nerves at S2–S4. The vagus carries a great deal of the remaining afferent information to the brainstem and this is discussed on p. 000. Compared to cutaneous input, remarkably little is known about visceral afferent terminations, although some interesting work is now beginning to appear.

Input from the splanchnic nerve spreads over at least eight segments (Downman 1963). Large myelinated fibres appear to travel up the dorsal columns to the DCN *without* sending collaterals to the spinal cord. This has not been categorically proven but certainly many investigators recording in the thoracic and upper lumbar cord have consistently reported A and C splanchnic nerve input to dorsal horn cells but no Aß responses (Pomeranz et al 1968, Foreman et al 1981, Hancock et al 1975, Fields et al 1970). The same is true of the inferior cardiac nerve input to upper thoracic cord cells (Foreman 1977) even though a clear but small Aß component could be recorded on the incoming volley of the lower thoracic sympathetic chain. Intracellular records also show no EPSP following Aß splanchnic nerve stimulation (Hancock et al 1973). The large Aß fibres, many from Pacinian corpuscles, travel dorsomedially in the dorsal columns and terminate in the nucleus group of the ventral portion of the DCN (Rigamonti et al 1978). However, it has recently been shown that thinner sensory fibres, with conduction velocities of 13–43 m/s also travel directly from the white rami, through the dorsal roots, up the dorsal columns to terminate in the medulla (Dembowsky et al 1982). Their origin is as yet unknown.

The actual site of termination of sympathetic A and C fibres in the cord is not certain. Using the N wave as a signal of the site of afferent termination following sympathetic chain stimulation, Selzer & Spencer (1969) found that lamina V was the major site in the L1–L2 segments of the cat (Selzer & Spencer 1969). Certainly many cells in laminae IV–VIII of the thoracic and upper lumbar cord have convergent input from visceral nerve and somatic nerves (Hancock et al 1975, Pomeranz et al 1968, Fields et al 1970, Hancock et al 1973, Foreman et al 1981).

Parasympathetic afferents enter the cord at sacral levels. Large myelinated afferents appear to enter the dorsal columns, send collaterals into the lumbar cord and then travel up to the medulla (Kuru 1965).

The spinal termination of visceral afferents in the pelvic nerve has recently been carefully examined in the cat by Morgan et al (1981) using the transganglionic HRP tracing technique. The input was largely in S_2 with less in S_1 and S_3 and still less in L7 to L4 and contralateral S1 and S3. Labelling was in tracts up to the medulla in dorsal columns and the medial dorsolateral funiculus. In the cord, all fibres appeared to be Aδ and C fibres. By far the densest staining, however, was in Lissauer's tract. Two bands of collaterals appeared from Lissauer's tract, one lateral pathway [LP] and one medial pathway [MP]. These are illustrated in Figure 16, showing that they form a horseshoe shape

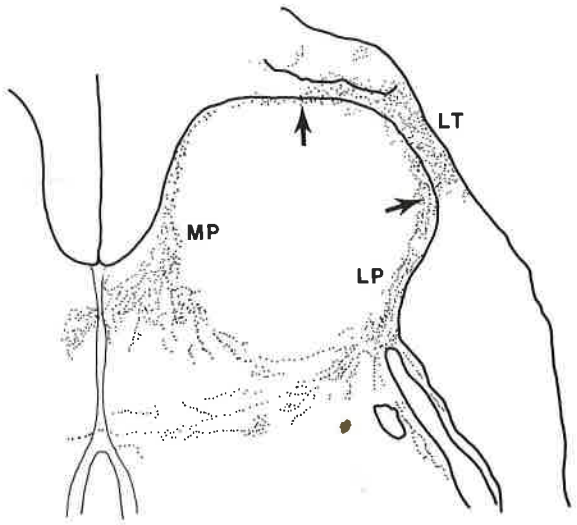

Fig. 16 Patterns of pelvic nerve afferent collaterals from Lissauer's tract in the S2 segment of cat spinal cord. The pelvic nerve was labelled with HRP; ventral roots were cut to eliminate efferent labelling. The lateral pathway (LP) terminated at the junction of laminae I and V, or in lamina V or the lower third of the dorsal grey commissure. The medial pathway (MP) terminated in the ipsi- and contralateral upper dorsal grey commissure or in medial lamina V. (from Morgan et al 1981.)

around the dorsal grey matter. Collaterals from LP are sent off into lamina I and into laminae V and VI and VII in discrete dorsoventrally-oriented bundles about 200 μm apart in the saggital plane. Collaterals from MP also terminate in the gelatinous area around the central canal (lamina X) and again with a periodic distribution of collaterals. Labelled areas were often interconnected by rostrocaudal axons (de Groat et al 1981). LP and MP have also been seen at the L3 spinal level following labelling of the sympathetic hypogastric nerve in the cat (Morgan et al personal communication) and in the rat (Neuhuber 1982) where there is also some termination in lamina X ventral to the central canal. A similar pattern of termination has been reported in cat thoracic cord from the splanchnic nerve (Connell & Cervero 1983).

Interestingly, Knyihar & Csillik (1977) have described a distribution of FRAP-containing terminals in the rat outside the classical layer in substantia gelatinosa in the lumbar enlargement (see p. 000). In L5–S2 and mid-T to L1 segments, Lissauer's tract stains very heavily with FRAP and in T6–L1 and L5–S2 'two embracing arms' are described as reaching forward over the dorsal horn. These areas of staining disappear following root section and it seems likely that they are from visceral afferent terminals (Knyihar and Csillik 1977).

Ventral root afferents

Both myelinated and unmyelinated afferents are found in the ventral roots. Myelinated afferents are rare, making up two to five fibres in the cat L7 ventral root (Loeb 1976, Coggeshall & Ito 1977). Those that are present respond to limb motion, joint movement, hair movement and natural stimulation of the viscera. Unmyelinated afferents in the ventral roots are more common. 30% of ventral root fibres

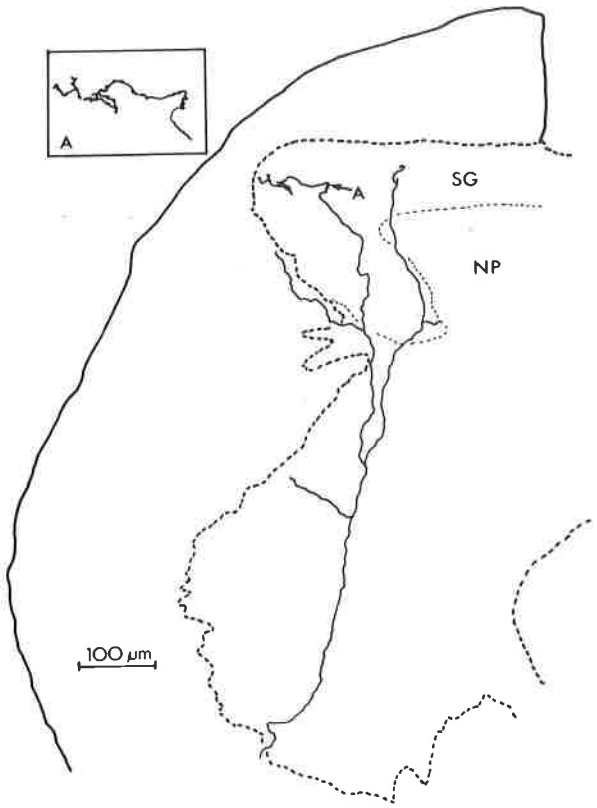

Fig. 17 Camera lucida drawing of a small-diameter afferent labelled by HRP on to the ventral roots. The fibre has *en passant* and terminal enlargements in substantia gelatinosa. The reconstruction was from serial transverse sections of coccygeal cord. SG = substantia gelatinosa; NP = nucleus proprius, or laminae III–VI. The parent axon was 0.9 μm in diameter. (From Light & Metz 1978.)

are C fibres and most survive ventral root rhizotomy (Coggeshall et al 1974). At T11–T12 and S3–Ca1 the proportion is 15%, the rest being preganglionic efferents (Applebaum et al 1976). The information carried by C afferents in L6 and S1 ventral roots of the cat is largely somatic (70%) and also visceral (30%). The somatic fibres and some of the visceral fibres respond to painful stimulation (Coggeshall & Ito 1971). The question really is whether these fibres enter the cord and make functional terminations. Ventral rhizotomy results in degeneration in the dorsal horn, but this could be due to motor axon collaterals. Maynard et al (1977) injected the cord with HRP and cut dorsal roots and showed that many small cells in the DRG were labelled in the cat. Light & Metz (1973) crushed HRP on to proximal ventral roots in coccygeal and sacral cord and found several apparent afferents, traceable from the ventral roots up to SG and lamina I. They projected longitudinally for about 300 μm, with many *en passant* terminae enlargements in laminae I and II. Their diameter was 0.5–1.2 μm and they were therefore Aδ and C fibres. Such a fibre is illustrated in Figure 17. Occasionally they went into the contralateral dorsal horn. These authors also observed some larger afferents of 2–4 μm diameter which gave fine terminal collaterals to lamina IV. The functional role of these ventral root afferents is still not clear and the subject requires more investigation (see Coggeshall 1980 for further discussion).

COURSE AND TERMINATION OF TRIGEMINAL AFFERENTS

The fine structure of the Gasserian ganglion is similar to that of dorsal root ganglia (see Darian-Smith 1973).

Apart from muscle spindle projections to the mesencephalic nucleus, primary afferent fibres project through the spinal trigeminal tract and terminate in the trigeminal complex or upper cervical cord. The tract is somatotopically organised with fibres of the ophthalmic maxillary and mandibular divisions lying successively more dorsomedial.

Distribution of afferents to trigeminal nuclei

Injection of tritiated amino acids into the Gasserian ganglion reveals a widespread distribution, the most heavy labelling being in the main sensory nucleus and nucleus caudalis (sometimes called the medullary dorsal horn because of its structural and functional similarities with the spinal dorsal horn). HRP labelling, however, of five peripheral branches of the trigeminal nerve reveals that all the nuclei receive substantial afferent input, although the distribution varies between different facial areas (Marfurt 1981). Contralateral projections were only seen at C1 and C2 and not in the trigeminal complex (Marfurt 1981, Arvidsson & Gobel 1981). All the face and oral cavity apparently has *some* representation at each level of the complex but there appear to be relative differences in intensity of projection. Figure 18 illustrates this. Input from the oral cavity, for instance, appears to predominate in n. oralis and interpolaris (Marfurt 1981).

Somatotopy

There is general agreement that in the trigeminal complex the ophthalmic division is represented ventrally, the mandibular division dorsally and the maxillary division is interposed. Despite the wide distribution of each root throughout the length of a given nucleus, there is a true somatotopic pattern of termination in the nuclei analogous to that in the spinal cord. This is brought about by the so-called 'onion-skin' organisation and is illustrated in Figure 19, where it is superimposed on the map of peripheral distribution of the three nerve divisions. Projections of primary afferents are organised: 1. in a radial mediolateral pattern such that oral structures are represented more medially; and 2. in a rostrocaudal progression of concentric bands such that oral and perioral (anterior) fields are rostral and posterior, periauricular fields are more caudal (Wall & Taub 1962, Darian-Smith 1973, Arvidsson & Grant 1979, Panneton & Burton 1981).

This map seems particularly clear in substantia gelatinosa of the medullary dorsal horn, as has been shown by FRAP depletion (Rustioni et al 1971) and transganglionic HRP transport into terminals in SG (Panneton & Burton 1981).

Course and termination of large A fibres

Myelinated fibres mostly divide on entering the brain stem, the rostral branch ascending to terminate with the main sensory nucleus and the caudal branch descending a vari-

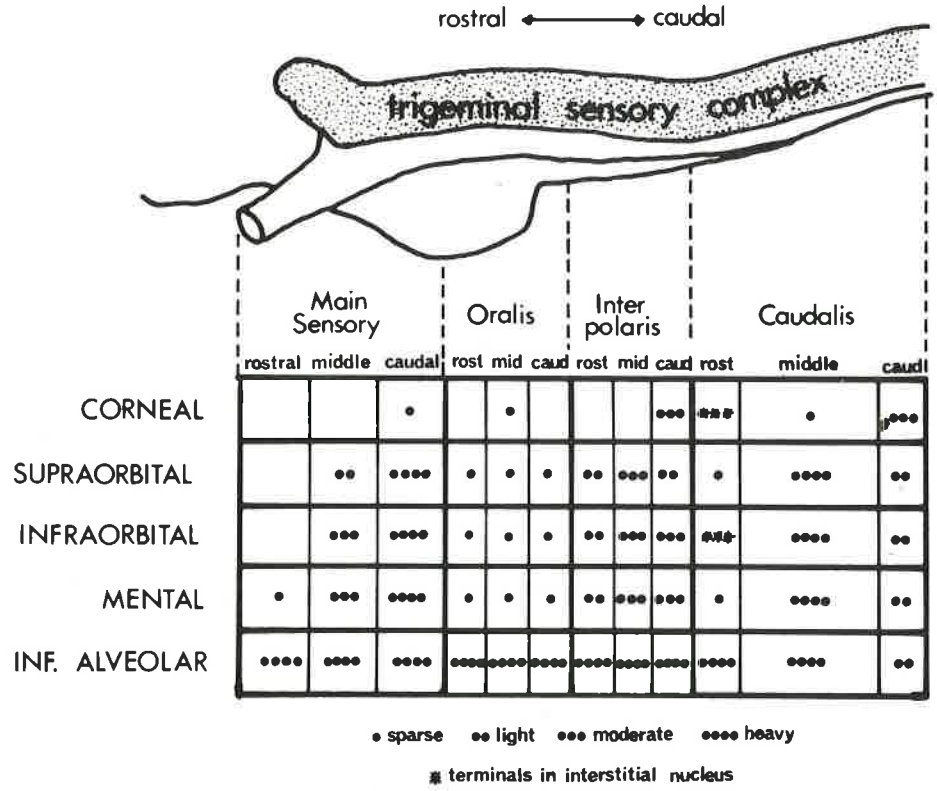

Fig. 18 Summary diagram illustrating the central projections of the corneal, supra-orbital, inferior alveolar and mental nerves to the ipsilateral trigeminal brainstem complex. Transganglionic HRP labelling was used. (From Marfurt 1981.)

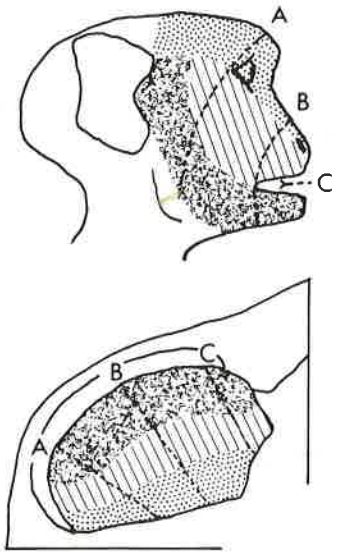

Fig. 19 Diagram of the somatotopic projection of the ipsilateral face and oral structures on to a transverse plane through the trigeminal nuclear complex. The skin fields of the separate trigeminal roots are differentiated by shading and project dorsoventrally. In the nucleus, the ophthalmic division projects most dorsally. The radial projection of primary afferents is also shown resulting in an ordered mediolateral pattern with the oral structures (**C**) being represented most medially — the 'onion-skin' representation. (From Darian Smith 1973.)

able distance along the tract. In Golgi preparations these descending fibres can be seen to give off collateral branches in adjacent nuclei and to continue as smaller branches (Cajal 1909). Accordingly, conduction of impulses along these fibres slows progressively (Wall & Taub 1962). By the time they reach nucleus caudalis, 75% of them are less than 2 μm in diameter (Kerr 1966). The collaterals penetrate the grey matter in a spatially-ordered radial pattern, contrasting with the terminal projection in the dorsal horn of the spinal cord where A fibres enter from the medial side. In the trigeminal complex they terminate in sharply defined arborisations extending deeply into the nucleus, overlapping neighbouring projections only very slightly (Cajal 1909, Hayashi 1980). The larger fibres terminate mainly deep in the medullary dorsal horn, laminae III, IV and V (sometimes called the adjacent reticular formation) (Arvidsson & Gobel 1981). From antidromic stimulation of the spinal tract it has been shown that more than 80% of A fibres project to the rostral part of nucleus caudalis whereas only 10% project as far down as C2 segments (Darian Smith et al 1965). Under the electron microscope the large terminals of these A fibres have round, bulbous ends and synapse mainly on dendritic shafts. Their axoplasm is pale (Gobel 1979). These terminals and those in the main sensory nucleus are often seen to terminate in 'glomeruli'. Dilatations along the course of primary collaterals constitute the central boutons of such glomeruli in which synaptic contact is made with small dendritic branches as well as with other axons (Gobel & Hockfield 1977, Gobel 1979).

Course and termination of C fibres

Approximately 50% of trigeminal root afferents are C fibres, fewer than in dorsal roots. They enter the spinal trigeminal tract without bifurcating and descend to nucleus caudalis. They apparently terminate exclusively in this nucleus and the upper cervical dorsal horn, although lamina 1 of the medullary dorsal horn does extend rostrally parallel to nucleus interpolaris and they may terminate there also (Panneton & Burton 1981). Certainly substance-P-containing trigeminal afferents are found only in this nucleus (Cuello et al 1978) although the degeneration of C fibre terminals observed following neonatal capsaicin administration was seen to spread beyond caudalis into a small area of nucleus oralis, at the level of the facial nucleus (Jancso & Kiraly 1980).

C fibres penetrate radially into the medullary grey matter along with large A fibres. Their terminal plexuses seem in many ways similar to those in the spinal dorsal horn and they largely terminate in the superficial layers of the medullary dorsal horn. Substance-P-containing afferents are concentrated in SG, although a few are found in deeper layers (Cuello et al 1978), and FRAP-containing terminals are also only found in SG (Rustioni et al 1977). From a combination of Golgi and degeneration studies Gobel has demonstrated that the smallest terminals belonging to C fibres terminate most superficially in lamina I. Larger terminals belonging to A fibres terminate in layers IIo and IIi, those in IIo being smaller than IIi (Gobel & Hockfield 1977). The largest terminals belonging to Aß fibres terminate deeper. Various lines of evidence supports this. Following neonatal capsaicin, the most intensive degeneration was seen in lamina I, with less in lamina II (Jancso & Kiraly 1980). Furthermore, transganglionic labelling from the cornea, which is known only to contain fine diameter afferents, shows terminations only in laminae I and IIo, with none deeper (Panneton & Burton 1980). In the same study it was shown that the frontal nerve innervating periocular hairy skin terminated only in laminae IIi and III. Despite the fact that the cornea only has fine afferents, terminations were found in the main sensory nucleus, and n. oralis and interpolaris, as well as in nucleus caudalis (Panneton & Burton 1981, Marfurt 1981).

Small afferent terminals in the medullary substantia gelatinosa are ultrastructurally very similar to those in the spinal dorsal horn (Gobel 1979). However, it appears that the glomerulus type of synaptic endings described on p. 000 are more common in the trigeminal system than the spinal cord.

Tooth pulp

Particular attention has been paid to the central representation of the tooth pulp because of the claim that only pain is elicited from tooth pulp stimulation. The input seems to be largely from Aδ fibres, although there some may be C fibres (see Chapter 1.1).

Results from tooth pulp extirpations and resultant degeneration suggested a fairly restricted termination of afferents. Degeneration is found predominantly ipsilaterally in ventral nucleus interpolaris, and nucleus caudalis (Westrum & Canfield 1977, Gobel & Black 1977). Recent reports, using transganglionic HRP labelling show that the input is ipsilateral only in the brainstem and is very widespread, including the main sensory nucleus, pars oralis and interpolaris and pars caudalis down to C2 spinal cord (Westrum et al 1980, Arvidsson & Gobel 1981). Contralateral terminals are seen in the cervical cord. Arvidsson & Grant (1981) describe two ipsilateral areas of termination. One is a long column extending from caudal main sensory nucleus, right through to lamina V of the medullary and C1 dorsal horns. The second is in laminae I and IIo of the medial dorsal horn. Therefore it appears that only the rostral main sensory nucleus is free of tooth pulp afferents.

COURSE AND TERMINATION OF SENSORY AFFERENTS IN NERVES VII, IX and X

General visceral afferent fibres occur in the vagus, glossopharyngeal and facial nerves. In fact, the (vagus) is made up of 80% afferents, the majority of which are C fibres. The extent to which these fibres contribute to conscious sensation and pain is not fully established. Classically, visceral sensation is attributed to the sympathetic nervous system and the most severe sensation evoked from the vagus is usually said to be nausea. Of course, many of the afferents of IX and X are involved in autonomic reflexes and a review of the extensive studies on these are beyond the scope of this chapter. A brief survey of the main aspects of the afferent terminations is given below.

A number of IX, X and VII afferents are thought to course through the spinal tract of V to terminate in areas of the trigeminal complex in the SG of n. caudalis and at or below C1. Mapping of FRAP containing terminals in SG shows fibres from V, VII, IX and X at the C2 level of the spinal cord, and mainly spreading from C1 to C4 (Rustioni et al 1972). The distribution of IX and X were found to be highly variable, whereas that of VII was more predictable (Rustioni et al 1972). Labelling of the periocular branches of VII with HRP, however, produced no evidence of projections to the trigeminal complex (Panneton & Burton 1981) and this topic deserves more study.

The majority of these afferents, however, have been shown from nerve degeneration and nerve labelling studies to terminate in the nucleus of the solitary tract (NST). There is some somatotopy in these terminations in that facial nerve afferents terminate largely in rostral NST, IX afferents in its middle and X afferents in its caudal part. The extent of crossing is reasonably large although no contralateral input is recorded electrophysiologically. Many of the neurons in NST have direct, short latency input from small myelinated afferents from for instance larynx and pharynx (see Dubner et al 1978 for more details).

10% of axons in the vagus have substance P in them (Gamse et al 1979) and much SP is seen in the tractus solitarius some of which is lost following neonatal destruction of sensory C fibres with capsaicin (Cuello et al 1981) or by removal of IX and X nerves (Gillis et al 1980). A dense area of FRAP in the rostral medulla close to the obex in the

'alar cinerea' is lost on vagotomy (Knyihar & Csillik 1977). Following neonatal capsaicin, degeneration of small afferent terminals are seen in the area postrema, heavily in the n. commissuralis (the caudal continuation of the nucleus of the solitary tract) and very heavy in the medial and dorsal parts area subpostrema. Rostral to the level of entry of the vagus, the NST degeneration is less intense and above the dorsal vagal nucleus there is none (Jancso & Kiraly 1980). The 'area subpostrema' is the gelatinous portion of NST, said to be analogous to substantia gelatinosa of the spinal cord. Removal of the nodose ganglion results in degeneration along the whole length of area subpostrema as well as the NST (Gwyn & Leslie 1979).

Recent use of transganglionic HRP transport has allowed careful study of the terminations of the vagus complex. It shows again terminations in most subnuclei of NST bilaterally and in area postrema and the dorsal motor nucleus (Kalia and Mesulam 1980a).

One of the sections obtained is illustrated in Figure 20. Injections of HRP into individual visceral organs larynx, extrathoracic trachea, intrathoracic trachea, bronchus, lung, heart of stomach reveal a remarkable absence of topography for different organs. Similarly no pattern was seen in the nodose ganglion. The nucleus tractus solitarius was the main receiving area with a few fibres from the larynx terminating in the ipsilateral spinal tract of V and a few from the bronchus, lung and stomach in area postrema. Unpaired or midline viscera projected bilaterally, whereas unilateral or paired organs projected ipsilaterally with about a third of the density to the contralateral side (Kalia & Mesulam 1980b). Of course many of these organs have a sensory projection to the spinal cord.

In the last decade, our understanding of the pattern of primary afferent terminations in the CNS has increased enormously. The advent of labelling techniques, such as HRP transport, has led to great advances in our knowledge. It is hoped that over the next decade the controversies will be settled and the gaps in our knowledge filled, for until we have a complete understanding of the distribution of primary sensory input to the CNS, we cannot hope to understand the pathways involved in pain.

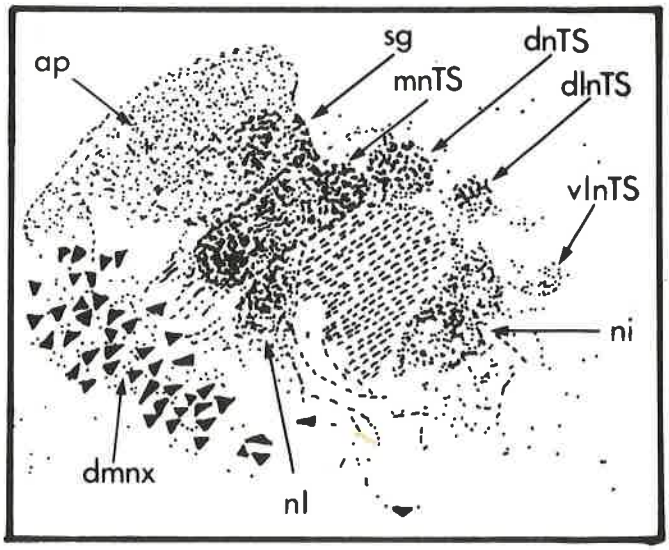

Fig. 20 A. Dark field photomicrograph of the dorsal medulla a the level of the obex, following HRP labelling of the nodose ganglion. The HRP label is in the area postrema (ap), nucleus solitary tract (nTs), the solitary tract (TS) and motorneurones in the dorsal motor nucleus of X. (From Kalia & Mesulam 1980a.) **B.** Line drawing of micrograph in Figure 20A showing the distribution of the HRP reaction product. Interrupted lines and dots represent labelled fibres and nerve terminals. The greater the density of lines and dots, the greater the HRP labelling. The filled triangles represent motoneurone cell bodies, labelled anterogradely. The subnuclei of the nucleus of the solitary tract (nTs) are shown medial (m), dorsal (d), dorsolateral (dl), ventrolateral (vl), subnucleus gelatinosa (sg), n. interstitialis (nI), n. intermedius (n.i.) (Kalia Mesulam 1980a.)

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exclusive, suggest themselves. The first possibility is that DRG cells are actually more than nutritive depots and that their impulse activity has some hitherto unsuspected function. The second is that elevated DRG excitability is an undesireable, but unavoidable flaw in the design of sensory nerves. Consider an action potential propagating centrally along a sensory axon and approaching the T-junction in the DRG. Part of the inward Na^+ current expected to contribute to triggering subsequent nodes of Ranvier is necessarily shunted into the T-stem branch and attached soma, at most a few internodes away. Such shunting threatens conduction failure (Parnas & Segev 1979). One way to overcome this would be to counterbalance the shunt by providing for extra Na^+ (or Ca^{++}) permeability (channels) in the stem axon and/or DRG soma. Such extra channels, however, would automatically tend to create an impulse generating capability.

Given the pathophysiological significance of regions of elevated excitability in peripheral nerves, it would be highly desirable if one could demonstrate such regions histologically. Until specific affinity probes or antibodies to channel protein come into use, the only such histological method available is Quick & Waxman's (1977) ferric ion-ferrocyanide stain. This staining procedure has been shown to label selectively a number of membrane sites believed on biochemical, electrophysiological or biophysical grounds to be regions of high Na^+-channel density (Quick & Waxman 1977, Waxman & Quick 1978, Waxman & Foster 1980). Figure 25 shows two examples: the node of Ranvier (Fig. 25B and D) and the axon hillock region of a spinal motoneuron (Fig. 25A). Unfortunately, the basis of the stain's selectivity is not known and therefore caution must be applied in interpreting results from its use. This having been said, it is noteworthy that the initial segment of the DRG stem axon and a variable proportion of the adjacent soma surface react strongly with the Quick & Waxman procedure (Fig. 25C). This zone is likely the DRG impulse generator.

CROSSTALK AND SENSITISATION AS FACTORS IN HYPERALGESIA

A frequent consequence of nerve injury is pain evoked by weak and otherwise innocuous stimuli on the skin (hyperalgesia). Given the known specificity of primary afferent fibres, hyperalgesia implies either that there has been abnormal crosstalk between high- and low-threshold sensory channels in the peripheral or in the central nervous systems, or that the threshold of nociceptor endings has fallen (sensitisation). Although the mechanism(s) underlying clinical hyperalgesia cannot be stated with certainty, both crosstalk and sensitisation have been detected in experimental preparations following injury to peripheral nerves.

Crosstalk in the periphery

Two forms of fibre-fibre crosstalk in damaged nerve, chemical (sympathetic) coupling and 'crossed after-discharge', were described above. There is also a third form, high safety-factor ephaptic (electrical) crosstalk. In the mid-1940s Granit et al (1945) discovered that acute transection short-circuits the insulation between neighbouring axons in a nerve so that current from the cut end of one fibre can now excite others. This acute ephaptic coupling is unlikely to be of much functional significance, however, because it decays and vanishes within minutes. However, it has recently been discovered that, several weeks after injury, ephaptic crosstalk once again develops but now in a form that remains stable for very long periods of time (Seltzer & Devor 1979, Blumberg & Janig 1981). An example is illustrated in Figure 26. Here electrical stimulation of dorsal root fibres ending in a sciatic nerve neuroma evoked a time-locked impulse in a single axon contained in a fine ventral root filament (Fig. 26A). Stimulation of the ventral root filament, in turn, drove the coupled axon in the dorsal root (Fig. 26B). Such high safety-factor, bidirectional ephaptic crosstalk between closely-coupled axon pairs can occur within a nerve-end neuroma or between regenerating sprouts far distal to the site of injury (Seltzer & Devor 1979).

At about the same time that high safety-factor ephaptic crosstalk was found in nerve-end neuromas, Rasminsky (1978, 1980) discovered independently that it can also occur between demyelinated but otherwise in-continuity axons.

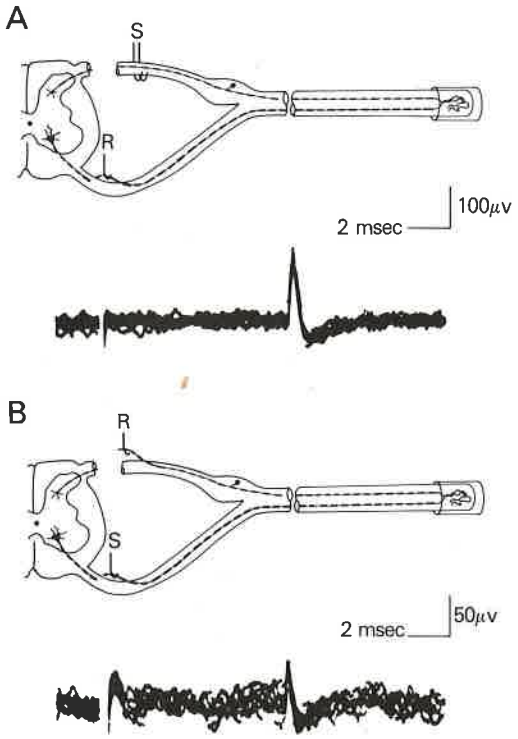

Fig. 26 Bidirectional ephaptic coupling between a pair of fibres ending in an experimental neuroma **A.** First a fibre was found in the L5 ventral root that responded (R) at fixed latency to electrical stimulation (S) of the ipsilateral dorsal roots **B.** Then stimuli were applied to the ventral root filament containing the responding fibre and the dorsal roots were searched for responding fibres. Eventually a filament in the L4 dorsal root was found that contained such a fibre. Note that the response latency for conduction in the two directions is identical. (From Seltzer & Devor 1979.)

Since ephaptic crosstalk can occur between large- and small-diameter axons, this mechanism could bring about the activation of nociceptors following stimulation of low-threshold sensory afferents. Up until now electron microscopic observations have failed to reveal specialised structures such as tight or gap junction at sites of nerve injury. However, there have been several reports of close membrane apposition between neighbouring fibres without an intervening Schwann cell process. This is currently considered to be the most likely morphological substrate of ephaptic crosstalk (Rasminsky 1980, Blumberg & Janig 1981, Devor & Bernstein 1982, Bernstein & Pagnanelli 1982).

Crosstalk among afferent terminals in the spinal cord

Impulses that propagate into the spinal terminals of many classes of afferent fibres partially depolarise the terminals of their neighbours (Lloyd 1952). A small minority of afferent terminals receive such intense depolarisation from their neighbours that they reach threshold and generate propagated action potentials (dorsal root reflex). Calvin et al (1977) have suggested that augmentation of the trigeminal dorsal root reflex could contribute to pain elicited by stimulation of low-threshold trigeminal afferents in tic doloureux. However, recent data indicating that primary afferent depolarisation and the dorsal root reflex are substantially *reduced* by peripheral nerve trauma do not favour this hypothesis (Wall & Devor 1981, Horch & Lisney 1981b).

Sensitisation

In 1930s and 40s, Lewis and other authors placed a great deal of emphasis on neural and chemical mechanisms of peripheral receptor sensitisation in relation to pain (Lewis 1942). Among other things, they demonstrated that impulses carried out toward the periphery along small-diameter afferent fibres can produce vasodilation, plasma extravasation, oedema and tenderness (hyperalgesia). These symptoms are also part of the inflammatory response to local skin trauma. It was proposed that antidromic impulses in sensory fibres directly or indirectly release 'algogenic' substances into the skin. These substances, perhaps including serotonin, kinins, histamine or various peptides, then produce the cutaneous and sensory symptoms. It was not known at the time, and it remains unknown, whether the mechanism underlying such chemogenic sensitisation involves changes in the mechanical properties of the skin, actions directly on ion-specific channels in the membrane of nociceptor endings, or some other process.

More recent studies of sensitisation using electrophysiological techniques have confirmed that antidromic stimulation of a nerve can sensitise nociceptive afferent endings in the nerve's cutaneous distribution, and that following skin injury, nociceptor sensitisation can spread locally as a result of impulses conducted by axon reflex among preterminal branches of nerve fibres within the skin (Fitzgerald 1979). Sensitisation of several classes of afferents can also be accomplished by repeatedly heating the skin to noxious temperatures (e.g. Fitzgerald & Lynn 1977, Kenshalo et al 1982). Thinly myelinated (Aδ) nociceptors are particularly affected and the detailed parameters of their sensitisation account well for thermal hyperalgesia (Meyer & Campbell 1981). Interestingly, it is possible to heat-sensitise half of the receptive field of a cutaneous nociceptor without sensitising the rest of it (Thalhammer & LaMotte 1981). This result is an indication that the impulses involved in sensitisation by antidromic nerve stimulation and by activation of the axon reflex, might, in fact, be carried in different fibres from those that actually become sensitised.

Thermal sensitisation would appear to be an adaptive reaction of the peripheral sensory system to heat injury. A burn to the skin certainly lowers the intensity at which a strong stimulus becomes tissue-threatening, and sensitisation-induced hyperalgesia would offer appropriate protection. The functional significance, if any, of sensitisation by antidromic impulses in the normal organism is less obvious. Antidromic receptor sensitisation does however, provide a possible explanation of hyperalgesia in pathological circumstances. Following partial nerve injury, for example, many of the pathophysiological processes discussed in this chapter could produce a prolonged antidromic barrage and consequent receptor sensitisation and hyperalgesia.

On the basis of the evidence available, Lewis (1942) proposed that there exists a special class of small-diameter fibres whose role it is to mediate cutaneous flare and receptor sensitisation. These special fibres were termed ('nocifensors'.) The premature insistence on a novel class of nerve fibres, combined with a general shift in research interest away from peripheral and toward central mechanisms of pain, has brought about a relative stagnation of thinking about hyperalgesia and its mechanisms. In recent years, however, a number of unexpected and paradoxical findings have emerged that underline the importance of renewed research on this problem. These include:

1. The facts that peripheral nerves contain more than two axons on average for every DRG cell, but that the electrophysiological phenomena expected from such an arrangement (e.g. frequent double receptive fields) are not in evidence (Langford & Coggeshall 1981). Could it be that actually only one of the branches is a classical cutaneous afferent and that the other plays some unconventional role?
2. The recent discovery of synapses on DRG cells (Kayahara et al 1981) and the indications, discussed in this chapter, that these cells possess impulse generating capability.
3. The gradual accumulation of evidence for efferent influences on peripheral cutaneous receptor sensitivity (Santini 1976, Akoev 1980).

SUMMARY

The last 20 years have witnessed an impressive accumulation of information about spinal and brain stem mechanisms of pain and a general appreciation of their complexity and subtleness. By contrast, there has been little change in the common conception of peripheral nerves as elements that

either propagate or, if injured, fail to propagate action potentials. This chapter has reviewed pathophysiological processes through which damaged nerves can come to contribute actively to chronic pain by the injection of abnormal discharge into the nervous system and by the amplification and distortion of naturally-generated signals. The primary change appears to be an increase in nerve excitability. This is probably a result of abnormalities in membrane properties of outgrowing sprouts and patches of demyelinated axolemma. Normal nerves are capable of generating rhythmic discharge only at specialised terminal endings. Damaged nerves can acquire this capability at ectopic sites. Once a rhythmic impulse generator has been established, spontaneous discharge may occur. Correspondingly, the nerve may become sensitive to a broad range of depolarising stimuli including changes in mechanical, chemical, ionic and metabolic conditions.

Associated with abnormal impulse generation in damaged nerves are several mechanisms that can amplify normal or pathological impulse discharge. The most striking of these processes depends on the fact that rhythmic impulse generators have threshold properties. In fibres and DRG cells that are silent but near the threshold for rhythmic impulse generation, small stimuli that bring the rhythmic generator to threshold have disproportionately large and prolonged effects. Other impulse amplification and distortion mechanisms include 'extra-spike' production, ephaptic crosstalk and receptor sensitisation.

There is a fundamental difference between the mechanisms of 'normal' and 'pathological' pain. 'Normal' pain is pain that arises from acute or chronic stimulation of normal afferent nociceptor endings by intense stimuli. 'Pathological' pain is pain that occurs spontaneously, or in response to weak stimuli due to pathological alterations of nerve excitability. Peripheral afferents are highly complex and specialised neurons and the maintenance of normal excitability properties in their various functional zones undoubtedly requires a complex machinery. A better understanding of this machinery, and of the ways it can break down, promises new insights into pain syndromes that sometimes accompany peripheral nerve injury and disease.

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1.5

The dorsal horn

Patrick D. Wall

INTRODUCTION

My task in this chapter of describing the relationship of dorsal horn mechanisms to pain is made easier and briefer by the comprehensive chapters which surround it written by Lynn on the afferents (Chapter 1.1), Fitzgerald on afferent terminations (Chapter 1.2), Willis on transmission pathways (Chapter 1.6) and Basbaum & Fields on descending control systems (Chapter 1.11). I have already written an overall survey on the physiological basis of pain in the introduction. Furthermore two recent books written by scientists who have made major contributions give a very complete picture of the anatomical and physiological literature (Willis & Coggeshall 1978 and Brown 1981). Here I will summarise the present situation in the dorsal horn and point to those issues which seem important. The trigeminal nuclei are organised anatomically and physiologically in similar ways to the dorsal horn (Gobel et al 1981).

CELLS AND THEIR EXCITATORY RESPONSES

Given the presence of strong interactions between incoming afferents and the marked effects of segmental and supraspinal mechanisms, it is not possible to assign a single categorical function to dorsal horn cells. The control mechanisms have the effect of selecting which particular afferents will succeed in exciting a given cell. This means that the same cell will behave in a markedly different way in an anaesthetised or decerebrate or spinal animal let alone in a freely moving animal (Wall 1967, Wall et al 1967). This has led to apparent confusion in the literature but should be taken as a compliment to the subtlety of the nervous system, which is not designed to run an animal as though it were a puppet operated by strings with single functions. There is no reason to concentrate only on the small minority of cells which signal only the presence of injury. The very common wide dynamic range cells transmit information about large and small events and neural mechanisms are easily capable of decoding this information. It is very convenient to subdivide the spinal cord into the laminae described by Rexed (1952) on the basis of cell body shape, size and distribution. However it is crucial to realise that these laminae do not have rigid exact edges and furthermore that the dendrites of the cell bodies in one lamina can range widely into neighbouring laminae and sometimes into white matter (Brown 1981).

Lamina I: the marginal layer

Rolando (1824) noticed that the dorsal horn was capped by a clear zone which he named the substantia gelatinosa. The reason for this clearness is the absence of myelin. Cursory inspection of unstained sections immediately reveals an outer part of substantia gelatinosa which is lamina I with the dorsal columns on its dorsal edge and tightly packed bundles of longitudinally running fibres marking its ventral edge where lamina II begins. Because of the clear separation of lamina I and its special input, function and projection there are some who now label lamina II as the substantia gelatinosa. This is confusing and does not conform to Rolando's use of the words, and it is better to retain the original meaning and to use Rexed laminae when subdividing substantia gelatinosa. A cell stained section of lamina I is visually dominated by the large transverse Waldeyer cells, but one should not miss the very large numbers of smaller cells also present (Bennett et al 1981, Beal 1979). In cat, the dendrites of lamina I cells are flattened within the lamina, but in rat, monkey and man they spread ventrally at least into lamina II (Beal 1979, Woolf & Fitzgerald 1983, Schoenen 1982).

This lamina has received particular attention in relation to nociception because it is a specialised region for the termination of nociceptive afferents (Chapter 1, 2) and contains cells which respond only to noxious stimuli (Perl 1980). While both of these statements are true they should not be exaggerated, since many different types of cell response are found (Handwerker et al 1975, Price et al 1979, Menetry et al 1981, Wall et al 1979). Fitzgerald (1981), in cat, has shown a gradient extending from lamina I through II with cells responding only to pinch in larger numbers dorsally and those responding only to brush more common in inner lamina II. Marked cells in rat with brush only, pinch only or, most commonly, responding to a wide range of mechanical, thermal and chemical stimuli, are located in lamina I (Fitzgerald & Woolf 1983). In rat, a group of cells with axons projecting to mid brain by way of the contralateral dorsolateral fasciculus are particularly common (McMahon & Wall 1983). These respond to a wide range of stimuli but rarely to light pressure. Electrical stimulation of

nerves similarly shows that cells respond to A beta or A delta or C afferents or more commonly to mixtures of these groups (Fitzgerald 1981).

The area of the receptive fields of the majority of cells is restricted to some fraction of their dermatome but some extend to include as much as a whole leg. There are three novel characteristics of these cells which they share with lamina II and which make them particularly interesting. Some cells exhibit such striking habituation of the stimulated fraction of their receptive field that they may be considered as novelty detectors (Wall et al 1979). Some cells produce very prolonged responses after brief stimuli. Finally many cells show slow amoeboid changes in the receptive fields they subserve (Dubuisson et al 1979) and we will return to these signs of plasticity. It is disappointing that no correlation has been found between the anatomical and physiological properties of lamina I cells (Light et al 1981).

Lamina II

Lamina II extends from the ventral edge of lamina I to lamina III, whose dorsal boundary is clearly defined by the presence of opaque myelin. It has been subdivided on physiological and anatomical grounds into inner and outer regions (IIi and IIo; Gobel 1979). Cajal (1982) recognised two special cell types, islet cells and stalked ceells, which have been particularly intensively studied by Gobel and his colleagues (Gobel et al 1980). However there are a number of other morphological types with clearly defined dendritic field orientation (Schoenen 1982). Their excitatory RFs and their properties do not differ qualitatively from those described in lamina I (Price et al 1979, Kumazawa & Perl 1978, Wall et al 1979, Wall & Fitzgerald 1983, Bennet al 1980). Quantitatively the gradient continues, so that the ventral region (IIi) contains a predominance of units responding only to light brush, while the more dorsal part has the largest number responding to light and heavy mechanical stimuli and to noxious heat and chemicals, and some are specialised nociceptive cells (Fitzgerald 1981). We lack knowledge of how visceral afferents are represented. Electrical stimulation of nerves shows the same admix of response to be expected from the response to natural stimuli. Some respond to one group of afferents while most respond to various combinations. A particularly interesting group respond with fixed latencies to C afferents and are good candidates to be monosynaptically excited (Fitzgerald & Wall 1980).

Lamina III

Lamina III has its ventral border marked by the appearance of large cell bodies in lamina IV and its anatomy is dominated by the extensive dendritic trees rising from the deeper cells. There are also small cell bodies with shapes similar to those found in lamina II. Some small cells have very small low threshold excitatory RFs which make up part of the larger RF of the nearest large cell (Wall et al 1979). No specific function has yet emerged for this zone, which may well represent a transition area between laminae II and IV. However, a special study by Bennett et al (1981) shows that the cells are particularly concerned with low threshold afferents which terminate in the region.

Lamina IV

Lamina IV contains large cells with dorsally-rising dendrites and small stellate cells. The physiological specialisation of this area, which is in contrast to the two more ventral laminae, was described by Wall (1967) and has been largely confirmed by later detailed analysis (Brown 1981). The commonest cell type is excited only by light mechanical stimuli to the skin and the response of these cells does not increase if the intensity of the pressure stimulus is increased.

Lamina V

Lamina V contains large cells with cell bodies and dendrites directed transversely. The commonest cells have wide dynamic ranges and respond to a variety of inputs from low to high threshold mechanical, thermal and chemical stimuli by way of the full range of diameters of afferent fibres. Some cells respond to A delta and C fibres of visceral origin and also to cutaneous low-threshold mechanical stimuli reminiscent of the pattern of referred pain (Pomeranz et al 1968). The organisation of the RF shows a smaller central area where the cell responds to all types of stimuli surrounded by a large excitatory area where only intense stimuli excite the cell (Hillman & Wall 1969). RF size is larger than the lamina IV cells but still normally restricted to a fraction of the dermatome, although they can vary in pathological conditions, as we shall see, and a few cells in the normal animal have mirror image contralateral fields (Fitzgerald 1982). Since many of these cells send axons to the brain, they, with the lamina I cells, are the major candidates for informing the brain of the existence of injury. While, as we have said, all groups of cells may contribute to pain, the lamina V cells may be particularly important (Mayer et al 1975; Price & Dubner 1977).

Lamina VI

These cells, which include Clarke's column, make up the ventral boundary of the dorsal horn. They are characterised by their response to low-threshold muscle afferents (Wall 1967). However they also, respond to low and high-threshold cutaneous afferents. This convergent input from both specialised muscle receptors and cutaneous and visceral inputs is under selective modality control by way of systems descending from the head (Wall 1967).

Other cells

The great bulk of afferents terminate on cells in the six laminae which constitute the dorsal horn. However, there are three other groups of cells which should not be neglected. Lamina VII makes up the ventral horn other than the motor neurons and is continuous with the medullary reticular formation. It includes cells with large, often bilateral, receptive fields which are excited, presumably in-

directly, by a wide range of stimuli and which project to the brain (Meyers & Snow 1982). A specialised group of cells gathered around the central canal make up lamina X. They may be related to pain mechanisms, since some respond to high intensity bilateral stimuli (Nakin & Giesler 1982) and contain the same array of peptides which characterise laminae I and II (Gibson et al 1981) and could be one of the polysynaptic chains linking the entire length of cord and brain stem (Collins & Randt 1960, Noordenbos 1959). Finally, cell bodies occur within white matter in some species, including dorsal columns — where their properties appear similar to lamina I (Woolf & Fitzgerald 1982) — and in rat dorsolateral white matter (Menetry et al 1982).

Excitatory links

The extraordinary and beautiful work by Jankowska and Lundberg and their colleagues (1981) on circuits related to muscle afferents shows that it is now technically feasible to unravel cell links. However, work on cells related to nociception remains in relative infancy because of soluble but difficult technical problems related to the small size of cells and fibres and their variable physiology and close packing.

The monosynaptic termination of nociceptive afferents on cells concentrated in laminae I, II and V is reviewed by Fitzgerald (Chapter 1.2) and by Willis (Chapter 1.6). We know regrettably little about the undoubtedly crucial polysynaptic systems. The Bethesda group identify the stalked cells in lamina II as excitatory interneurons ending on lamina I cells (Bennett et al 1980). As yet unidentified lamina II cells are likely to transfer C fibre excitation to lamina V cells (Fitzgerald & Wall 1980). Many anatomical possibilities for interconnection exist (see review by Wall 1980) but the overall picture fits a general flow of excitation from dorsal to ventral in a cascade fashion (Fig. 38). For example, the plantar cushion reflex afferents terminate in laminae III and IV (Egger et al 1980) and induce intense metabolic activity in laminae II and II (Proshansky et al 1980). They excite interneurons in laminae III and IV (Egger & Wall 1971) which project ventrally and excite motoneurons whose dendrites extend toward them (Egger et al 1980).

Interneurons are necessary to explain not only the direct excitatory linkage but also presumably the very prolonged facilitations such as the wind-up phenomenon (Mendell 1966). From lamina III to lamina VII the response of cells becomes increasingly complex with each lamina being excited by more and more inputs. Some of each additional input can be explained by the arrival of additional and special types of afferent fibres, and some of the excitation can best be explained by the cells in each lamina being excited by the cells immediately dorsal to them (Wall 1968). In addition to this overall plan for segmental circuitory, each successive dorsal-to-ventral stage from lamina III sends axons to the brain. The brain is thereby informed of the state of excitation of each of the stages. It is proposed that lamina II influences the firing of cells ventral to it but this lamina has only minimal projection to the brain (see Chapter 1.6). This leads to the proposal that a function for lamina I is to inform the brain of the excitatory state of lamina II. A complete cascade would then be formed, starting with the linked complex of lamina I and II and extending to lamina VII, in which each lamina receives and computes additional information in part from its dorsal neighbour, and projects to the brain and to its ventral neighbour.

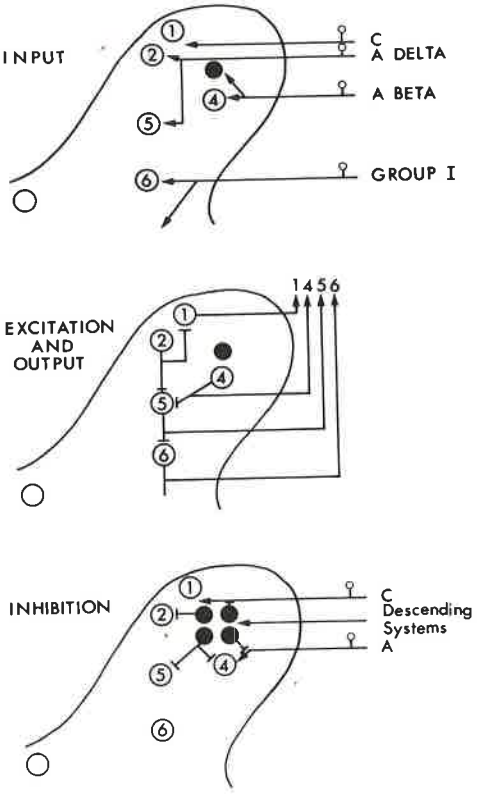


Fig. 38 Diagrams of the dorsal horn. The clear circles represent the major groups of neurons in the six laminae which make up the dorsal horn. The dark circles represent groups of inhibitory interneurones. *Input* shows the overall scheme of the laminar distribution of primary afferents with the smallest fibres, C, ending only in the upper two laminae and the largest, the group 1 afferents from muscle, ending in lamina VI. *Excitation and output* shows the cascade model of excitatory coupling. From lamina II ventrally cells receive excitation from afferents and from the cells located in the laminae dorsal to them. Lamina I is the only exception to this model, since it is excited by afferents and by the cells ventral to it. Laminae I, IV, V and VI project to the brain. *Inhibition*: Groups of inhibitory interneurones are shown as dark circles. They receive inputs from afferent fibres from descending systems and from local interneurones. They project presynaptically on to the terminals of A and C fibres and postsynaptically on to dorsal horn cells.

Inhibitory links

Inhibitory links obviously have the greatest basic and practical interest in relation to a gate control. The descending inhibitions are discussed by Basbaum & Fields (Chapter 1.11), so that we may concentrate here on interactions between afferents and on segmental mechanisms.

Presynaptic control

Axoaxonic synapses are seen on the terminals of fine afferents in the upper laminae and also on large afferents in

deeper laminae (Chapter 1.2). As we shall discuss below in the section on the chemistry of inhibition, it may now be necessary to take into account distant terminals as well as the classical closely applied terminals. The location of the cells which project on to afferent terminals remains uncertain but lamina II is the most likely origin (Wall 1980). The depolarising effect of afferent volleys on the terminals of large myelinated afferents and the association of this with inhibition are well established (Wall 1958, Eccles 1964, Wall 1964, Schmidt 1971). Only recently has it become afferent that C fibre terminals are also affected (Hentall & Fields 1979, Fitzgerald & Woolf 1981). It is still not certain if presynaptic facilitation can be achieved either by removal of inhibition or by an active hyperpolarisation. Similarly the mechanism of the undoubted presynaptic control remains in doubt since it could be achieved by the blockade of afferent impulses in the terminal arbor (Howland et al 1955, Wall 1964) and or by modulation of the amount of transmitter release (Eccles 1964).

Postsynaptic control

It is also clearly established that afferents may produce postsynaptic inhibitions (Hongo et al 1968). It is possible that pre- and postsynaptic mechanisms could be in operation, sometimes simultaneously and sometimes independently. Presynaptic control allows the independent manipulation of convergent inputs onto a cell without affecting the overall excitability of the cell. Inhibition of high-threshold inputs while leaving low-threshold input excitation unaffected has been reported frequently. This could be achieved by presynaptic control on afferent terminals and/or by postsynaptic control of excitatory interneurons.

The ability of low-threshold afferents to inhibit the effects of high-threshold inputs only makes sense if we take into account the spatial origin of the conflicting inputs (Hillman & Wall 1969). If this is not done, wide dynamic range cells in lamina V appear to respond in a jumble of excitations and inhibitions produced by all types of afferent. An extreme example of the importance of spatial origin has already been mentioned where there is excitatory summation of small-diameter afferents from viscera with large-diameter afferents from skin (Pomeranz et al 1968). If the receptive field of a lamina V cell responding only to skin is examined, it is found that the receptive field excited by brush or touch is surrounded by a much larger inhibitory surround activated by the same stimuli. If stimulus intensity is now increased to include nociceptors, the excitatory RF is found to be much larger than that produced by light stimuli, which means that the inhibitory surround to light stimuli overlays some of the excitatory field of the high-threshold afferents. This conflict is the basis of the immediate effect of TENS (Wall & Sweet 1967, Chapter 3.D.1). If the intense input is applied beyond the edge of the high-intensity excitatory RF, a high-intensity inhibitory surround is revealed (Le Bars et al 1979, Fitzgerald 1982).

All of these inhibitions, whether pre- or post synaptic, require the existence of inhibitory interneurons. Their identification has yet to be achieved with the precision of Jankowska & Lundberg for proprioceptive interneurons (1981) but it strongly indicated that they include lamina II cells (Wall 1980). Behavioural studies of the analgesic effects of stimulation of peripheral nerves (Woolf et al 1980) or of descending brain systems (Chapter 1.11) correlates well with the inhibition of the response of deep dorsal horn cells to noxious inputs. It is therefore reasonable to search for interneurones which are excited at the time when physiological and behavioural inhibitions are found. There is a reciprocal relationship between the response of lamina II cells and of lamina V cells in the following conditions; stimulation of the DLF (Dubuisson & Wall 1980), stimulation of the raphe magnus and nucleus reticularis gigantocellularis (Dubuisson 1981), stimulation of Lissauer's tract (Yaksh & Wall, unpublished), selective blockade of A fibres (Fitzgerald 1981), contralateral stimuli (Fitzgerald 1982), the effect of naloxone (Fitzgerald & Woolf 1980). In these manipulations of excitability, lamina I cells change in the same direction as lamina II cells whereas lamina V cells change in the opposite direction. In a study of identified projecting lamina I cells in the rat (McMahon & Wall 1983) DLF stimulation which inhibits deep cells was found to excite lamina I cells and to expand their receptive fields. This is additional evidence that lamina I cells may be informing the brain of the state of laminae I and II and not triggering pain reactions, since lamina I cells are facilitated during procedures that produce analgesia.

Chemistry

Chemicals present in afferent fibres are described by Cuello & Matthews (Chapter 1.4), in local systems by Terenius (Chapter 1.10) and in descending systems by Basbaum & Fields (Chapter 1.11). We do not know the identity of the excitatory transmitters released by afferent fibres, although there are a number of likely candidates. It is not sufficient to show that the candidate fulfills the initial three requirements; presence in terminals, release with activity, effect on the postsynaptic membrane. Carbon dioxide is a putative transmitter on these grounds.

The success in the identification of acetyl choline as a transmitter depended on a series of analytic stages including: 1. the presence of isolated points of action such as the neuromuscular junction where pre- and postsynaptic action could be studied, 2. quantitative analysis of the amount released and the demonstration that this amount imitated the effect of nerve impulse transmission, 3. the ability to alter concentration by specific control of release and breakdown, 4. the identification of the receptor and of receptor antagonists.

Even the preliminary approach to final success occupied 50 years between the Nobel prizes of Loewi and Katz. With this in mind let us examine the two groups of compounds, the aminoacids and the peptides, which are proposed as different transmitters. Glycine, arginine, taurine, aspartic acid and glutamic acid possess the initial requirements and have their proponents (reviewed in Bowman & Rand 1980). The firm evidence for their action comes largely from isolated preparations whose simple anatomy differs from the jumble of structures surrounding afferent terminals. These compounds are present in all cells and play a part in many

1.9

Deafferentation

Ronald R. Tasker

INTRODUCTION

That certain pain states may not depend upon transmission of nociceptive impulses, at least not as currently understood, may be a startling suggestion in this era of rapidly expanding knowledge of pain physiology. Yet neurosurgeons, particularly, have long been aware that procedures such as neurectomy, rhizotomy, or cordotomy, which interrupted nociceptive transmission, often failed to relieve particular types of pain, or else did so only temporarily. This phenomenon was first considered to be a feature of any pain not caused by cancer, attributable to plasticity of the nervous system in circumventing the interruption of pain transmission, given sufficient time. That it was pain caused by damage to the nervous system itself that resisted surgical treatment rather than just any type of pain not caused by cancer was first clearly stated by Livingston (1943). He went on to suggest that the process responsible for chronic pain in causalgia, minor causalgia, post-traumatic pain syndromes, chronic low back disability and phantom limb pain was some central nervous perturbation which, once established, persisted despite subsequent removal of the cause. Livingston's work was then overlooked and largely forgotten until the recent 'renaissance' of thinking about chronic pain.

We first began to realise the differences between 'dysaesthetic' and 'somatic' pain while reviewing the results of our percutaneous cordotomies (Tasker 1975), a distinction now increasingly familiar in the literature under the terms 'deafferentation' and 'nociceptive' pain.

DEFINITIONS

The term 'deafferentation pain' will be used to refer to discomfort arising in any part of the body whence the flow of afferent nervous impulses has been partially or completely interrupted. While theoretically also resulting from injury to receptors, in practice it is caused by lesions of nerves, dorsal roots, spinal cord, brain stem or cerebral cortex, interruption at any anatomical level being capable of inducing pain. Such a definition implies clinical evidence of increased threshold to one or more modalities of somatosensory function and most patients with deafferentation pain do show sensory loss. There are, however, patients with lesions that could have inflicted nervous injury and whose pain resembles that seen in patients with sensory loss who do not themselves show increased somatosensory thresholds clinically. Presumably their deafferentation is sub-clinical.

Though pain in the distribution of sensory loss is the essential feature of deafferentation pain, certain other clinical features may be present, such as reflex dystrophy, thought to be due to associated sympathetic malfunction as described by Weir Mitchell (1872) in the American Civil War. Somewhat more common are certain associated perversions of sensation with excessive reaction to stimuli applied in or near the deafferented area. Unlike the hyperaesthesia associated with tissue injury caused by burning, which Kenshalo et al (1982) found in animal models to be associated with enhanced background firing of noxious thermoreceptors and probable central facilitation of response to non-noxious mechanoreceptors, that found in patients with deafferentation pain such as 'neuralgia' of a traumatic or entrapment type showed somewhat different features (Lindblom 1979, Lindblom & Verillo 1979). Some of these patients with deafferentation pain showed no excessive reaction to stimuli and sometimes hypo-aesthesia with elevated perception threshold or reduced subjective intensity or both. If hyperaesthesia occurred with the reverse of these features, it was accompanied by slight to moderate elevation of threshold to mechanical, warm or cold stimuli in all patients, some of whom showed reduced, others increased, thresholds to thermal pain; others exhibited painful responses to normally non-noxious mechanostimulation. Thus, in general, whether patients exhibited exaggerated painful responses at lowered, normal or elevated thresholds, they exhibited increased threshold to at least some modality of sensation and the induced pain, once felt, whether elicited by a normally noxious or innocuous stimulus, was of unusually unpleasant quality referred to as 'dysaesthetic'. Studies of conduction velocity showed that dysaesthetic sensation induced by tactile stimuli was mediated by large peripheral nerve fibres, not by small pain fibres. Moreover the dysaesthetic effect was poorly localised, delayed in perception, and prolonged and radiating in nature. It was felt that these effects, which Foerster (1927) termed 'hyperpathia' were of central origin. Hyperpathic phenomena accompany only some cases of deafferentation pain and only those with partial lesions, disappearing after total denerva-

tion except, sometimes, at the boundary of the new anaesthetic area.

CLINICAL FEATURES OF DEAFFERENTATION PAIN

In order to derive a clearer understanding of the clinical pictures of deafferentation pain syndromes, we undertook a retrospective review of 168 patients seen consecutively with lesions capable of damaging the afferent nervous system and in whom there was pain in the deafferented or potentially deafferented area (Tasker et al 1980).

ETIOLOGY

17% of our 168 patients suffered from pain attributable to lesions of the brain stem, usually vascular in nature. 19% had suffered lesions to the spinal cord, usually traumatic, 11% had postherpetic neuralgia and 9% had undergone multiple unsuccessful procedures for disc disease. 44% suffered from stump or phantom pain syndromes or traumatic, iatrogenic or cancerous neuropathies.

That such a variety of neurological insults can produce pain is curious; more so is the unpredictability of pain after any particular neurological lesion. The studies by Inbal et al (1980) implicate a genetic factor in rat models of deafferentation pain while Levitt & Levitt (1981) showed that stump tail macacques develop deafferentation pain more readily than other species of primates after identical surgical lesions. Moreover, age plays a role. Unusual in children, deafferentation pain becomes increasingly common after middle life. A quarter of our 168 patients developed pain between 20 and 39 years of age; 32% between 40 and 59; one third over the age of 60. (Postherpetic neuralgia), for example, is more likely to follow attacks of herpes zoster the older the patient. Finally, certain neurological lesions, such as thoracotomy-induced damage to intercostal nerves and brachial plexus avulsion, are much more likely than others to result in deafferentation pain. Wynn Parry (in Chapter 2.C.1) shows that brachial plexus lesions central to the dorsal root ganglion are much more commonly associated with pain than more peripheral lesions. The fact that 61% of our 168 patients with deafferentation pain were males is difficult to explain.

SITE OF PAIN

The distribution of pain throughout the body in our 168 patients conformed to the relative sizes of the parts concerned, 20% of the patients suffering from pain in the head or neck and 12% in the upper, 31% in the lower, extremities. The trunk was involved in 33% and multiple areas in 22%.

DISABILITY

Pain caused significant disability in our 168 patients: 2% are known to have committed suicide and only 28% were capable of full activity.

QUALITY OF PAIN AND PRESENCE OF HYPERPATHIA

Our patients could be divided into two groups. One, comprising 86% of the total, suffered only from spontaneous pain, constant or intermittent in pattern without hyperpathia. The other, comprising the remaining 14%, also exhibited hyperpathia. 'Hyperpathia' took the form either of unpleasant sensations induced by normally non-noxious stimulation within or adjacent to areas of increased somatosensory threshold, or else of abnormally unpleasant sensations induced by normally noxious stimuli in such areas. It might be selectively elicited by a single somatosensory modality, or else by multiple modalities. Features of delayed perception, impaired localisation, spread and abnormal prolongation of sensation were also seen.

Our patients described their pain in terms which differed from those used by patients suffering from nociceptive pain, 51% as burning, raw or searing, 43% as having a tingling numb sensation and 21% with formications. In many patients the pain exhibited multiple qualities, often varying with time and bodily site.

TIMING OF ONSET OF PAIN

It has often been remarked that pain that follows nervous injury may not appear immediately while it usually worsens with time and seldom disappears spontaneously. In those of our 168 patients in whom the moment of the causative event could be identified, 36% stated that pain began immediately, 33% within a year and 24% after a year had passed. One patient appeared to develop typical deafferentation pain 31 years after a neurological lesion.

SOMATOSENSORY LOSS

By definition, sensory impairment is the underlying cause of deafferentation pain. In our 168 patients we correlated sensory loss with location of pain using a computer graphics technique. 2% had amputations. Of the remaining 93% of our 168 patients from whom data were available, 9% showed no clinically detectable impairment of appreciation of pin-prick in the painful area, whereas 62% showed partial and 19% total loss of appreciation of pin-prick while in 10% it induced hyperpathia. Of the remaining 83% in whom data were available for appreciation of light touch, 12% showed no loss, 52% partial and 22% complete loss in the area of pain; in 14% it induced hyperpathia. Similar less complete data were available for temperature appreciation.

In the 5% of our patients with no clinically detectable sensory loss the diagnosis of deafferentation pain might be questioned. In all of these patients who suffered from post-thoracotomy syndrome, stroke or postherpetic neuralgia, the clinical picture was so similar to that of other patients

whose pain was caused by demonstrable sensory loss that it was felt justified to assume that 'subclinical deafferentation' had occurred.

THE EFFECT OF LOCAL ANAESTHETIC BLOCKADE

It is generally believed that if a pain syndrome is temporarily relieved by proximal local anaesthetic blockade, then surgical deafferentation at the same site will afford long term relief. 37 of our 168 patients underwent such local anaesthetic blockade either at the peripheral nerve, dorsal root or spinal cord level proximal to a clinically identifiable deafferenting lesion. Of the 95% of these 37 patients in whom the block achieved appropriate anaesthesia in the area of pain, 65% reported total temporary relief of pain, 24½% significant reduction and only five and one-half percent no relief at all.

EFFECT OF INTRAVENOUS SODIUM THIOPENTAL

Having learned the usefulness of sodium thiopental for distinguishing pain of hysterical and nociceptive origin from Allan Walters (1961), we administered 50 mg aliquots of the drug intravenously every 3–5 min until either pain relief or somnolence ensued in 28 of our patients. To our surprise the drug relieved deafferentation pain at least as readily as it did hysterical pain, while nociceptive pain was unaffected. 50% of the patients reported complete relief with doses insufficient to interfere with communication or to alter the appreciation of pin-prick or other noxious stimuli. Another 14% reported significant reduction in pain. In half the patients these effects were achieved with dosages of less than 100 mg.

EFFECT OF NARCOTICS

Intravenous dosages of 3 or 4 mg of morphine sulphate were given every 10 minutes to a total dose of 18–20 mg in a small number of our 168 patients with deafferentation pain and to 17 subsequent similar patients undergoing chronic spinal epidural stimulation. Of the latter, two reported complete, seven partial and seven no relief of pain. Data were lost in one. In no case, however, did 0.4–0.8 mg naloxone, given intravenously, reverse any pain relief reported after morphine. These observations suggest that the narcotic action of morphine does not inhibit pain of the deafferentation type.

SUMMARY

Thus the deafferentation pain in our 168 patients was the result of either peripheral or central nervous lesions, was nearly always causalgic or dysaesthetic in quality and usually co-existed with clinically demonstrable sensory loss. It was often delayed in onset, often dramatically ameliorated by intravenous dosages of sodium thiopental but not by morphine and was usually relieved by proximal local anaesthetic blockade. 14% had accompanying hyperpathia.

THE EFFECT OF DESTRUCTIVE SURGICAL LESIONS ON DEAFFERENTATION PAIN

Neurosurgeons first discovered that lasting relief of pain caused by non-cancerous lesions was seldom achieved by making destructive lesions in the nervous system. We reviewed our experience with various surgical procedures performed for the relief of pain, comparing results between patients with deafferentation and nociceptive pain, the latter usually caused by cancer. Some of the 168 consecutive patients described above are included in these reviews.

NEURECTOMY

Patients undergoing percutaneous radiofrequency intercostal neurectomy at sites where previous local anaesthetic blockade had produced complete relief of pain provided a consistent group in which to examine the effects of neurectomy. Out of a series of 35 only 25% of those with deafferentation pain, usually post thoracotomy syndrome or postherpetic neuralgia, enjoyed significant persisting relief while 75% continued to suffer from pain within or adjacent to areas rendered anaesthetic although some reported improvement lasting days to weeks. In four patients with cancerous involvement of the chest wall, however, surgically induced anaesthesia in the area of pain achieved significant pain relief until the patients died.

CORDOTOMY

In a series of 234 consecutive patients undergoing 244 percutaneous cordotomies at the high cervical level using the lateral approach, it was possible to identify 179 with nociceptive pain, 15 with deafferentation pain and 40 with elements of both (Tasker et al 1980, 1982b). Technique and follow-up intervals were similar in all. At discharge from hospital a high percentage of patients in all groups was significantly relieved of pain, incidence of relief being higher in patients with nociceptive pain. At post-discharge follow-up, 70% of patients with nociceptive pain were still totally free of the pain for which the cordotomy had been performed, 12% partially so, only two patients complaining of persisting pain in an analgesic area. Of the 15 patients with pure deafferentation pain, only 2, or 24%, were totally relieved at this time, while partial relief, even of the slightest degree, was observed in only 3, or 43%. Of the 40 patients with mixed pain, the somatic element was totally relieved in 73%, partly in 18%, at the time of post-discharge follow-up. As far as it could be distinguished from the somatic element, the deafferentation element appeared to be alleviated in 10, or 52.6% at this time, lessened, at least slightly, in 3 or 15.8%; in one patient it was worse. Persist-

ing deafferentation pain in all but one patient was located in a clinically analgesic area. Lest the data for patients with mixed pain be construed as suggesting a useful role for cordotomy in deafferentation pain, it must be pointed out that the indications for cordotomy in these patients were based on the severity of the somatic element, the deafferentation element often being minor, that distinction of the two types of pain is often difficult when they occur in the same site in a single patient, perhaps giving an over-optimistic view of the effects of cordotomy in deafferentation pain, and that the period of follow-up was relatively short, over 6 months in only 19 of our cordotomy patients.

THE EFFECT OF STEREOTACTIC ABLATIVE PROCEDURES

A review of the world's literature (Tasker 1982a) based on publications sufficiently detailed to allow differentiation of patients with nociceptive and deafferentation pain revealed that stereotactic ablative lesions, no matter in what structure, produced significant reduction in the degree of pain in 32% of patients with deafferentation pain and in 70% of those with nociceptive pain. No target could be identified with significantly higher success than any other.

In our own experience, 65% of 20 patients undergoing stereotactic destructive surgery for the relief of nociceptive pain and 25% of 12 others operated upon for deafferentation pain obtained significant relief. Lesions were made in the mesencephalic spino-reticulo-thalamic tract and the centrum medianum–parafascicular nucleus area in 19, in the posterior thalamus in three. Postoperatively, deafferentation pain persisted in analgesic areas. Anatomical confirmation of the sites of exploratory electrode trajectories and of the lesion sites have been published for four of these patients (Tasker et al 1982a).

CORDECTOMY

No procedure intended for the relief of pain is more dramatic than 'cordectomy'. We have now had personal experience with six patients in whom the cord was transected several segments proximal to complete traumatic transection. In none of these was causalgic or dysaesthetic pain in the anaesthetic lower limbs relieved although in one, severe intermittent sharp pain disappeared allowing him to return to work. Druckman & Lende (1965) and Durward et al (1982) report similar experience, while Melzack & Loeser (1978) report five similar cases only one of whom enjoyed relief for 11½ years before recurrence of pain.

EFFECT OF SURGICAL DEAFFERENTATION ON HYPERPATHIA

Despite the failure of surgical deafferentation at any level to relieve most patients of deafferentation pain, hyperpathia, which always occurs in incompletely deafferented areas, is usually relieved by surgical completion of the deafferentation, though it may persist at the periphery of the sensory loss.

PATHOPHYSIOLOGY OF DEAFFERENTATION PAIN

INTRODUCTION

Any hypothesis seeking to explain deafferentation pain must take into account its production by both peripheral and central nervous lesions, its co-existence with sensory loss, often delayed onset, peculiar qualities, amelioration by sodium thiopental but not by morphine, and its relief by proximal local anaesthetic blockade but not by surgical destructive lesions at the same site. Obviously, for the patient in pain, nervous impulses must impinge on consciousness probably at the cerebral cortical or at least at the upper brain stem level. The essential questions are: where do they originate and by what process?

As Loeser (1981) points out, there are a number of possibilities capable of explaining deafferentation pain: ephaptic connections, spontaneous activity generated at the injury site, alterations in somatotopy either for somatosensory function as a whole or for some modality of it, loss of inhibitory connections, alterations in ascending or descending inhibitory pathways, disinhibition of pattern generating systems, spontaneous activity in denervated neurons. Such alterations could result from simple loss of connectivity or from abnormal connectivity caused by denervation through regenerative sprouting, development of new synapses, utilisation of previously unused synapses, alterations in 'balance' between existing transmitters at existing synapses or from combinations of these in a manner influenced by genetics and age.

Obviously, changes that induce pain may arise at any site in the nervous system, presumably at or proximal to precipitating peripheral and central neurological lesions. Wall (1981) and Wall et al (1979) have most elegantly demonstrated changes arising at the site of a peripheral nerve lesion in animal models which could account for deafferentation pain by transmitting impulses over peripheral nerves. Such a mechanism could explain the small proportion of patients with deafferentation pain who are relieved by peripheral surgical deafferenting procedures. However, a larger group of patients, including some with pain resulting from peripheral nerve lesions, fails to experience relief from surgical deafferenting procedures including cordectomy, suggesting that their pain is not the result of nociceptive transmission in peripheral nerves or spinal cord, as Noordenbos & Wall (1981) and Wall (1982) have pointed out. Rather a central mechanism is suggested, and one which continues to function even though totally disconnected from the original site of injury.

CLINICAL PHYSIOLOGICAL OBSERVATIONS DURING STEREOTACTIC STIMULATION OF THE HUMAN BRAIN STEM

Is there clinical evidence which could bear on the pathophy-

siology of deafferentation pain? Over the past 20 years we have employed threshold electrical stimulation in the conscious patient undergoing stereotactic procedures for the control of pain or movement disorders for physiologically verifying our lesion site (Tasker et al 1982a). The anticipated target site is explored by stimulating at threshold with 60 Hz monophasic trains of 3 ms pulse duration using a concentric bipolar electrode of 1.1 mm external diameter and 0.5 mm pole separation in 2 mm steps as the electrode is advanced toward and beyond the target. Alternate trajectories in the same parasagittal plane are separated by 2 or 3 mm. Using a computer graphics display the results of stimulation at 9383 sites in 198 consecutive patients were displayed in two sets of diagrams. One set mapped the bodily location and quality of each response elicited in each patient using figurine charts. The other displayed on separate series of sagittal brain diagrams, extending from 2.5–18.5 mm from the midline, the locations of all responses of each different type elicited in our 198 patients, after first standardising the intercommissural distance. A limited variety of somatosensory effects was observed referred to specific parts of the body, usually contralaterally. Paraesthetic effects were elicited in the medial lemniscus and ventrobasal complex, usually 9 mm or more from the midline, where lesions produce extensive somatosensory deficit. Warm and cold effects arose in the neospinothalamic tract from the level of the midbrain to that of the posterior thalamus, usually lateral to the 7 mm sagittal plane in the upper brain stem where lesions produce dissociated sensory loss. Responses consisting of the illusion of movement in some body part, thought to arise in the muscle afferent pathway, were found in medial lemniscus and ventral intermediate nucleus of thalamus.

There remained a group of responses described as burning or painful which proved to be of unusual interest. Their locations are displayed in Figures 50–60. (Tasker 1982b, Tasker et al 1980, 1982a, 1983).

As the figures show, these responses occur, intermingled with warm or cold effects, throughout the extent of the neospinothalamic tract as in Figures 52 and 59, and of ventrobasal thalamus, as in Figures 53–56 and Figure 60. But they also extend, and indeed become more prominent, medial to the 7 mm sagittal plane and to the bulk of paraesthetic and warm or cold effects in midbrain and thalamus, into sites where lesions produce no clinically detectable sensory loss, as in Figures 50, 51, 57 and 58. At these medial sites they occur in groups in individual patients, whereas laterally they tend to occur as single isolated responses. This distributional pattern is shown in Table 2. Moreover the paraesthetic and warm and cold responses in the lemniscal and neospinothalamic pathways respectively, are somatotopographically arranged (Tasker et al 1982a) while the medially-located burning and painful responses are not, being referred to large portions of the contralateral body.

In addition to their distributional characteristics, burning and painful responses have another unusual characteristic; they are not equally prevalent in all patients explored. Our 198 patients fell into three groups — those with movement disorders in whom the medial brain stem planes were sel-

Table 2 Threshold stimulation of the brain stem in 198 patients. Percentage incidence of burning, painful, warm or cold responses by sagittal plane

Response	Sagittal plane, mm from midline <6.5	9.0	15–16.5
Pain	56	12.6	0
Burning	44	31.5	15.4
Warmth or cold	0	55.9	84.6

Figs 50–60 Explanation of symbols used in figures

Ce	centrum medianum
Cm	mammillary body
Cos	superior colliculus
Cpi	internal capsule
Gm	medial geniculate
Grpo	pontine grey
Hpth	hypothalamus
Lm	medial lemniscus
M	dorsomedian nucleus
Ni	substantia nigra
Pspd	basis pedunculi
Pu	pulvinar
Ru	red nucleus
Sth	subthalamic nucleus
Tcsp	corticospinal tract
Tmth	mammillothalamic tract
Vc	ventrocaudal nucleus of thalamus
Vim	ventral intermediate nucleus of thalamus
Voa	anterior ventral oral nucleus of thalamus
Vom	medial ventral oral nucleus of thalamus
II	optic nerve

In Figures 50–60, the computer has plotted each response in the one of the listed sagittal planes closest to that in which it was actually elicited.

All the Figures are reproduced from Tasker et al 1982a, by kind permission of the publishers, Charles C Thomas, Springfield, Illinois.

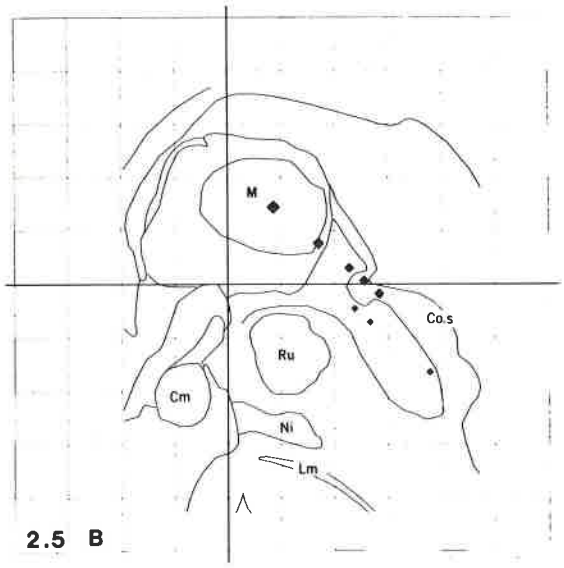


Fig. 50 Computer-generated diagram showing locations at which threshold stimulation elicited the sensation of burning in the 2.5 mm sagittal plane in 198 consecutive patients explored stereotactically. Data were standardised to a single intercommissural distance. The heavy horizontal line marks the intercommissural plane; the heavy vertical line passes through the mid-commissural point. The lighter grid depicts 5 mm squares. The sizes of the diamond-like symbols are proportional to threshold current.

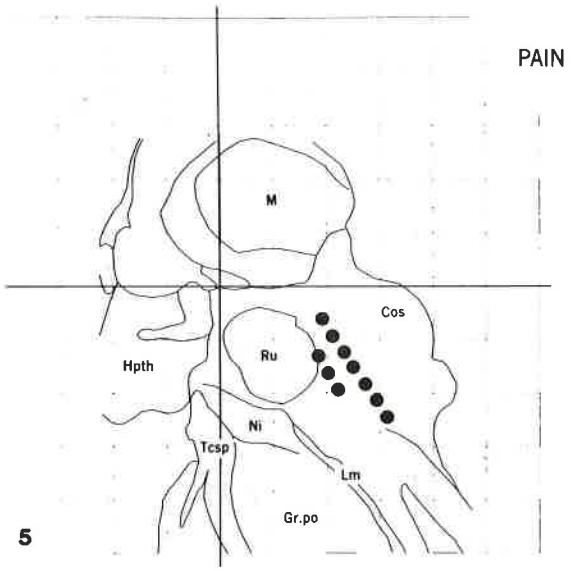
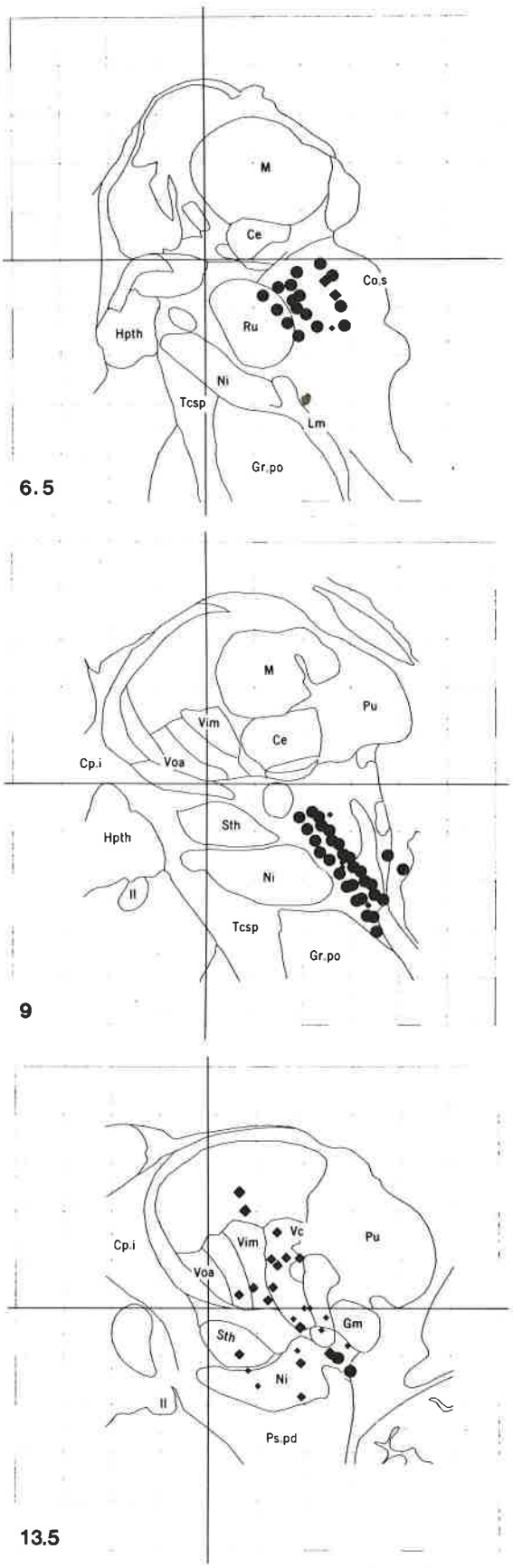


Fig. 57 As in Figure 50. Sites at which stimulation induced pain in the 5 mm sagittal plane. Filled circles indicate sites at which the pain resembled that from which the patient suffered. Filled diamonds (size proportional to threshold current) indicate sites at which pain was induced that was unlike that from which the patient suffered.

dom stimulated, and those with deafferentation pain and nociceptive pain caused by cancer in whom they were. The diagnoses responsible for the deafferentation pain in our patients were: brain stem vascular accidents 6, other brain stem lesions 2, lesions of the spinal cord 2, diabetic peripheral neuropathy 1, and iatrogenic trigeminal anaesthesia dolorosa 1. In all three groups, scattered burning and painful responses were found in more lateral planes intermingled with warm and cold responses. The bulk of burning and painful responses in the medial planes, however, occurred in the 12 patients with deafferentation pain, but not in the 13 with nociceptive pain, even though both groups were explored in the same manner. First, the likelihood of any somatosensory response at all beng elicited in planes medial to the 8 mm sagittal plane was four times greater in patients with deafferentation pain than it was in those with nociceptive pain. Then of the total of 162 burning sites recognised in our 198 patients, 74 arose in 9 of the 12 patients who suffered from deafferentation pain; only 18 occurred in the 13 with nociceptive pain, the rest being found at scattered sites in lateral planes in patients with dyskinesias. Of the 67 sites at which pain was elicited, 33 occurred in the 12 patients with deafferentation pain, only 8 in the 13 with nociceptive pain. The rest were found in patients with movement disorders. Now at all 33 sites at which patients with deafferentation pain reported that stimulation elicited the sensation of pain, that pain resembled, in quality and location, the pain from which the patient suffered. This phenomenon has not been observed in patients with nociceptive pain. Moreover, at a further 23 sites, all in patients with deafferentation pain, at which stimulation induced the sensation of burning, that burning also resembled the patient's discomfort. This phenomenon was never seen in patients with nociceptive pain either. Finally, out of a total of 56 sites at which stimulation induced a conscious



Figs 58–60 As in Figure 57. Locations of pain sites in the 6.5, 9 and 13.5 mm sagittal planes respectively.

effect resembling the patient's pain, all in patients with deafferentation pain, 54 were located in or medial to the 9 mm sagittal plane. The other two sites lay in the 13.5 mm sagittal plane.

Thus, in certain patients with deafferentation pain, and, in our experience, only in patients with deafferentation pain, the medial midbrain tegmentum appears to be unusually sensitive to electrical stimulation compared with patients with nociceptive pain explored in the same way, often giving rise to the sensation of burning or pain, referred, non-somatotopographically organised, to the opposite side of the body. Such stimulation-induced pain always, and the burning often, resembles the patient's discomfort. Similar observations have been reported by Nashold & Wilson (1966), who even demonstrated epileptic foci in the medial mesencephalic tegmentum of patients with deafferentation pain whose activity coincided with exacerbations of the patient's pain. Stereotactic lesions here relieved the pain. We have seen one such patient.

Now the 198 patients explored stereotactically upon which this review was based antedated our use of chronic brain stem stimulation for the control of chronic pain. Thus, although the medial mesencephalic tegmentum was frequently explored in the process of performing destructive lesions, the medial thalamus was not. Subsequently 11 patients with deafferentation pain have been explored in planes extending from the midline to the internal capsule 20 mm from the midline. The lesions responsible for the pain in these patients were: brain stem vascular accident 4, traumatic transection of spinal cord 3, unknown brain stem lesion 1, postcordotomy dysaesthesia 1, phantom limb pain 1, post traumatic trigeminal anaesthesia dolorosa 1.

The results of stimulation in the medial mesencephalic tegmentum in these 11 patients confirmed those described in our previous series of 198.

The new data from stimulating the *thalamus* medial to the 9 mm plane and the medial border of ventrocaudal nucleus showed that this area, comprising centrum medianum, medial thalamic lamina and parafascicular nucleus, resembled the medial mesencephalic tegmentum. For here it was also common to find clusters of burning or painful responses, often resembling the patient's own pain, in areas which were silent to stimulation in patients who did not suffer from deafferentation pain. Sano et al (1977) have reported similar findings. Figure 61 illustrates such responses in one of our patients explored in the 5 mm sagittal plane. In these medially-located thalamic and mesencephalic structures which are usually silent to stimulation, stimulation reproduced this patient's pain (sites marked PDO) caused by a brain stem vascular accident.

Denervation neuronal hypersensitivity as a possible cause of deafferentation pain

We have discussed possible mechanisms which could account for deafferentation pain. For many patients we must invoke a central process because of the failure of peripheral deafferenting procedures, or even neuraxis transection, to stop the pain. The clinical features of the pain, already described, taken with the results of brain stem stimulation, are consistent with denervation neuronal hypersensitivity as the underlying mechanism. Obviously, they may be consistent with other mechanisms as well and do not exclude the possibility of different processes at work in different patients. This process could be the central vicious cycle that Livingston (1943) talked about, set in motion by deafferentation and which, once established, persists despite elimination of the cause. As reviewed by Stavraky (1961) and proposed by many authors as the basis of deafferentation pain (Melzack & Loeser 1978), central neuronal denervation hypersensitivity could account for the time taken for pain to develop, its relationship to areas of sensory loss, its failure to be relieved by surgical denervation and its temporary relief by intravenous sodium thiopental, a barbiturate-like drug to which such neuronal hypersensitivity is known to be sensitive. The paradoxical relief by local anaesthetic blockade might be explained by Condouris's (1976) evidence that local anaesthetics function as central modulators of neural information.

There are many sites at which such denervation neuronal hypersensitivity might occur, both in the spinal cord and in the brain stem. It has been demonstrated experimentally in the spinal cord by Kennard (1953) and Loeser & Ward (1967), in the trigeminal nucleus by Black (1970) and Anderson et al (1971), in the lateral cuneate nucleus by Kjerulf & Loeser (1973) and Kjerulf et al (1973) as well as in the human spinal cord by Loeser et al (1968). Neuronal hypersensitivity at the dorsal horn or trigeminal level would account for the relief of deafferentation pain observed by Nashold & Ostdahl (1979) with destructive lesions of the dorsal root entry zone and by Hitchcock & Schvarcz (1972) and Schvarcz (1978) in the trigeminal nucleus. Though denervation neuronal hypersensitivity at the dorsal horn level must indeed be at work in certain patients, there are other patients in whom the pathophysiology must be more central, particularly those with distal pain not relieved by cordectomy. Our stereotactic stimulation data are consistent with the notion that medial mesencephalic tegmental and thalamic structures may become hypersensitive as a result of deafferentation, at least in those patients in whom stimulation reproduced their pain, possibly the reticulothalamic tract. One could postulate that this system, normally not sensitive to electrical stimulation, is activated by deafferentation till it responds to electrical stimulation, and presumably to normal traffic in the brain, to induce the feeling of burning or pain in the deafferented part of the body. But how does such a diffusely-organised system as the reticulothalamic tract achieve conscious awareness and spatial localisation so that sensory effects are perceived in a precise part of the contralateral body?

A review of published experience sheds further light on these questions (Tasker 1982b, Tasker et al 1980, Tasker et al 1982a). Though electrical stimulation of the human brain rarely elicits the sensation of pain; when it does, tegmentum and medial thalamus are not the only sites at which the phenomenon has been observed. In patients who suffered, according to published protocols, from deafferentation pain, the patient's pain has been reported reproduced or aggravated by electrical stimulation in Hassler's nucleus caudalia parvicellularis, thalamic radiations, and soma-

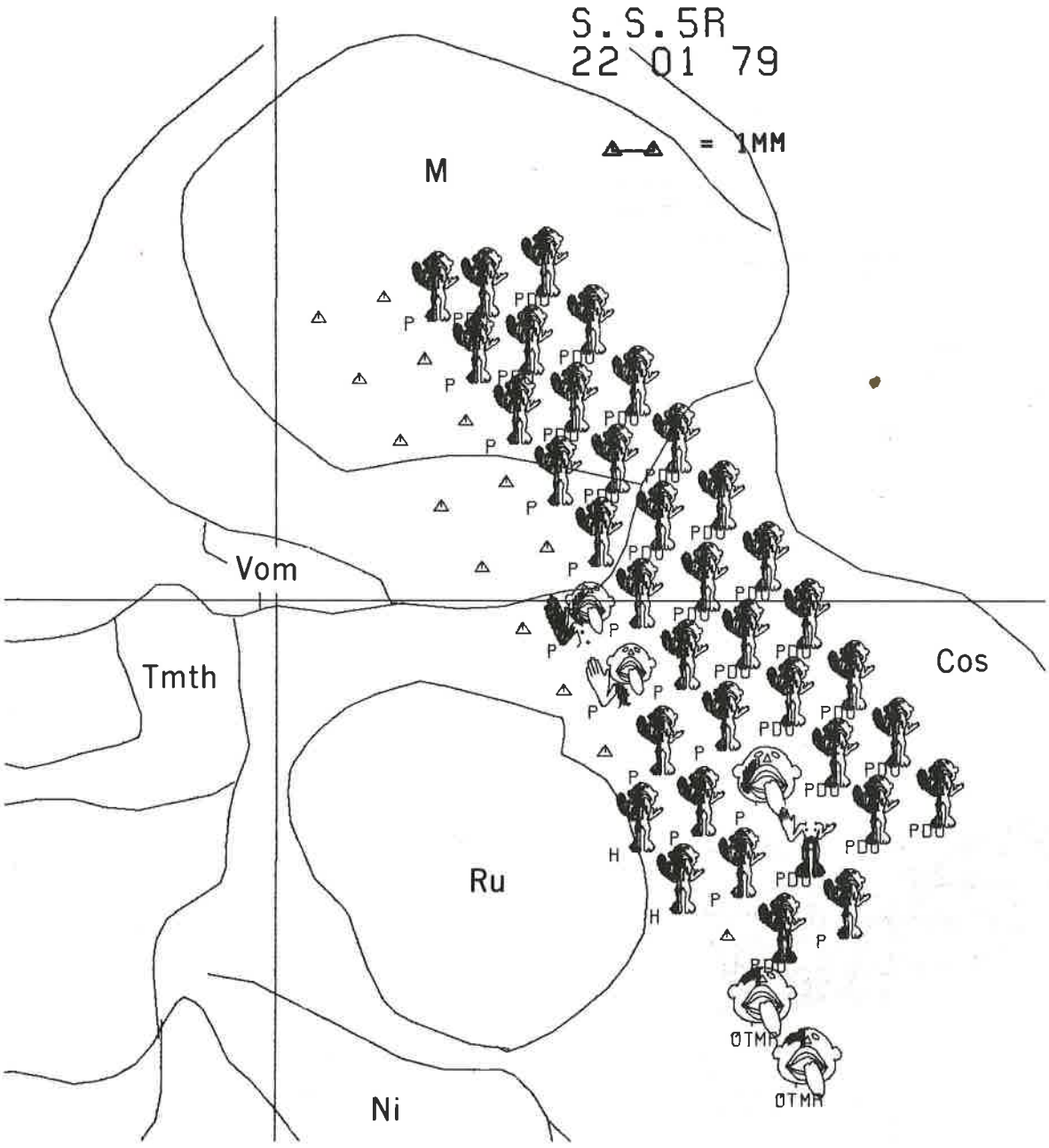


Fig. 61 Computer-generated figurine diagram of responses obtained by threshold electrical stimulation of the right brain stem in patient SS in the 5 mm sagittal plane. The figurine shading localises induced responses whose qualities are indicated by the symbols: P = paraesthetic; Do = pain; H = hot; OTMR = motor response plus an unspecified visual response. Triangles mark sites whose stimulation at 1.0 mA yielded no response. The scaling symbol at upper right marks 1 mm on the diagram. The horizontal line marks the intercommissural plane with a vertical through its centre. At each of the sites marked PDo, in medial thalamus and mesencephalic tegmentum, the patient's pain (caused by an infarct of the brain stem) was reproduced by the stimulation. (From Tasker et al 1982a, by kind permission of the publishers).

tosensory cortex. It has also been observed that when a a stimulating electrode is moved out of that portion of the sensory cortex somatotopographically related to the part of the body in which deafferentation pain is being experienced into an adjacent portion of somatosensory cortex representing a part of the body not affected by pain, a typical paraesthetic response referred to that non painful area replaces the reproduction of the patient's pain elicited at the previous site. These observations suggest the possibility that, in these patients with deafferentation pain, the activated medial brain stem structures gain access to the somatosensory cortex and thereby consciousness, and bodily localisation.

Now, if it is the reticulothalamic tract that is so activated by deafferentation that its stimulation in the brain stem gives rise to burning and painful responses, one might

expect similar effects in the spinal cord. Accordingly we reviewed the data collected in the course of 244 consecutive percutaneous cordotomies at the high cervical level using the lateral approach. For the entire series, consisting of 15 procedures in patients with deafferentation pain, 179 in patients with nociceptive pain, and 40 with mixed pain, threshold stimulation at 100 Hz in the lateral spinothalamic tract at sites where lesions produced contralateral dissociated sensory loss induced the contralateral sensation of warmth or cold at 94% of the sites, burning or painful sensations at 5%, paraesthetic effects at 1%. In 29 patients with deafferentation pain caused by lesions of peripheral nerves, roots or spinal cord, including the 15 in the above series, contralateral warm or cold effects occurred at only 38.25% of sites, burning at 24%, paraesthetic feelings at 13.75%. Reproduction of a patient's pain was not recorded, however. Thus there was a difference in the quality of response elicited by electrical stimulation of the spinothalamic tract in patients with deafferentation pain undergoing percutaneous cordotomy compared with the whole series of patients, most of whom suffered from nociceptive pain. This would be consistent with the notion that the sensitivity of neospinothalamic fibres had changed, perhaps through denervation neuronal hypersensitivity, or else that accompanying reticulothalamic fibres, relatively insensitive to stimulation in other patients, had become sensitive as a result of deafferentation, as they appeared to do in the mesencephalic tegmentum and medial thalamus, giving rise to the increased incidence of burning and painful sensations in the spinal cord. The increased number of contralateral paraesthetic effects are interesting, possibly representing dysaesthetic effects; such responses would not be detected amongst the numerous lemniscal paraesthetic responses in brain stem.

Thus, denervation neuronal hypersensitivity affecting the reticulothalamic system is a possible explanation for the clinical features of at least some cases of deafferentation pain.

In this regard the laboratory observations of Levitt & Levitt (1981) and Albe-Fessard & Lombard (1981) are of great interest. Levitt & Levitt studied the production of what they took to be deafferentation pain by lesions made in the spinal cord in various species of monkeys. Apart from the demonstrated predilection of stump tail macacques to develop pain compared with other species, they concluded that deafferentation pain, which took about a week to develop in their models, always resulted from a contralateral cord lesion that produced hypoalgesia, particularly section of the anterolateral column and hemisection, and that it was independent of the integrity of the dorsal columns. This pain was not altered when a second, extensive, surgical lesion was made in the cord approximately four segments proximal to the first. Neither proximal transection of the cord nor administration of morphine had any effect on the pain. They concluded that denervation neuronal hypersensitivity in dorsal horn neurons was not a likely cause of the pain in their monkeys, nor was the transmission of abnormal discharges over most of the recognised ascending tracts of the cord. Rather, they suggested that the pain resulted from abnormal activity in a somatotopically-organised brain structure such as ventrobasal complex.

The studies of Albe-Fessard & Lombard (1981) carry this thinking further. These authors found that rats developed pain after section of five consecutive brachial dorsal roots associated, first, with temporary epileptic-like hyperactivity in denervated dorsal horn neurons and, later, after this dorsal horn activity had faded, with similiar activity in ventrobasal thalamus and possibly other sites.

Now, our studies described above are consistent with implication of the reticulothalamic pathway in deafferentation pain; we had not noticed abnormal stimulation-induced effects in ventrobasal complex in our stereotactically-explored patients, though others have reported such findings and we have referred to similar observations made in thalamic radiations and somatosensory cortex (Tasker 1982b, Tasker et al 1980, Tasker et al 1982a, 1983).

Our original series of 198 patients explored stereotactically predated the use of chronic brain stem stimulation for the control of pain. Since most of them were operated upon for the relief of movement disorders, stimulation data in ventrobasal nucleus were biased towards the 14 mm sagittal plane. In the 11 patients with deafferentation pain previously mentioned who have subsequently been explored for the purpose of chronic brain stimulation much more complete data are available for ventrobasal nucleus. These were added to data from selected patients with deafferentation pain from our previous series of 198 in whom extensive stimulation data were also available. In all, 19 patients with deafferentation pain were studied. Eight suffered from vascular lesions of the brain stem, two from other brain stem lesions, three from traumatic section of spinal cord, two from other cord lesions, two from trigeminal anaesthesia dolorosa and one each from phantom pain and diabetic neuropathy.

The different types of somatosensory response elicited by stimulation were counted and separate tallies made for the responses elicited medial to the 8 mm sagittal plane, presumably medial to most spinothalamic and lemniscal responses, for the 8–9 mm sagittal planes, site of most neospinothalamic fibres, for the 10–12 mm sagittal planes containing most medial lemniscal fibres and for planes lateral to these, containing most of the ventrobasal nucleus. The data are presented in Table 3. A variety of responses occurs medial to the 8 mm sagittal plane, especially burning and painful effects with frequent reproduction of a patient's pain. Intermediate planes yield an increasing proportion of paraesthetic and 'temperature-coded' effects reflecting stimulation of medial lemniscus and spinothalamic tract. Lateral to the 12 mm plane, however, where responses arise chiefly in ventrobasal thalamus or internal capsule, 87.1% are paraesthetic in patients with deafferentation pain. Only 9.7% are burning or painful, with the burning resembling the patient's pain in 9.1%. Such responses were obtained in only three of the 19 patients with deafferentation pain.

Thus, unlike the medial brain stem, the ventrobasal thalamus in our patients with deafferentation pain was not prone to give rise to burning or painful responses and reproduction of the patient's pain, a phenomenon that might have been expected on the basis of the observations of Albe-Fessard and Lombard (1981), was much more rarely

Table 3 Somatosensory effects of brain stem stimulation in 19 patients with deafferentation pain — percentage of responses in each sagittal plane

Response	Sagittal plane stimulated, mm from midline			
	<8	8–9	10–12	>12
Paraesthetic	18.9	49.2	52.4	87.1
Hot, warm, cold	12.9	25.1	23.8	3.2
Burning, or pain unrelated to patient's pain	16.9	4.8	3.6	0.6
Burning resembling patient's pain	14.9	14.5	10.7	9.1
Pain resembling patient's pain	36.4	6.0	0	0
Other	0	0.4	9.5	0
Total responses in plane	201	248	84	154

elicited here than it was in medial brain stem. Rather, the results of threshold stimulation of the ventrobasal complex in this group of patients with deafferentation pain were what would be expected from stimulation of the normal lemniscal relay here. In 36 patients with involuntary movement disorders, 83% of somatosensory responses in these planes were paraesthetic.

Thus our human data are consistent with the notion that, at least in some patients, deafferentation pain is caused by denervation neuronal hypersensitivity affecting the reticulothalamic pathway, the conscious awareness of which activity, in the form of pain, together with bodily localisation, are achieved by projection upon somatosensory cortex.

THE USE OF CHRONIC STIMULATION FOR THE CONTROL OF DEAFFERENTATION PAIN

Since surgical deafferentation has proven so disappointing in the treatment of deafferentation pain, other therapy is urgently needed and much attention is being directed to the use of chronic stimulation, either of the dorsal cord or of the brain stem.

Acute stimulation of peripheral nerves (Wall & Sweet 1967) and chronic stimulation of peripheral nerves (Sweet & Wepsic 1968) and then of dorsal cord (Shealy et al 1970) were initially instituted in an attempt to put into practice the Gate Theory of Pain (Melzack & Wall 1965), suppressing pain transmission in small fibres through stimulation of large. After the pioneering work of Pool and his associates, of Heath & Mickle and of others before 1970, reviewed by Sweet (1977), chronic brain stimulation for pain relief was instituted by Mazars, at least as early as 1970, in the ventrobasal complex. Following the work of Reynolds (1969) chronic stimulation in the periventricular grey of man was instituted by Richardson (1976) in an attempt to block access of nociceptive impulses into the spinothalamic tract.

At first, stimulation techniques were applied indiscriminately to patients with various types of pain attributing success to manipulation of the entry of nociceptive impulses into the spinothalamic system. It was soon recognised, however, that at least in some instances deafferentation pain did not depend upon nociceptive transmission. Yet acute and chronic stimulation of peripheral nerves and chronic stimulation of dorsal cord had been shown capable from the first of sometimes ameliorating it; and indeed, chronic dorsal cord stimulation has become the treatment of choice for some types. Obviously some mechanism other than manipulation of nociceptive transmission in spinothalamic tract had to be considered. Ventrobasal thalamic or somatosensory capsular stimulation as the rostral extension of this dorsal cord stimulation, so effective in some patients with deafferentation pain, was spearheaded by Hosobuchi and Adams and their associates (Hosobuchi et al 1973) and Turnbull (1980). The current status of chronic stimulation of the brain for the treatment of chronic pain remains unclear, however. Experience reported at the Third World Congress on Pain in Edinburgh in 1981, while demonstrating consensus that chronic dorsal spinal stimulation is highly effective in certain patients with deafferentation pain, revealed no agreement that chronic periventricular stimulation, manipulating as it does the spinothalamic system, is selectively effective for nociceptive pain as one would expect, nor lemniscal-ventrobasal nuclear-sensory capsular stimulation for deafferentation pain.

In an attempt to identify those patients most likely to be relieved of deafferentation pain by chronic spinal stimulation, we undertook a study of 44 consecutive patients undergoing treatment with the Medtronics PISCES system (Tasker et al, 1983). We found, during one week's trial of percutaneous stimulation prior to internalisation, that pain was reduced in 67% of patients whose pain arose after lesions of peripheral nerves or roots but in only 33% of those with cord lesions. It was necessary for relief that the stimulator-induced paraesthesiae be felt where the pain was, an observation previously made by Larson et al (1974). Success was unrelated to the chronicity of the pain. There was correlation between successful pain relief and suppression of the events after 100 ms in the scalp potentials evoked from stimulation of either median nerve at the wrist, no matter where in the body the pain was felt. This suppression of scalp evoked potentials had been previously recorded by Blair et al (1975) and Larson and his group in man and by Grieshop et al in monkeys (Grieshop et al 1970). Strassburg et al (1979) have demonstrated the suppression of the late events of the scalp somatosensory potential evoked from median nerve by stimulation of medial lemniscus in man but enhancement with periaqueductal grey stimulation. The latter inhibited the early components. Gildenberg & Murthy (1980) demonstrated in two patients with deafferentation pain that dorsal cord stimulation suppressed the late events of the potential evoked in intralaminar nuclei by stimulation of median nerve on either side, whether the dorsal cord stimulation was applied above or below the somatotopic level of the median nerves. The isolated early events evoked in ventrocaudal nucleus were not altered. Augustinsson et al (1979), on the other hand, evoked early and late events in ventrocaudal nucleus of a patient with stump and phantom pain by peroneal nerve stimulation, the late components being suppressed by dorsal cord stimulation. In our patients, dorsal cord stimulation appeared to be more effective the smaller the dose of in-

travenous thiopental required to relief of the pain as well.

By what means does chronic spinal epidural stimulation exert its effect on deafferentation? And what, if any, is the significance of the suppression of late events in the somatosensory scalp evoked potential by chronic stimulation? Though local block was one suggested mechanism considered by Larson et al (1974), their observations in man and monkeys also suggested a central effect and local block was not supported by the observations of Lindblom & Meyerson (1975) that stimulation-induced pain relief considerably outlasted accompanying elevation of somatosensory thresholds. Some local or central inhibitory effect is more likely, possibly exerted upon denervated hypersensitive neurons, possibly transmitted over pathways other than those in the dorsal columns and one which is independent of the integrity of the anterolateral columns (Bantli et al 1975).

It is of interest that Nyquist & Greenhoot (1973) and Nishimoto et al (1980) in cats and Modesti & Waszak (1975) in man demonstrated suppression of firing of medial thalamic neurons by dorsal cord stimulation, Dong & Wagman (1976) the suppression of firing of posterior group thalamic neurons in cats by dorsal cord stimulation and Tsubokawa & Moriyasu (1975) the suppression of medial thalamic nociceptor firing in man by stimulation of ventrocaudal nucleus. The fascinating studies of Emmers (1981) exploring in rats the clearly patterned neuronal activity of medial thalamus and second somatosensory cortex which he associates with noxious stimulation and its response to cord lesions, opiates, barbiturates and to cord and brain stimulation will require integration into our thinking about these pain mechanisms.

The pathways responsible for the somatosensory evoked potential are unknown, apparently several cord systems contributing (Powers et al 1982). It is generally believed, however, that polysynaptic pathways support the late events which are known to be susceptible to suppression by barbiturates, probably involving small fibres which traverse the anterolateral quadrants (Powers et al 1982). These authors also review the laboratory evidence demonstrating loss of predominately later events of the evoked potential by peripheral nerve conditioning stimuli. Such observations are in keeping with the hypothesis that deafferentation pain is associated with denervation neuronal hypersensitivity of the reticulothalamic pathway which is in turn susceptible to suppression by therapeutic stimulation, which suppression is signalled by the concomitant suppression of the late events of the somatosensory scalp evoked potential. The greater likelihood of success in relieving deafferentation pain by chronic dorsal spinal stimulation when caused by peripheral rather than central lesions is capable of various explanations, possibly association of peripheral lesions with a preponderance of distal rather than central hypersensitive reticulothalamic neurons.

one or more modalities of sensation at any level in the peripheral or central nervous system. In some patients the deafferentation may be so incomplete that ordinary clinical testing discloses no sensory loss. The resulting pain is referred to all or part of the deafferented region of the body or to its periphery. With incomplete deafferentation, hyperpathia may also be present either within or immediately peripheral to the deafferented tissue.

Features that distinguish pain of the deafferentation type from nociceptive pain include its localisation to areas of sensory loss, its quality, usually dysaesthetic or causalgic, the delay sometimes observed between the time of neurological damage and the onset of pain, the likelihood of its being relieved by intravenous administration of sodium thiopental but not by narcotics, and the fact that surgical deafferentation proximal to the causative neurological lesion usually fails to relieve the pain even though local anaesthetic blockade at the same site usually does.

The underlying pathophysiology of deafferentation is unknown, different mechanisms possibly being at work in different patients. Genetic factors may explain why every patient with a given neurological lesion does not develop pain, and increasing age increases its incidence. Causative mechanisms suggested by laboratory studies include the initiation of nociceptive impulses at peripheral nerve injury sites which might explain why a quarter to a third of patients are relieved by proximal surgical deafferentation. A frequently proposed pathophysiological process is denervation neuronal hypersensitivity. Its appearance at the dorsal horn level has been demonstrated in animals and man and may account for the success both of destructive lesions of the dorsal horn and of chronic dorsal cord stimulation in relieving such pain. The manner of cephalad transmission of impulses so as to induce the perception of pain in instances of dorsal horn hyperactivity is unknown. The infrequent beneficial effect of cordotomy in deafferentation pain suggests that spinothalamic pathways are, at most, rarely involved. Dorsal horn hypersensitivity is most unlikely to be the cause of pain in patients whose pain is unrelieved after cordectomy. More proximal structures possibly implicated in denervation neuronal hypersensitivity include the dorsal column nuclei and ventrobasal thalamus, though our clinical physiological studies made during stereotactic procedures have not supported involvement of ventrobasal thalamus in man.

Rather, neurophysiological observations in the course of stereotactic operations and percutaneous cordotomy in man point to hypersensitivity in the anterolateral cord, medial mesencephalic tegmentum and medial thalamus as an underlying mechanism in deafferentation pain, possibly in reticulothalamic tract. Projection upon somatosensory cortex could give conscious somatotopic representation of the pain.

SUMMARY

In addition to that caused by acute or chronic activation of nociceptive pathways, pain can result from partial or complete interruption of afferent nervous pathways, affecting

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1.11

Endogenous pain control mechanisms

Howard L. Fields and Allan I. Basbaum

INTRODUCTION

Although the concept of a specific pain-control system is a recent development, as early as 1911 Head & Holmes explicitly postulated modulatory influences on pain. They proposed that the thalamus is the centre for the perception of pain and that the neocortex, the discriminative perception centre, continuously modulates the responses of the thalamus to noxious stimuli. According to this hypothesis, modulation of pain is a necessary part of the ongoing process of discriminative sensation.

Clear cut examples of centrifugal control of sensory transmission were subsequently described. Hagbarth & Kerr (1954) provided the first direct evidence that supraspinal brain sites could control ascending (presumably sensory) pathways, and Carpenter et al (1965) demonstrated descending control of sensory input to ascending pathways. However, the existence of a specific pain modulatory system was first clearly proposed in 1965 by Melzack & Wall in 'The Gate Control Theory of Pain'. Supraspinal influences on the 'Gate' were proposed in their model, but evidence for the existence of descending control was limited. In 1967, Wall reported that cells in lamina V of the dorsal horn of decerebrate cats are more responsive to noxious stimuli when the spinal cord is cold-blocked, thus showing that structures in a brain stem inhibit putative pain transmission cells in the spinal cord. The hypothesis that descending systems contribute to pain modulation was strongly supported by the discovery of the phenomenon of stimulation produced analgesia (SPA) (Reynolds 1969, Mayer & Liebeskind 1974). SPA is a highly specific suppression of pain related behaviour produced by electrical stimulation of certain discrete brain sites. During SPA, animals remain alert and active, and although their responses to most environmental stimuli are unchanged, responses to noxious stimuli such as orientation, vocalisation, escape and defecation are absent. Thus SPA is both powerful and highly selective. Electrical stimulation in analogous brain loci in patients with persistent pain produces a similar phenomenon: pain subsides with no other consistent changes. The specificity of the analgesic effect and the fact that it is consistently elicited from discrete homologous brain sites in a variety of species is powerful evidence for a specific pain modulating system.

A parallel and equally significant breakthrough in the study of pain modulating systems was the discovery of the endogenous opioid peptides (endorphins). This subject is covered in detail by Terenius in this volume. Suffice it to say here that, by a variety of techniques, endorphins have been demonstrated to be intimately associated with numerous regions involved in the control of pain. Furthermore, largely through the technique of immunocytochemistry, endorphins have served as a major key to further unravelling of the anatomy and physiology of the systems that modulate pain.

Although there are probably several CNS networks that modulate pain, we know most about one that has endorphin links (Fields 1981). This endorphin-mediated analgesia system (EMAS) has well-established components in the midbrain periaqueductal grey (PAG), the rostral ventromedial medulla (RVM) and the superficial layers of the dorsal horn. The PAG receives afferents from frontal cortex and hypothalamus, and projects to neurons in the rostral ventromedial medulla; RVM neurons in turn project to and control pain transmission neurons in the superficial dorsal horn. Both PAG and RVM contain opioid peptides and produce analgesia when stimulated. Thus pain modulation is subserved by a spatially extensive system. It is distributed along the entire neuraxis and includes neocortical, limbic, brain stem and spinal components (Fig. 66). Endogenous opioid peptides are also widely distributed and overlap extensively with many of the component nuclei of this pain-modulation system. Recently, attention has focused on the mechanisms of activation and the behavioural role of the EMAS. The system can be turned on by appropriate combinations of pain, stress and conditioning. Knowledge of this system's operation has provided considerable insight into the variability of the pain experience.

In the following discussion we will highlight anatomical, physiological and behavioural aspects of this system and will also briefly discuss pain-modulation by non-endorphinergic systems.

ENDOGENOUS OPIOID AGONISTS AND THEIR RECEPTORS

ENDORPHINS

The characterisation of CNS opiate binding sites stimulated an intense hunt for endogenous opiate ligands (which we

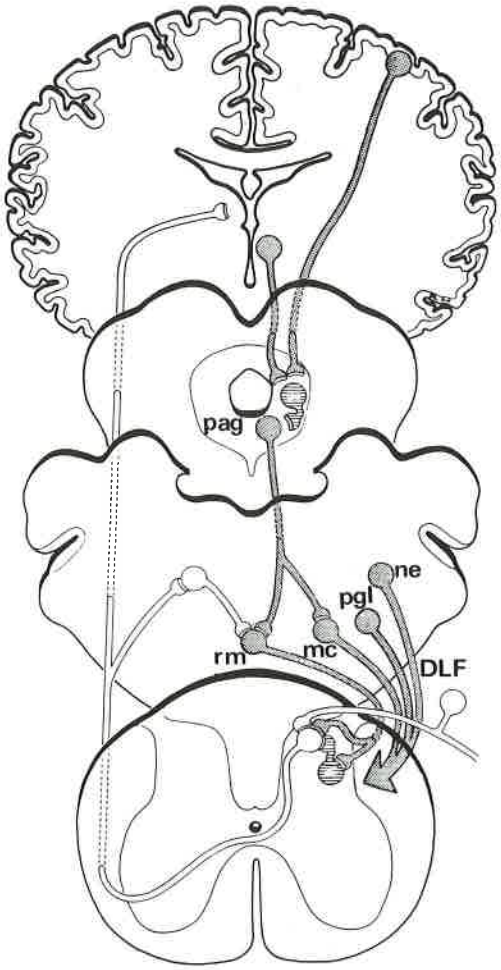

Fig. 66 Pain modulating network. Diagram of critical structures that contribute to control of pain-transmission neurons. The network includes connections from midbrain periaqueductal grey (pag) to medullary nucleus raphe magnus (rm)/recticularis magnocellularis (mc) and, via the dorsolateral funiculus (DLF), to the spinal cord dorsal horn. Additional bulbospinal pathways potentially relevant to analgesia arise from the nucleus paragigantocellularis (pgl) which also receives input from pag and the noradrenergic medullary cell groups (ne) lateral to pgl.

In addition to this brain stem to spinal cord network, connections from neocortex and hypothalamus to the PAG have recently been documented. Hypothalamic stimulation produces analgesia but the role of the cortex in pain modulation has not been elucidated.

At the spinal level descending pathways inhibit nociceptive projection neurons through direct connections as well as through interneurons in the superficial layers of the dorsal horn.

There is evidence that endorphin-containing interneurons (cross hatched) in PAG and dorsal horn play an active role in pain modulation (see text).

will refer to by the generic term endorphin). In 1975, Hughes and Kosterlitz and their colleagues isolated the first endorphins from the pig brain: the pentapeptides leucine(Leu)- and methionine(Met)-enkephalin(Enk). Since that discovery, several other endorphins have been characterised; most mimic narcotic analgesics in bio-assay and analgesia tests (Miller 1981). One of the most potent of the opioid peptides is ß-endorphin (BE), a 31-amino acid peptide, the N-terminal of which is identical to metenkephalin. More recently, two other endorphins with N-terminal

Table 8 Sequences of endogenous opioid peptides involved in pain modulation

Leucine-enkephalin	Tyr-Gly-Gly-Phe-Leu-OH
Methionine-enkephalin	Tyr-Gly-Gly-Phe-Met-OH
ß-endorphin	*Tyr-Gly-Gly-Phe-Met*-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Gly-Gln-OH
Dynorphin	*Tyr-Gly-Gly-Phe-Leu*-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Tyr-Asp-Asn-Gln-OH
α-neoendorphin	*Tyr-Gly-Gly-Phe-Leu*-Arg-Lys-Tyr-Pro-Lys

Leuenkephalin have been isolated: dynorphin, a 17-amino acid peptide, and the decapeptide α-neoendorphin (see Table 8) (Goldstein et al 1979, Weber 1981).

Peptide transmitters and hormones are not synthesised directly; they are derived by cleavage of larger, usually inactive, precursor polypeptides. While it was originally proposed that BE and dynorphin are precursors for Met- and Leu-enkephalin respectively, this is clearly not the case. Met- and Leu-enkephalin are derived from a common precursor, pro-enkephalin, each molecule of which generates multiple copies of Met-enkephalin and one of Leu-enkephalin (Comb et al 1982). Met- and Leu-enk are found throughout the neuraxis in numerous cell groups and, consistent with their having a common precursor, Leu- and Met-enk have been found to have completely overlapping distributions.

BE is cleaved from a large precursor, pro-opiomelanocortin, which also gives rise to ACTH, α-MSH and several other fragments whose biological function is unknown (Mains et al 1977). There is only one copy of BE in each pro-opiomelanocortin molecule. Most BE is derived from cells in the anterior and intermediate pituitary. Although the intermediate lobe contains more BE than the anterior lobe, much of the intermediate lobe BE is acetylated at its N-terminal or shortened at its C-terminal, modifications which block its analgesic potency. In addition to pituitary BE there are discrete populations of neurons in the hypothalamus which contain BE, α-MSH or both (Watson & Akil 1980). These neurons may have a role in pain modulation (see below). While BE is the only pro-opiomelanocortin cleavage product with known analgesic activity it is of interest that ACTH acts as a physiological *antagonist* of the analgesic effect of BE (Smock & Fields 1981).

Dynorphin and α-neoendorphin are cleaved together from still another precursor molecule. While some brain areas contain dynorphin, α-neoendorphin and Leu-and Met-enkephalin, considerable segregation of these two systems is present. For example, while dynorphin/α-neoendorphin are the predominant endorphins in the substantia nigra they overlap considerably with enkephalins in the dorsal horn and PAG.

In summary, there are at least three distinct populations of endorphin-containing cells. All presumably release peptides with opioid activity at their terminals but differ in their distribution within the brain.

OPIATE RECEPTOR

Prior to the characterisation of opiate binding sites in the brain, synthetic modification of the opiate molecule had produced compounds with a broad range of analgesic potency. Knowledge of structure–activity relationships, especially of the rank-order of potencies for a number of these opiate agonists, was used to establish that particular binding sites in brain were involved in opiate analgesia (Kosterlitz 1977). Thus it was determined that the opiate binding site relevant to analgesia is stereospecific and of high affinity.

It was subsequently demonstrated that brain membrane preparations show just such high-affinity, saturable, stereospecific binding sites for opiate agonists and antagonists. Moreover, among a group of narcotic analgesics there is a positive correlation between binding affinity and analgesic efficacy. Dextrorotary isomers of opiates neither bind with high affinity to these sites nor have any biological activity.

There is now evidence for at least two, and probably three, biologically significant binding sites. The two best characterised binding sites, 'mu' and 'delta', are defined primarily by differences in rank order of potency of various opioids to displace a high affinity labelled ligand from one or the other binding site (Chang & Cuatrecasas 1979). Available ligands show, at best, only relative specificity for μ or δ binding sites, and autoradiographic methods indicate that there is significant anatomical overlap of mu and delta binding sites (Herkenham & Pert 1980). It has in fact been suggested that the two binding sites are physically linked, i.e. that there is a single, two-site receptor (Vaught et al 1982, Lee & Smith 1980). Part of the solution of this problem of linkage of the two binding sites lies in the development of more specific μ and δ ligands. It could then be determined whether the location of the two binding sites is identical. Except for the demonstration that certain types of neuroblastoma cell cultures contain only δ binding sites, it has not been possible to show clearly that the two binding sites are totally separate.

If there are two binding sites and possibly two distinct receptors, are their functions different? There is evidence that μ ligands are potent in the production of analgesia. Whether the δ receptor is related to analgesia is more complex. Both potent analgesia and antagonism of opioid analgesia have been reported after intracerebroventricular administration of δ ligands. Tung & Yaksh (1982) have recently shown that in morphine tolerant rats, D-Ala-D-Leu-enkephalin (a relatively specific delta ligand) remains a potent analgesic. This suggests that both μ and δ sites are relevant to analgesia.

The existence of the κ receptor was originally proposed by Martin (1976) on the basis of distinct actions of the prototype κ agonist, ketocyclazocine. In the chronic spinal dog both morphine and ketocyclazocine produce miosis, depression of nociceptive reflexes and sedation, but only morphine causes hypothermia and bradycardia. With repeated administration, tolerance to both drugs occurs and all of these effects are blocked by the antagonists naltrexone and naloxone. However, when morphine-tolerant dogs are withdrawn from morphine, ketocyclazocine does not suppress the morphine abstinence syndrome indicating that the two drugs act at separate receptors. Further confirmation that the κ and μ receptors are distinct has recently been provided by studies demonstrating high affinity selective binding sites (Kosterlitz & Patterson 1980). Perhaps the most fascinating aspect of κ agonists is that they may have a distinctly higher analgesic potency on tests of nociception that use mechanical stimuli (Upton et al 1982, Tyers 1980). This contrasts with μ agonists which are more effective than κ agonists on tests employing noxious heat as the painful stimulus. This raises the possibility that pains arising from the activation of different classes of primary afferents would be susceptible to different drugs. Another possibility is that there are two or more endorphin-mediated pain modulation systems which are activated through different opiate receptors. Perhaps the multiple systems control different modalities of pain sensation or different types of responses to noxious stimulation. Support for this hypothesis comes from studies showing that κ agonists produce analgesia largely through a direct spinal action, whereas systemic morphine's (see below) effect on the spinal nociceptors has both a supraspinal and a spinal component (Wood et al 1981).

DESCENDING SYSTEMS FOR THE MODULATION OF PAIN

SITES AND CONNECTIONS

As mentioned above, one of the critical discoveries for understanding analgesia networks was that of stimulation-produced analgesia (SPA). The selectivity of SPA and the discrete location of brain stem sites from which it can be elicited support the concept that SPA is a manifestation of the action of an endogenous system that operates normally to modulate pain.

Shortly after SPA was discovered, two of its important features were established. First, that nociceptive cells in the spinal cord dorsal horn are selectively inhibited by stimulation at analgesia-producing brain stem sites (Guilbaud et al 1973). Second, that discrete lesions of the spinal cord dorsolateral funiculus (DLF) block the suppression of both spinal reflexes (e.g. tail flick) and more rostrally-organised responses (e.g. vocalisation) to noxious stimulation (Basbaum et al 1976). These observations demonstrated that there is a descending limb of the analgesia system. In fact, most of our knowledge of pain modulation concerns this descending system (Basbaum & Fields 1978, Mayer & Price 1976).

Figure 66 illustrates the major CNS structures which have been implicated in generating analgesia. The three most extensively studied regions are the mesodiencephalic periventricular and periaqueductal grey (PVG and PAG), the rostral ventromedial medulla (RVM) and the spinal cord.

Recent anatomical studies of the PAG emphasise that it is cytoarchitectonically and chemically heterogeneous, although it is not clear whether different subdivisions of the PAG differ in their contribution to analgesia.

Our original model depicted the PAG at the 'origin' of a descending pain-modulating circuit (Basbaum & Fields

1978). There are now considerable anatomical data on the inputs to the PAG. Some of these inputs may be critical for initiating the powerful descending control systems that act on spinal nociceptors. Consistent with studies demonstrating that it contributes to a variety of functions, the PAG receives its afferents from widely distributed sources. We will focus on inputs that appear to be relevant to analgesia.

The major source of afferents to the PAG is the hypothalamus (Beitz 1982). Electrical stimulation of certain hypothalamic regions produces analgesia and this effect may be mediated via the PAG. Since the fibres from the hypothalamus to the PAG have a periventricular course, they are probably stimulated by PAG/PVG electrodes and may contribute to SPA in human pain patients.

Other important inputs of PAG are derived from frontal granular and insular cortex (Hardy & Leichnetz 1981) and from the amygdala. Whether the cortical inputs to PAG have a role in analgesia is unknown. Analgesia can be elicited by stimulation of the amygdala, and lesions of the amygdala reportedly block some analgesic actions of systemically-administered opiates (Calvino et al 1982).

The major brain stem inputs to the PAG arise from the nucleus cuneiformis, the locus coeruleus and the pontomedullary reticular formation. The locus coeruleus is of interest since it is a major source of noradrenergic input to the PAG (see below). The PAG is also reciprocally connected to those structures of the rostral-ventromedial medulla which give rise to the bulk of descending pain-modulatory fibres. Finally, in addition to these supraspinal PAG afferents, there is a small but significant direct spinal input to PAG.

The rostral ventromedial medulla (RVM) includes the midline nucleus raphe magnus (NRM) and the adjacent reticular formation ventral to nucleus reticularis gigantocellularis. The RVM includes the n. reticularis magnocellularis (RMC) in the cat and the n. reticularis paragigantocellularis (RPG) in the rat. The PAG is the major input to this region and thus both PAG and RVM produce analgesia when subjected to electrical stimulation or to opiate microinjection. Furthermore, this direct input to the RVM from the PAG is excitatory (Fields & Anderson 1978). The transmitter(s) that mediate the PAG-induced excitation of NRM neurons are not known but recent studies have demonstrated that significant numbers of neurons that project to the RVM contain neurotensin (Beitz 1982). Furthermore, intracisternally-administered neurotensin produces potent analgesia (Clineschmidt 1979). Although the PAG contains a large number of enkephalin and substance P neurons (Hökfelt et al 1977a, b, Moss et al 1983) these neurons apparently do not project to the RVM (Prichard & Beitz 1981).

In addition to the major input from the PAG and the posterior hypothalamus, the RVM receives a significant input from 5HT-containing neurons of the midbrain (B8 and B9, Beitz 1982). Direct spinal projections to RVM are sparse but RVM does receive a projection from the adjacent medullary nucleus reticularis gigantocellularis which in turn receives a large projection from nociceptive spinoreticular neurons.

The RVM is the major brain stem source of axons which project to the spinal cord via the DLF and are relevant to analgesia. The terminals of these descending axons are most dense in the superficial layers of the dorsal horn, in just those regions where small-diameter primary afferents terminate and where there are large numbers of nociceptive dorsal horn neurons (Basbaum et al 1978). Stimulation of the RVM selectively inhibits dorsal horn neurons responding maximally to noxious stimulation and this inhibition is blocked by DLF lesions (Fields et al 1977, Willis et al 1977). Since there are few direct PAG-spinal projections, it is likely that the descending pain-modulating action of the PAG is relayed through the RVM. This is supported by the observation that lesions of, or local anaesthetic injections into, RVM abolish the analgesia produced by stimulation of PAG (Behbehani & Fields 1979).

In summary, there is a pathway that extends from frontal cortex and hypothalamus through the PAG to the RVM and then to the superficial layers of the dorsal horn via the DLF. Activation of this system by opiates or electrical stimulation produces a selective suppression of nociceptive dorsal horn neurons and consequent analgesia.

DISTRIBUTION OF TRANSMITTERS AND THEIR ROLE IN DESCENDING PAIN-MODULATION

Many component neurons of the pain modulation system are located in regions rich in either peptides or biogenic amine transmitters or both. In this section we will discuss the evidence implicating peptides and biogenic amines in the function of the pain modulation system.

1. Endorphins (see Table 9)

a) Periaqueductal Grey (PAG)

Both electrical stimulation of, and opiate microinjection into, the PAG produce profound analgesia. Within the PAG there is a high density of opiate binding sites and immunocytochemistry reveals that several species of endorphins are present there in significant quantities. Endorphins present in the PAG include enkephalin, ß-endorphin (BE) and dynorphin/α-neoendorphin. Unlike BE, which derives exclusively from cells in the hypothalamus, enkephalin and dynorphin cell bodies are located in PAG. Analgesia-producing stimulation of the nearby hypothalamic periventricular grey in humans raises the concentration of immunoreactive BE in the CSF (Hosobuchi et al 1979). It seems likely that the release of endorphins from their terminals in the PAG is a critical step in eliciting analgesia.

b) Rostral ventromedial medulla (RVM)

Many RVM neurons contain enkephalin and the region has enkephalin-containing terminal fields. Although there has been no report of high opiate receptor density in RVM, micro-injection of opiates in RVM produces potent analgesia. In fact, this region may be the most sensitive site for opiate micro-injection (Azami et al 1982, Takagi et al 1977). As mentioned above, RVM receives afferents from 5HT and neurotensin-containing midbrain neurons.

Table 9 Endorphins and analgesia: anatomical relationships (after Fields 1981b)

Anatomical Site	ß-endorphin, enkephalin or dynorphin/∝ neoendorphin	Opiate receptor	Opiate microinjection analgesia	Stimulation produced analgesia	Local naloxone blocks analgesia
Amygdala	+	+	+(1)	+	?
Periventricular diencephalon	+	+	+	+	?
Periaqueductal grey	+	+	+	+	+
N. raphe magnus	+	o	+	+	+
N. reticularis paragigantocellularis	+	o	+	+	+
Dorsal horn	+	+	+	o	+

+ = present
o = not demonstrated, or very low
? = unknown
(1) Rodgers R J 1977 Pharmacology Biochemistry and Behaviour 6: 385–390

c) Superficial dorsal horn

Both enkephalins and dynorphin/α-neoendorphin terminals and cells are present, as are dense concentrations of opiate receptor (Glazer & Basbaum 1981). Local application of a variety of opiates (either μ or κ agonists) leads to analgesia (see below).

It is clear that the endorphins are closely associated with the analgesia system at several levels, and, given the naloxone sensitivity of this system, the endorphins must be critical to its operation. The cellular mechanism of action of opiates is not known. Opiates generally exert inhibitory actions on CNS neurons. On the other hand, electrical stimulation is presumably excitatory. Since both opiate micro-injection and electrical stimulation produce analgesia when applied to either PAG or RVM, the endorphins may act, as in the hippocampus, by inhibiting inhibitory interneurons thus disinhibiting the effect neurons in these analgesia-producing regions.

2. Biogenic amines (Basbaum et al 1982)

Brain stem neurons that project to the cord via the DLF include many that arise in nuclei rich in biogenic amines. In fact, the superficial layers of the dorsal horn are rich in both norepinephrine (NE) and serotonin (5HT), which are largely, if not totally, derived from the brain stem.

While numerous medullary loci contribute axons to the DLF and may relay PAG inhibitory influences, most attention has focused on bulbospinal serotonergic projections.

The analgesic action of systemic opiates can be blocked by depletion of 5HT by inhibiting its synthesis (Tenen 1968), neurotoxic destruction of spinal 5HT terminals with 5–7 dihydroxytryptamine (Vogt, 1974) or lesions of medullary 5HT cells. The analgesia produced by intracerebral morphine can be blocked by intrathecal methysergide, a serotonin antagonist, in combination with the α-adrenergic antagonist phentolamine (Yaksh 1979). Iontophoresis of 5HT inhibits the response of dorsal horn neurons to noxious stimulation (Headley et al 1978, Randic & Yu 1976, Jordan et al 1979) and when 5HT is applied directly to the spinal cord it produces analgesia. Furthermore, drugs that block 5HT reuptake are effective analgesics in animals and man (Fields 1980).

The contribution of norepinephrine (NE) to analgesia is much more complicated and controversial. First, the association of NE neurons with analgesia-producing CNS sites is not as definite as for 5HT. Second, pharmacological studies of NE effects have been contradictory. NE can antagonize or enhance morphine analgesia depending on where it is injected. When phentolamine is injected into the lumbar intrathecal space with methysergide, morphine analgesia is blocked. This is consistent with the potent analgesia produced by lumbar intrathecal NE, and with the profound inhibitory action of NE on spinal nociceptive interneurons (Headley et al 1978). On the other hand, phentolamine, when micro-injected into the NRM, produces analgesia, indicating that, at the level of the medulla, NE acts to inhibit the analgesia system (Hammond et al 1980).

The anatomical basis for these contrasting NE actions is unclear. NE terminals are present in both the NRM and in the superficial layers of the dorsal horn. While earlier studies implicated the locus coeruleus as a source of NE terminals in NRM, these terminals are now believed to arise mainly from the A1, A3 or A5 cell groups of the medulla (Takagi et al 1981). The source of the descending axons giving rise to spinal NE terminals that 'produce' analgesia is not known.

Thus, although there is still controversy, there appear to be separate descending NE and 5HT pathways from brain stem to spinal cord via the DLF. The blockade of opiate analgesia after DLF lesions could reflect damage to either or to both systems.

Recent studies further emphasise the multiplicity of transmitters involved in bulbospinal modulatory systems. First, not only are there multiple brain stem sources of axons in the DLF, but within the RVM there are cells with different transmitters. For example, there are neurons in RVM which contain 5HT, substance P, enkephalin, thyrotropin releasing hormone or almost any combination of the four. Furthermore, 5HT, substance P and enkephalin are present in RVM cells that project to the spinal cord (Bowker et al 1981; Gilbert et al 1982). This multiplicity of transmitters in apparently parallel descending neurons presents

methodological problems for functional analysis. The use of any single pharmacologic antagonist will be insufficient to block completely analgesia evoked by electrical stimulation of the region.

In addition to providing separate pathways to the spinal cord these parallel systems also interact at the brain stem and spinal level. For example, just lateral to the NRM, there is a non-5HT cell group (RPG in rat or RMC in cat) which receives a projection from the PAG, projects to the cord via the DLF and inhibits spinal nociceptors. RPG is exquisitely sensitive to opiate micro-injection and the resultant analgesia from RPG is blocked by noradrenergic antagonists (Satoh et al 1980). While Azami et al (1982) confirmed that RPG and NRM analgesia are mediated by NE and 5HT respectively, thus suggesting parallel and independent pathways to the cord, they also demonstrated that lesions of NRM block the analgesia elicited from RPG. This indicates that at least part of the RPG analgesia is mediated via NRM.

The situation is further complicated by the presence of another group of 5HT-containing neurons in the nucleus reticularis paragigantocellularis lateralis (RPGL) located lateral to RPG/RMC. RPGL also receives a direct projection from PAG and projects via the DLF to the cord. It also contains Enk neurons, NE neurons (probably in A3) and some neurons in which Enk and 5HT coexist. Some of the Enk neurons in PGL project to the spinal cord (Hökfelt et al 1979).

DORSAL HORN CIRCUITRY RELEVANT TO ANALGESIA

To understand the neural mechanisms through which the medullospinal systems control the transmission of nociceptive messages, a detailed map of the circuitry in the dorsal horn is required. Immunohistochemical and intracellular electrophysiological characterisation of dorsal horn neurons have contributed greatly to developing an adequate pharmacological and anatomical circuit diagram (Basbaum et al 1983). Our discussion will focus on the superficial dorsal horn: lamina I (the marginal zone) and lamina II (the substantia gelatinosa, SG) (Fig. 67). Since the dorsally-directed dendrites of second-order nociceptive neurons in deeper layers of the dorsal horn (e.g. wide-dynamic range lamina V cells) are also influenced in the SG, the discussion may be applicable to these nociceptors as well.

Small diameter primary afferents, including all classes of primary nociceptors, terminate densely in lamina I and in the SG. Nociceptive and non-nociceptive small diameter afferents project to the outer (IIo) and inner (IIi) layers of the SG respectively. Consistent with this differential projection, neurons of the inner SG respond to innocuous mechanical stimulation.

While a variety of cell types are found in the superficial dorsal horn, a few predominate (Gobel 1978). The marginal layer consists of large fusiform 'Waldeyer' neurons and numerous smaller cells. Many marginal neurons are projection neurons: in fact lamina I in primate is the largest source of spinothalamic tract axons. Two classes of neuron, stalk cells and islet cells, predominate in the SG. The stalk cell body is located at the I–II border and its dendrites arborise ventrally. Some stalk cell dendrites penetrate to layers III and IV. Since the dendrites of stalk cells span the inner and outer SG, they receive both nociceptive (in IIo) and non-nociceptive (in IIi) primary afferent input. Consistent with this, stalk cells in outer SG some of which have been identified by combined intracellular recording and staining, respond to both noxious and non-noxious input (Bennett et al 1979). Since neurons in IIo are activated at

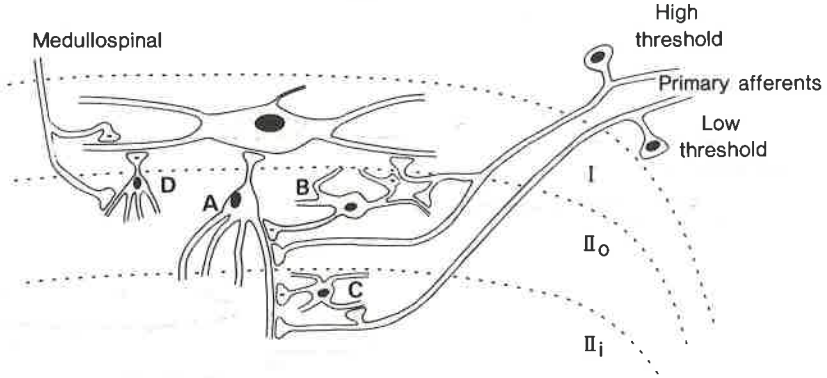

Fig. 67 Local circuitry in the superficial dorsal horn. Schematic illustration of afferent terminals and local circuitry within the superficial dorsal horn of the spinal cord. Nociceptive inputs, transmitted via high threshold, primary afferent fibres, excite the nociceptive projection neurons of the marginal zone, lamina I. The same afferents excite dendrites of stalk cell excitatory interneurons (A) and inhibitory islet interneurons (B) of lamina IIo. The stalk cell input results in further excitatory drive on to marginal projection neurons; the input to the islet cell interneuron (B) in lamina IIo provides a circuit that generates an inhibitory, feedforward control of marginal neurons by nociceptive inputs.

Low-threshold primary afferent fibres provide a non-nociceptive input to marginal neurons via their excitatory connections with dendrites of stalk cells (A) in lamina IIi. In contrast, the non-nociceptive input to islet cell interneurons of lamina IIi (C) may contribute to the inhibitory control of nociceptive marginal neurons.

The schematic also illustrates some possible descending control mechanisms. These may be exerted directly upon dorsal horn projection neurons. Alternatively, descending bulbospinal axons (some of which are 5HT containing), may excite inhibitory interneurons (e.g. enkephalin-containing stalk (D) or islet cells), which in turn postsynaptically control the nociceptive projection neurons. Another possibility, not illustrated, is that the descending systems inhibit the excitatory stalk cell (A).

shorter latency than overlying lamina I cells, and since stalk cell axons project to lamina I it has been suggested that stalk cells are interneurons that relay inputs from primary afferents to marginal neurons. Direct primary afferent connections to lamina I cells also exist, but these constitute a relatively small percentage of the total marginal cell input (Ralston & Ralston 1979).

While a few enkephalin neurons with stalk cell morphology have been described, the transmitter contained in most stalk cells is unknown. They may contain any of a number of peptides that have been found in neurons of the superficial dorsal horn.

The islet cell is a small, fusiform neuron of the superficial dorsal horn. Unlike the stalk cell, islet cell dendrites arborise longitudinally within the layer where the soma is located, either IIo or IIi, and its axon arborises within the domain of its dendritic tree. Islet cells provide a major input to primary afferents. Thus, both axo-axonic and dendroaxonic islet cell connections to primary afferent terminals have been described. On morphological grounds, it has been proposed that some islet cells contain GABA while others contain enkephalin or neurotensin (Hunt et al 1981). Although there is no direct evidence for it, the islet cell is the best candidate for the inhibitory interneuron which controls second-order nociceptive transmission (either pre- or postsynaptically).

Although the mechanism of action of opioid neurons in the cord is unclear, the evidence is compelling that enkephalin-containing interneurons in the superficial dorsal horn play an important role in pain modulation. Lumbar intrathecal injection of opiates produces profound analgesia in animals (Yaksh & Rudy 1976) and man (Wang et al 1979) and spinal naloxone blocks the effect of descending pain-modulation circuits. Since iontophoresis of opiate agonists into the SG selectively inhibits nociceptive responses of dorsal horn cells (Duggan et al 1976), it is possible that opiates act at a site presynaptic to dorsal horn nociceptive neurons. In fact, since primary afferent fibres are laden with opiate binding sites and since biochemical studies indicate that opiates inhibit the release of the peptide substance P (a putative primary afferent nociceptor transmitter) it has been proposed that opioid-containing interneurons presynaptically control primary afferents (Jessell & Iversen 1977). Other studies are consistent with a hyperpolarising action of opiates on C fibres (Carstens et al 1979, Hentall & Fields 1979). Unfortunately, ultrastructural studies have failed to demonstrate enkephalin-containing profiles making synaptic contact with primary afferent terminals (Glazer & Basbaum 1983). The most common arrangement is axodendritic, with enkephalin located presynaptically. This indicates that enkephalin interneurons exert a predominantly postsynaptic control of nociceptive projection neurons. In fact, enkephalin-containing terminals synapsing on identified spinothalamic neurons have been reported (Ruda 1982). At present the biological significance of the dense concentration of opiate binding sites on the primary afferents is unknown. Conceivably, a 'hormonal-like' nonsynaptic interaction exists. Alternatively, an endorphin other than enkephalin, e.g. dynorphin or α-neoendorphin, may provide synaptic input to primary afferent fibres.

While we have emphasised the segmental input to SG interneurons, supraspinal inputs feed into the same circuitry. The fact that intraspinal injection of naloxone reverses the analgesia produced by either RVM stimulation (Zorman et al 1981) or brain stem morphine injection (Levine et al 1981) is consistent with a medullary connection to opioid-releasing interneurons in the cord. Anatomical studies have also demonstrated synaptic connections from 5HT axons to enkephalin neurons in laminae I and II (Basbaum et al 1982). It should be emphasised that these inputs to spinal enkephalin-containing neurons are not the only connections through which segmental and descending influences operate to control sensory transmission in the dorsal horn. In fact, the large number of peptides present in neurons of the superficial dorsal horn makes it certain that a variety of transmitters modulate sensory transmission. Although enkephalin-containing dorsal horn neurons are involved in the control of pain-transmission, the control of pain-transmission, the contribution of the numerous other peptides is largely unknown.

PHYSIOLOGICAL ACTIVATION OF THE ENDORPHIN-MEDIATED ANALGESIA SYSTEM (EMAS)

We have described studies on the anatomy and physiology of specific modulatory systems for pain. Our information on the normal function of these systems is less certain. For example, we are not certain when these analgesia systems are called into play, nor to what extent they alter pain behaviour in awake animals.

Different approaches have been taken to address these questions; one is to characterise those stimuli which activate brain stem pain-modulating neurons; another is to search for manipulations that generate analgesia and either to look for endorphin release or to try, by making lesions and/or by using specific antagonist drugs, to discover what neural systems are involved.

The first approach has yielded quite consistent results. The majority of neurons in either PAG or RVM are activated by noxious stimuli, though a significant minority are inhibited by those same stimuli. Some PAG cells also increase their discharge with cortical arousal (Mayer 1982), suggesting perhaps that attentional as well as sensory factors control EMAS. Of the RVM cells which can be physiologically identified as projecting to the spinal cord, the majority are excited by electrical stimulation of the PAG and by noxious stimulation. The peripheral receptive fields of raphe-spinal neurons are very large, frequently including the entire body. In the cat, both noxious stimuli and light tapping of the skin consistently excite many raphe spinal cells (Fields & Anderson 1978).

Recently we have recorded from cells in RVM while monitoring the tail-flick reflex produced by noxious heat. In addition, we used microstimulation through the recording electrodes to map low-threshold sites for stimulation produced analgesia (SPA). Using this approach we found two classes of cell in low threshold SPA sites; those which discharge just prior or the occurrence of a tail-flick (on-cells) and those which shut off just prior to a tail-flick

occurrence (off-cells). On-cells are consistently excited by noxious stimuli over a large part of the body. Most off-cells are inhibited by noxious stimuli.

The fact that cells in RVM are most consistently affected by noxious stimuli suggests that a major element in the analgesia system is a negative feedback loop for nociception, i.e. noxious stimuli activate the system and it in turn suppresses pain transmission (Fig. 68). This hypothesis leads to some testable predictions: first, since pain-modulating cells can be activated consistently by noxious stimuli presented over most of the body surface, it follows that pains in different parts of the body should 'inhibit' each other. In fact, acupuncture and many other traditional pain therapies based on counter-irritation may work in this manner. Thus biting your lip, banging your head against the wall, mustard plasters, cupping, moxibustion, trephination and other manipulations would be expected to at least partially and temporarily relieve pain anywhere in the body. Another prediction is that, if the pain feedback system has enkephalinergic links, noxious stimuli should cause enkephalin release. In fact, release of enkephalin-like immunoreactivity is induced by noxious stimulation (Yaksh & Elde 1981, Cesselin et al 1982). A third prediction is that, if the analgesia system were blocked, nociceptive transmission would increase. In fact, naloxone does shorten the latency of nociceptor-induced reflexes such as the jump off a hot plate. It is of interest that the naloxone effect is best demonstrated when the baseline latency is relatively long (Jacob et al 1974). When the hot plate temperature is high, baseline latencies are short and there is no naloxone effect; when the baseline latency is long, naloxone produces a marked reduction of it (i.e. hyperalgesia). Similarly, in humans, naloxone has little effect on relatively brief experimental pains but significantly increases the reported intensity of more prolonged clinical pains such as dental postoperative pain (Levine et al 1979).

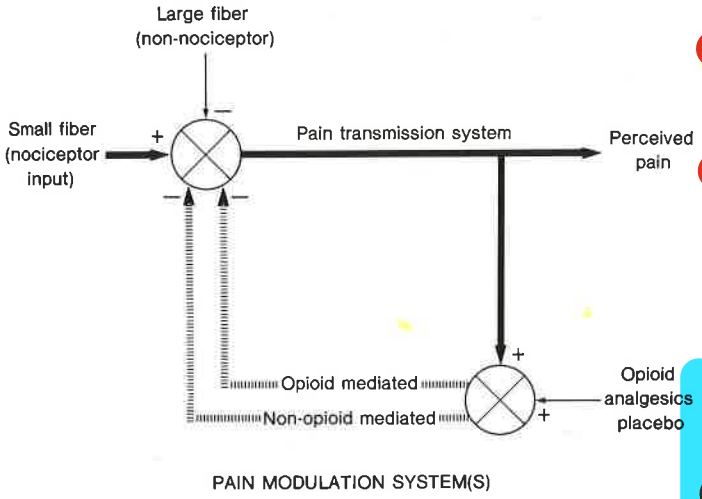

Fig. 68 Schematic diagram of systems concerned with pain. Nociceptor input activates the pain-transmission system. The pain-transmission system activates a negative feedback loop (pain-modulation system) whose action can also be enhanced by narcotic analgesics or other physiological stimuli (see text). There are both opioid and nonopioid components of this feedback loop. In addition to the feedback loop, pain input can be modulated by simultaneous input from non-nociceptive primary efferents. (Fields & Levine 1982 Pain: a clinical approach based on physiological principles. In: Isselbacher K J et al (eds) Harrison's Principles of Internal Medicine, Update II. McGraw-Hill, New York, pp 205).

The long latency required for activation of the endorphin mediated analgesia system (EMAS) is also apparent in certain animal studies. For example, Lewis et al (1980) showed that the 'analgesia' produced in rats by 3 minutes of foot shock is not naloxone-reversible whereas that produced by 30 minutes of foot shock is. Thus, although analgesia can be produced quite rapidly by shocking a rat's foot, naloxone blockade of analgesia can only be demonstrated after prolonged stimulation.

Lewis's study illustrates several important points. First, not all analgesic actions of the CNS are mediated by endorphins. Second, under certain conditions pain duration (or stress) instead of, or in addition to, pain intensity, is an important factor in activating pain-modulating systems. Third, activation of different analgesia-producing networks involves complex environmental, attentional and conditioning factors that may make straightforward pharmacological studies difficult to interpret.

Studies of stress-induced analgesia further illustrate these points. While a variety of stressful manipulations produce analgesia, different stressors activate different central pathways. Using several tests to evaluate analgesia, Hayes et al (1978) showed that naloxone had no effect on the analgesias produced by brief footshock, by intraperitoneally-injected hypertonic saline or by high-speed centrifugal rotation. In contrast, the analgesia produced by all of these manipulations was abolished by spinal cord transection. Watkins & Mayer (1982) used the tail-flick test to compare the analgesic effect of forepaw shock versus that of hindpaw shock. Both types of shock produce profound analgesia; and the analgesic effects of both are significantly reduced by DLF lesions. However, whereas hindpaw-shock-induced analgesia is blocked by naloxone and is reduced in morphine-tolerant rats, forepaw-shock analgesia is unaffected by these manipulations.

Analgesia can be conditioned by pairing an innocuous stimulus (e.g. light or tone) with an analgesia-producing stressor such as foot shock. After several sessions, analgesia is produced by the conditioning stimulus alone. The conditioned analgesia is blocked by DLF lesions, naloxone, NRM lesions and morphine tolerance (Watkins & Mayer 1982).

Maier and his colleagues (1982) offer an alternative interpretation of stress-induced analgesia. They propose that activation of the endorphin-mediated analgesia system is associated with learned helplessness. The latter refers to situations where animals effectively 'give up' when they cannot avoid a stimulus that is unpleasant. Many of the stressors used to produce analgesia (including for example, 30 minutes of inescapable shock) would be expected to provoke learned helplessness. Their hypothesis is that not only the intensity and duration of the shock, but also its controllability by the animal, is a major factor that determines whether endorphin-mediated analgesia systems are activated. They provided experimental support for this hypothesis. Identical stimuli were delivered through subcutaneous stimulating electrodes to yoked groups of rats;

only one of the rats in each group could terminate the shock by actively turning a wheel. Although all rats in a group received exactly the same shocks, only the rats who could not control the shocks developed significant naloxone-reversible analgesia. Thus, stress, fear or hopelessness, pain intensity and duration are all important factors for activation of EMAS. If several different analgesia systems exist, each with its own criteria for activation, a very careful approach would be needed to dissect out the role of each particular pain-modulating system.

SUMMARY AND CLINICAL IMPLICATIONS

The existence of neural networks that are specific for the modulation of pain has been established by anatomical, physiological, pharmacological, behavioural and clinical studies. We have concentrated on an endorphin-mediated pain-modulating network which extends from cortex to spinal cord and has major links in the hypothalamus, mid-brain and medulla. Significant concentrations of endorphin-containing cells and terminals are located in the hypothalamic, brain stem and spinal components of this system. High concentrations of several endorphin species are also found in the pituitary and adrenal medulla; however, the contribution of these peripherally-derived endorphins to analgesia has not been established.

Electrical stimulation of, or local micro-injection of either opiates or opioid peptides into, many CNS sites produces profound analgesia. Systemically-administered narcotics (e.g. morphine) are thought to act by mimicking endorphins' synaptic actions at several loci within the pain-control network. The endorphin-mediated analgesia system can be 'physiologically' activated by prolonged noxious stimulation or by exposing animals to a variety of stressful stimuli. Moreover, a naloxone-sensitive analgesic effect can also be elicited using classical conditioning paradigms which pair an innocuous conditioned stimulus (e.g. tone) with a stressful unconditioned stimulus (e.g. prolonged foot shock). While parallel pain modulating pathways without endorphin links also exist, their underlying pharmacology is unknown.

A more complete understanding of the pain experience requires knowledge of both transmission and modulation systems. This is also true for developing optimal pain therapy. While the discovery of endorphins has not yet led to the development of clinically useful drugs, the demonstration of opiate receptors in the dorsal horn has led to the use of spinal intrathecal and epidural morphine and pethidine for pain control. Conceivably, a more detailed analysis of the different analgesic effects of mu, kappa and delta opioid ligands could lead to better pain control.

One intriguing approach to pain management is to manipulate CNS endorphin levels by administering inhibitors of enzymes that degrade enkephalins. There are reports that such enzyme inhibitors produce a naloxone-sensitive analgesia (Ehrenpreis et al 1979). Another promising and potentially important approach is the development of potent non-opiate analgesic drugs that enhance the action of non-endorphin component neurons of descending control systems. For example, amitriptyline (a 5HT uptake inhibitor) is a clinically effective non-narcotic pain-relieving drug. Similarly tryptophan, presumably by building up 5HT stores in the CNS, has been shown to minimise tolerance to the analgesia produced by repeated electrical brain stimulation.

In addition to pharmacological and surgical management of clinical pain, it may be possible to trigger pain-modulating systems by psychological or physical methods. In certain situations, acupuncture or transcutaneous electrical stimulation can relieve pain. Suggestion, in the form of either hypnosis or placebo therapy can also be remarkably effective, even for severe clinical pains. As our knowledge of the sensory and psychological factors that activate pain-modulatory neurons increases, the tools for pain-management can be refined and extended. Thus future research on pain-modulating systems holds promise, not only for greater understanding of the variability of the pain experience but for significant advances in pain management as well.

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strychnine, penicillin) which in subconvulsive doses change the balance between excitatory and inhibitory processes either at postsynaptic or presynaptic sites. Sakai et al (1979) demonstrated hyper-irritability in the trigeminal sensory distribution of chronically prepared rats by injecting stimulants in the dorsal subarachnoid space overlying the caudal medulla. Hyperirritability elicited by picrotoxin or penicillin was associated with a localised trigger zone in the face, while that elicited by strychnine or brucine spread beyond the trigeminal region to the first cervical dermatome. D, L-homocysteic acid evoked only spontaneous scratching and vocalisation.

Alumina gel applied into the caudal portion of the spinal trigeminal nucleus of the cat produces behaviour suggestive of trigeminal neuralgia (King et al 1956). The syndrome of hyper-reactivity develops after several weeks. Neuronal hyperactivity in the dorsal horns of the spinal cord in the cats has also been produced by application of either subarachnoid or intramedullary aluminagel. The behavioural abnormalities, however, are not produced unless some of the aluminagel is present adjacent to dorsal root fibres in the subarachnoid space. Therefore application of aluminagel subarachnoidally is suggested to be a good model for human arachnoiditis (Loeser & Peirce 1978).

Kryzhanovsky et al (1974) presented a model of trigeminal neuralgia produced in the rat by local application of a purified tetanus toxin into the caudal nucleus of the spinal trigeminal tract. The rat's behaviour was characterised by paroxysmal scratching of the face and was spontaneous or could be evoked by touching. Later the facial skin became damaged by frequent scratching and finally a syndrome of generalised tetanus developed. In a subsequent study (Igonkina & Kryzhanovsky 1977), purified tetanotoxin was mixed with agar which was cut into slices after solidifying and placed on the dorsal surface of the lumbar spinal cord. A paroxysmal pain syndrome, triggered by touching, developed after 3–4 hours and was characterised by turning of the head and by licking and later by biting the leg.

There are probably other toxins which could produce paroxysmal pain when applied topically to the spinal cord or the trigeminal nuclear complex. It is difficult to devise such experiments in awake animals in order to meet the ethical criteria of experimentation. However, use of spinalised or decerebrate animals may reveal the mechanisms involved in the triggering of paroxysms of pain by inocuous stimuli.

PAIN VERSUS NOCICEPTIVE REACTION

Poggio & Mountcastle (1960) stated that 'there is no reason to suppose that in evolution the perception of pain appears as a wholly new sensory phenomenon in man'. It is, indeed, generally accepted that animals, at least mammals, suffer pain similar to human pain. When, however, any procedure on the central nervous system or a new drug is tested for its analgesic potency, dissociation of pain from the motor reaction cannot be excluded. Therefore the problem has been discussed whether the defense reaction can be considered to be equivalent to pain.

Charpentier (1968) recognised four responses to noceptive stimuli: 1. an elementary, rapid reaction: the startle reaction; 2. a simple, non-specific reaction: flight; 3. a reaction of an affective nature: squeak; 4. a final, coordinated reaction: biting of the electrodes in the case of cutaneous pain and rubbing of the muzzle in trigeminal pain. He suggested that the integration of the reflex action occurs in the medulla while the diffuse alertness, startle and flight reactions are integrated in the brain stem; affective alertness and squeak are integrated in the rhinencephalon; and intellectual alertness in the cortex. On the other hand, Carroll & Lim (1960) regarded the criteria which are employed to assay analgesic activity — namely, motor phenomena such as twitches, flicks, withdrawal, struggle and even vocalisation — as indistinguishable from somatic motor reflexes. They are therefore unable to compensate for the lack of verbal communication as an index of subjective experience.

The problem arose, for example, when estimating whether medial thalamic lesions (Mitchell & Kaelber 1966) or transection of the descending root of the spinal trigeminal tract caudal to the obex (Vyklický et al 1977) affected pain perception evoked by electrical stimulation of the tooth-pulp nerve. The persistence of the motor reaction, characterised by jaw opening and dorsiflexion of the head after the surgical procedure, could not exclude the presence of analgesic effects. Relatively simple learned responses, such as escape or avoidance, were therefore used to decide on the possibility of dissociating the motor reaction from pain perception. Mitchell & Kaelber (1966) applied a simple escape procedure. Cats with chronically-implanted electrodes in the dentine of a canine tooth were placed in a two-compartment shuttle box containing a V-shaped barrier between compartments and a window in front. The tooth pulp was stimulated with electrical pulses at a duration and voltage selected for each animal such that intense searching behaviour was elicited by stimulation. The animals were trained to cross the barrier, and the latency from the onset of the stimulation was recorded for each trial. The procedure continued until the latency of the barrier crossing became stable (i.e. the average latency did not vary by more than 2 s from day to day). Many other learned behavioural reactions which can be used to test the analgesic effects of various procedures in the central nervous system are described in a comprehensive review (Bureš et al 1976).

MODELS FOR STUDYING THE NEUROCHEMISTRY OF SYNAPTIC TRANSMISSION FROM NOCICEPTORS

There is no reason to believe that only the mammalian central nervous system is endowed with mechanisms for pain perception. The paleospinothalamic system, which is considered to be the main ascending pathway for nociception in the spinal cord, is developed in the frog nearly as well as in mammals (Mehler 1966). Adrian (1931) used the frog to carry out his pioneering study on afferent fibres for pain sensation and discovered that noxious stimuli produced slowly conducted spikes. There is no doubt that nociceptive mechanisms exist in the frog.

Mechanisms of spinal pain

John P. O'Brien

INTRODUCTION

Chronic spinal pain is an area of deep concern to the medical profession because it is still the most common cause of disablement and loss of mobility. For example, impairments of the back and spine are the most frequent cause of limitation of activity in persons less than 45 years old in the United States (Kelsey et al 1979). The etiology and prognosis of spinal pain are both uncertain and the effect on the quality of the sufferer's life has far-reaching consequences. More than 60% of patients admitted to hospital from the Chronic Spinal Pain Clinic at Oswestry are suicidal (Department for Spinal Disorders 1982). The tendency to ignore organic pathology and to label chronic spinal pain as largely psychogenic in origin is very common. Our experience has been that comprehensive clinical examination together with radiological studies (including discography) and other appropriate investigations will reveal the pain source in most instances. The purpose of this chapter is to present a rationale for spinal pain and to examine the basic pain syndromes.

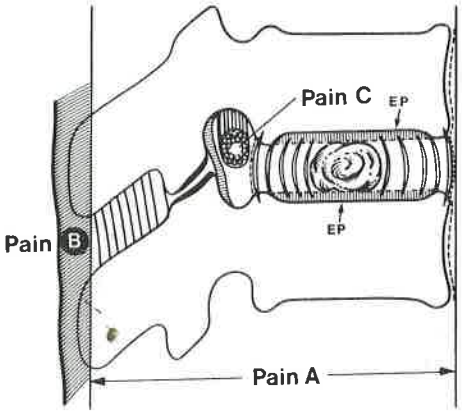


Fig. 80 Drawing to demonstrate the basic motion segment of the vertebral column. There are usually 23 complete motion segments. The vertebral bodies articulate through a triple joint mechanism which includes two facet joints and the disc composed of the nucleus pulposus and the annulus fibrosus. Note that the cartilagenous end-plates (EP) form an integral part of the disc complex and the bulk of the annular fibres insert into these plates.

Three anatomical sections have been arbitrarily marked to designate different pain sources. *Pain A* — deep, referred (sclerotome) pain. This includes the motion segment and vertebrae, the surrounding ligaments and deeper muscles. *Pain B* — superficial pain sources in skin, fascia, the tips of spinous processes and the most superficial muscles. *Pain C* — pain from the nerve trunks associated with the vertebral column (i) the spinal nerves and (ii) the sympathetic trunks

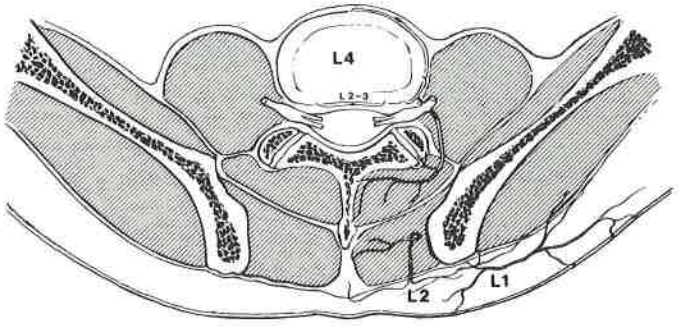


Fig. 81 Drawing of a transverse section of the spine and associated structures at the fourth lumbar motion segment to illustrate the complexity of innervation of tissues and ease of false localisation of the painful segment. The superficial tissues are shown supplied by the first and second lumbar nerve segments. The small descending nerve of Roofe (L2–3) on the posterior ligament supplies both that ligament and the anterior part of the dura mater. Four different nerve segments are shown supplying the tissues at the level of this motion segment (after Kellgren)

SECTION ONE: SPINAL PAIN

1. PAIN SOURCES IN THE VERTEBRAL COLUMN

Pain originating from the vertebral column and its related tissues may arise from three distinct anatomical areas each with differing qualities of painful sensation. These areas are described as:

Pain A, originating in the motion segment and its associated structures;

Pain B, emanating from the more superficial tissues clothing the vertebral column; and

Pain C (i) and (ii), caused by the involvement of the nerve trunks associated with the vertebral column (Fig. 80).

Spinal pain can originate from one area alone, for example, the intervertebral disc in the motion segment (Pain A); but because of the complex anatomy of the spine and its nerve supply (Fig. 81) these three different areas of pain (A, B and C) may occur in combination. This presents a bizarre

and confusing clinical pattern of spinal pain, which makes accurate diagnosis of the anatomical pain source difficult.

Pain A — the motion segment: structure and innervation

The motion segment (Fig. 80) is the complex triple articulation linking adjacent bony vertebrae. There are usually 23 motion segments which contain discs in the vertebral column. The basic structure of each segment includes the intervertebral disc complex with its cartilagenous end plates, adjacent vertebrae, and the two facet joints, with the appropriate connecting ligaments and muscles. The disc is the largest and most important structure in the motion segment and the outer half of its annulus fibrosus has a rich sensory innervation (Yoshizawa et al 1980) (Fig. 82). The inner half of the annulus and the nucleus are devoid of nerve supply.

Centrally placed in the motion segment between the disc and the facet joint is the intervertebral foramen for the emerging nerve root, which occupies up to 50% of the available space in the foramen (Sunderland 1975). The dura mater which surrounds and protects the neural tissue has a nerve supply on its anterior aspect which is absent on its posterior surface (Edgar & Ghadially 1976). A rich sensory nerve supply can be demonstrated in the vertebral body (Sherman 1963).

The facet joint capsule is well supplied with nerve endings. A nerve supply is lacking, however, in the articular cartilage and synovium of the joint (Kellgren & Samuel 1950). The nerve supply of the facet joint arises from several nerve segments (Mooney & Robertson 1975); in fact a triple level innervation of each facet joint in the lumbar spine has recently been identified (Selby & Paris 1981). It is likely that the disc receives its innervation from several sources as well.

The posterior longitudinal ligament in the lower lumbar spine receives a supply from above: the nerve described by Roofe (1940). The anterior ligament of the lower lumbar spine, as well as receiving an innervation at that level, probably also receives a descending supply from above. Clinical observations and pain provocation studies have in the past concentrated on the sensitivity of the posterior structures of the vertebral column and the nerve roots. In our present knowledge, however, the precise innervation of the front of the spine and the pain experienced with lesions of the anterior tissues and the vertebral column has not been clarified.

Anterior tenderness

Palpation of the anterior region of the lumbosacral joint in low-back pain sufferers has recently been described as a valuable clinical sign (O'Brien 1979). The patient often experiences tenderness over the lumbosacral promontory which is quite a different sensation from the discomfort of deep palpation of normal pelvic viscera. Significant anterior

Fig. 82 The nerve supply of the outer half of the annulus fibrosus of the lumbar disc — a profuse, non-myelinated axonal network in the outer half of the annulus fibrosus encircling and arranged at right angles to the fibro-cartilagenous bundles. Bielschowsky's silver impregnation (BSI). Thick section x 420.

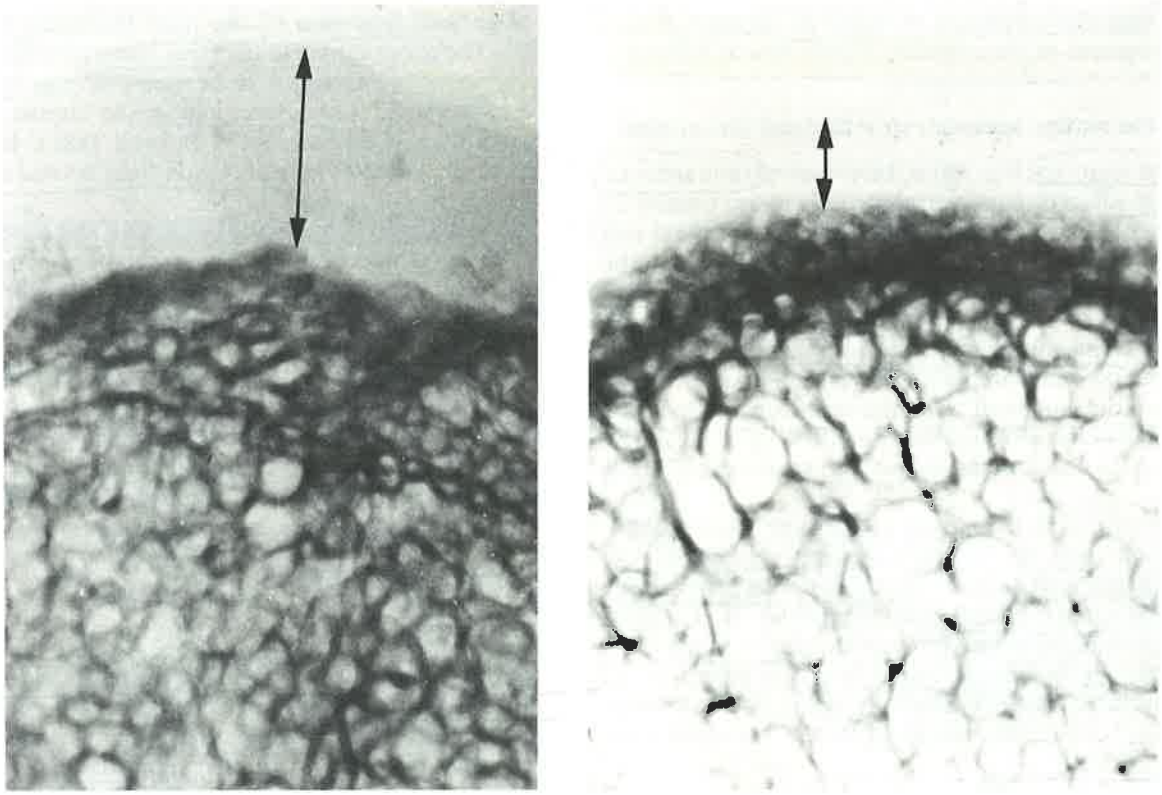


Fig. 83 Microfocal radiographs of the rims of the bodies of the fifth lumbar vertebra in 40-year-old male subjects. *Right*, normal control demonstrating a normal trabecular pattern with thickened cortical bone and thin overlying prevertebral tissue (arrow). *Left*, segment of bone removed at the time of anterior lumbar fusion when marked prevertebral inflammatory reaction and oedema was observed. Note the thickening of the prevertebral tissues (arrow) which was due to infiltration with chronic inflammatory cells. (Microfocals courtesy of Dr W.M. Park.)

tenderness may indicate a lesion of an adjacent motion segment and occasionally a non-specific inflammatory reaction in the thickened inflamed anterior ligaments is confirmed (Fig. 83). Pain felt in the buttock and leg with palpation probably indicates a defect in the fibres of the posterior annulus fibrosus, permitting fragments of the motion segment to irritate the nerve root and sensitive dura mater in the foramen.

The pain originating from the motion segment is dull, deep and aching in quality. It is poorly localised and may radiate proximally or distally without any obvious neurological findings. Deep tenderness of muscles and altered sensation, usually hyperalgesia, occurs in the area of referred pain (Kellgren 1939). The most puzzling feature of this pain is that its distribution is fairly constant, yet it does not correspond to an area of supply of any known peripheral nerve or nerve root (Inman & Saunders 1944). The onset of the pain following injury may be very acute or it may be delayed by days or weeks. The intensity of the pain will depend on the site and extent of injury as well as the density of the nerve endings in the injured tissues. McCall and colleagues (1979) demonstrated that the upper lumbar region was markedly more sensitive than the lower in their study of pain referral from lumbar facet joints.

There is often vasomotor response, including sweating and nausea, with the onset of pain. In clinical situations the severity of pain varies enormously from an aching feeling to an intense pain with weight-bearing or movement which restricts the patient to bed or to the house. Sitting is poorly tolerated, being a position in which intradiscal pressures are highest (Nachemson 1976). This 'sclerotome' pain was initially investigated by Kellgren (1939, 1977) who, together with Lewis (1942) was able to produce patterns of deep pain referral after the injection of the interspinous ligaments (Fig. 84).

Distally referred pain may cause diagnostic confusion. From the cervical spine pain may radiate to the eye, chest wall and elbow. In the thorax there may be pain referred to the anterior trunk where it may be mistaken for abdominal pain. In the lumbar spine pain referral to the groin, lower abdomen and foot is common (Fig. 85). Kellgren's classic studies showed that pain referral to the region of the groin was predominantly from upper lumbar segments. Later work by McCall (McCall et al 1979) has again shown this but has also indicated with accurate radiographic positioning that radiation to the groin can also occur from the lower lumbar facets.

The difficulty of identifying an anatomical pain source is made greater because not only is there overlap of innervation at each level, but also an overlap of pain patterns, especially in the lumbar region (Fig. 84). There is a surprisingly large overlap of pain patterns from the L1–2 and

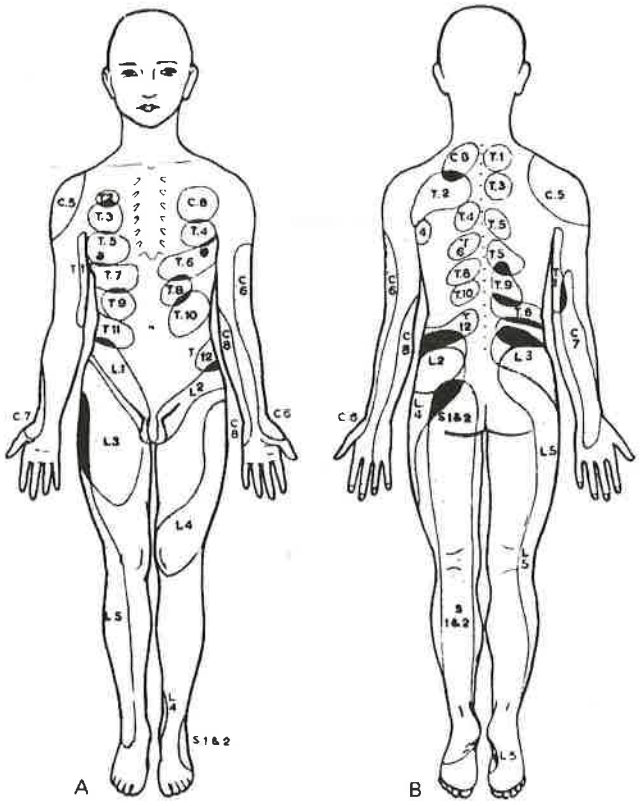
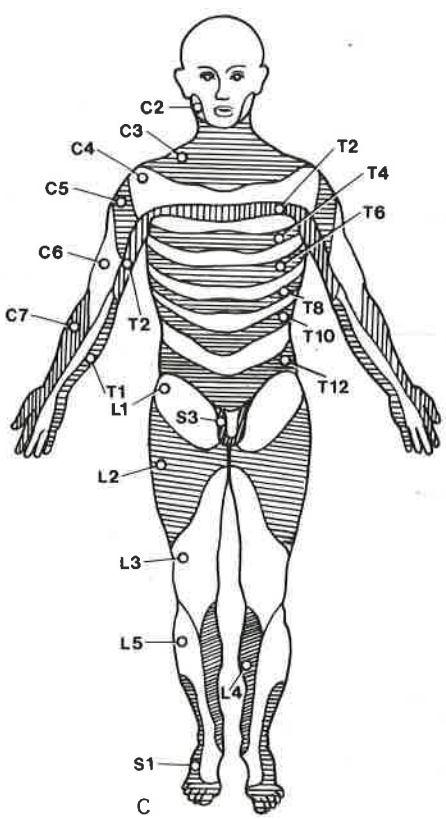
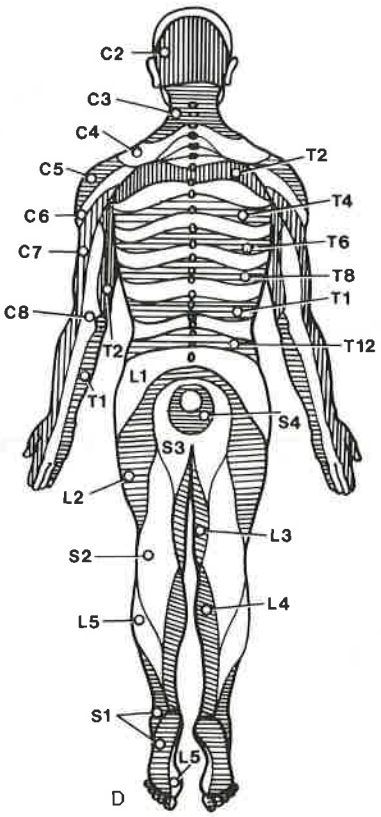


Fig. 84 A. and **B.** Homunculi to demonstrate the segmental areas of deep pain developed by the injection of the corresponding interspinous ligaments, diagrams constructed from Kellgren's material. When compared with the dermatome charts the chief divergencies are seen in the limbs (after Lewis). **C.** and **D.** The classic dermatome charts to be compared with **A.** and **B.** Pain of this distribution is characteristically due to irritation of the involved nerve root. (After Foerster).





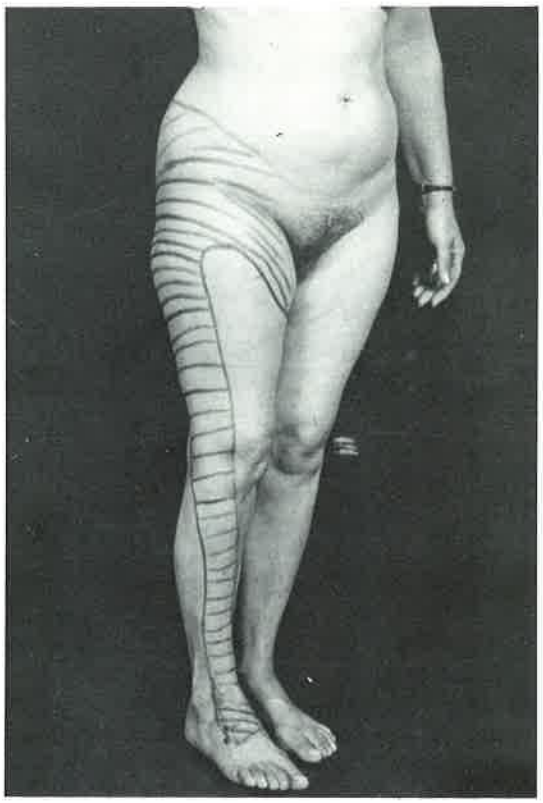


Fig. 85 Photograph of a female patient with skin markings to demonstrate where referred pain from the low lumbar lesion is often felt. Note the significant anterior groin component, which is easily mistaken for hip or pelvic disease. Referral of pain to the anterior groin is common with lesions of the lower lumbar motion segments (see text).

L4–5 facet joints. The innervation is complicated even further because different nerve segments supply the tissues at different depths within the same motion segment, more particularly in the lower lumbar spine (Fig. 81).

The sacro-iliac joint

Many motion segments have deep pain referral to the region of the sacro-iliac joint (Fig. 84B). This will be associated with tenderness and altered sensation overlying the joint and these features have been responsible for many causes of pain originating in the lumbar spine being diagnosed incorrectly as 'sacro-iliac joint strain'. Pain from the sacro-iliac joint is felt diffusely over the ischial tuberosity and into the groin down the whole thigh to the knee (Kellgren 1982).

Pain B — superficial tissues: (Fig. 80)

This second area of pain originates from the superficial tissues and includes skin, fascia, superficial ligaments and muscles, and tips of the spinous processes. Involvement of these tissues will produce pain which is felt locally. Skin pain is accurately localised. Deep fascia is sensitive, with pain accurately localised to within 1 cm of the stimulus. Irritation of most superficial muscles is felt locally with a fair degree of accuracy but irritation of the deeper muscles will produce patterns of referral typical of Pain A. Spinous process impingement produces superficial central pain relieved with spine flexion.

Pain C(i) — involvement of the spinal nerve

The spinal nerve emerging through the intervertebral foramen is vulnerable to compression or irritation with the disc as an anterior and the facet joint as an immediate posterior relation (Fig. 80). Pain produced with stimulation of the nerve is sharp, electric in quality, is superficial and may be intense. The intensity and extent of radiation along a dermatome depends on the stimulus strength, that is, the amount of compression or tension on the sensitive nerve root (Sunderland 1975). Compression of a nerve which is not sensitive produces only a sensation of numbness distally with ultimate motor paralysis. The pain characteristic of a ruptured disc syndrome is usually associated with an inflamed, reddened nerve root.

A prolapsed disc lesion often produces limb pain only. Altered sensation associated with nerve root compression may be hyperaesthesia or paraesthesia and is usually localised to the dermatome of the involved nerve root. Several charts demonstrate the dermatomal distribution of pain and a more recent one was compiled by Keegan & Garrett (1948). However, the accuracy of the pain dermatome distribution in defining the specific nerve root involved has been controversial. Foerster (1933) believed it was specific enough to nominate the nerve root affected. (Fig. 84C and D). On the other hand, Last (1978) stated that 'dermatome charts of the limb are probably today about as accurate as maps of the world were in the sixteenth century'.

Involvement of the motor component of the spinal nerve will affect the muscles supplied by that nerve; though this is practically insignificant in the thoracic segments. The symptoms may vary from spasm and tenderness to weakness and wasting of the involved muscles or frank paralysis, typified by foot droop, occurring with compression of the fifth lumbar nerve root.

The reduction or loss of reflexes, such as the biceps reflex (C5) or the ankle reflex (S1) in cervical and lumbar pain syndromes suggests further evidence of nerve root involvement, but their specificity in identifying the involved nerve segment is not certain (Mooney & Robertson 1975). Likewise, restricted straight-leg raising with reproduction of back and dermatome pain has been regarded in the past as absolute evidence of an involved nerve root. The site of pain reproduction with straight-leg raising is important because the lumbar facet joints are moved when the limb is raised and a painful facet joint will restrict straight-leg raising. The evidence suggests that the significance of the straight-leg raising test should be critically reviewed (Farfan & Kirkcaldy-Willis 1981).

Pain C(ii) — the sympathetic trunk

Pain fibres travel in the sympathetic trunks which lie laterally on the vertebral column, where they are vulnerable to irritation from instability or injury of the motion segment. From C2 to C6 level they surround the vertebral artery in

the bony transverse foramen where they may be irritated by osteophyte encroachment. Tears of the outer fibres of the annulus fibrosus adjacent to the trunk may produce a cold blue limb on the affected side. The sympathetic trunk is more involved with the nerve supply of the outer half of the annulus fibrosus than was previously considered (Bogduk et al 1981) (Fig. 86). Hodgson (1979) has observed a pattern of pain in patients with failed back surgery and leg pain. He described back pain associated with waves of pain extending down the leg and a cold foot. Histopathological examination of the sympathetic ganglia demonstrated large pools of blood in dilated veins without evidence of any inflammatory reaction. Histopathological changes have likewise been seen in sympathetic ganglia removed at the time of anterior spinal surgery performed for disabling back and leg pain (Department for Spinal Disorders 1982). The ganglia were removed because they were involved in a marked inflammatory reaction of the prevertebral tissues and were oedematous and hyperaemic (Fig. 83). On microscopic examination oedema was commonly seen but gross neurological damage was absent, although minor damage to the neural elements has been observed in some cases. The particular difficulty with this study has been the lack of suitable control material. These cases may account for some instances of bizarre limb pain. However, the precise quality of pain produced by sympathetic trunk involvement has not been defined.

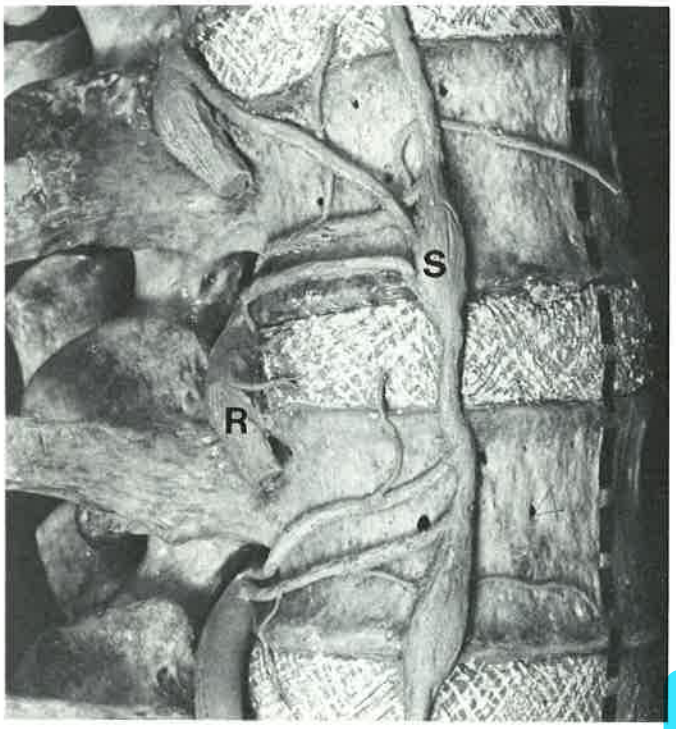


Fig. 86 Model of a human lumbar spine to demonstrate the nerve supply of the intervertebral disc. Nerve root (R) emerging from intervertebral foramen has two communications with the sympathetic trunk (S) at each segment. The anterior midline of the specimen is marked. Note the course and distribution of the nerve filaments supplying the outer half of the annulus fibrosus are fairly constant (after Bogduk).

2. PAIN FELT IN THE SPINE REFERRED FROM ELSEWHERE

a) There are several well defined clinical syndromes in which pain is *felt in the spine* but referred from elsewhere. Several examples include myocardial infarction, acute pancreatitis and perforation of a peptic ulcer. The nature of these lesions is usually clear-cut, the pain referred to the spine being part of the described syndrome and assisting in making the diagnosis.

b) The converse confuses further; that is, that spinal pathology may only be felt as abdominal pain, chest pain or odd pains in the arms and legs, without overt pain in the spine. This may account for incorrect surgical procedures performed for pain referral from pain sources in the lumbar spinee such as laparotomy, hysterectomy and hip joint replacement.

c) Psychiatric disorders presenting as spinal pain syndromes appear to be rare. Psychological disturbances are common but are usually secondary to chronic pain as in other chronic pain syndromes.

3. PAIN DUE TO OVERT SPINAL PATHOLOGY

Generalised disease such as osteomalacia or malignant metastases, if involving the spine, will produce pain. In metastatic disease, the vertebral body will usually be involved (Pain A). As the disease infiltrates and extends further inclusion of the nerve root (Pain C) may be superimposed. All tissues of the spine complex have a sensory innervation except for the nucleus pulposus, the inner half of the annulus fibrosus and the posterior aspect of the dura mater. Any disease of the spine affecting tissues other than these can produce pain.

SECTION TWO

1. PREDISPOSING FACTORS TO SPINAL PAIN

It is estimated that 50% of the population will suffer from back pain at some stage of their lives (Laurence 1977). There are several factors which make certain people more vulnerable to attacks of back pain.

a) Congenital anomalies

Congenital vertebral abnormalities can subject the spine to asymmetric loading of the motion segment and therefore degeneration, in which case even a minimal traumatic event can precipitate pain. The commonest anomaly involves the fifth lumbar lamina; the failure of normal development of this neural arch (spina bifida) or anomalous facet joints will expose the disc to early mechanical failure, particularly with repeated stresses or injury of any kind.

Spondylosis, hemivertebrae and other lesions are obvious with radiographs; they are not essentially painful but because of the associated secondary changes they may lead to pain.

b) Age

It is uncommon to find back pain in the very young. Adolescent back pain is being detected with increasing frequency. A study by Fairbank (1981) of normal teenage schoolchildren confirmed that 25% had experienced back pain, which may be a factor in the high incidence of lumbar scoliosis curves seen in the School Screening Groups (O'Brien 1980). The mechanism is not clear but injury seems to be a recurring factor. Episodes of spinal pain are a feature of middle life in both sexes (Laurence 1977). Predisposing factors predominant from maturity onwards are pregnancy, occupation and degeneration.

c) Pregnancy

Pregnancy is a potent cause of back pain. A prevalence study carried out in Shropshire (Department for Spinal Disorders 1982) confirmed that almost 20% of females developed back pain in the first trimester with no previous history of back pain and before any mechanical malalignment of the spine had occurred; this suggests a hormonal aetiology for this back pain. The pain often settles with delivery but in some women chronic spinal and leg pain persists.

d) Occupation

Certain types of occupations incur greater risks of spinal injury. Truck and tractor drivers who sustain prolonged vibration forces on the spine (Frymoyler et al 1980) and people in occupations requiring repeated lifting, bending and twisting of the spine, especially the nursing profession, are all at high risk. Unaccustomed activities such as weekend gardening, prolonged sitting or long car rides all put the person at greater risk for attacks of spinal pain. Some sports, such as weight-lifting and football are associated with a higher risk of back injury.

e) Degeneration

The development of degeneration in the spine begins in the early twenties and for the next 30 years there is a natural predisposition to injury of the motion segment. Degenerative changes are present on autopsy examination in the lumbar discs of all subjects by middle age (Vernon-Roberts 1977). The disc becomes dehydrated and loses its normal mechanical properties; it ultimately loses height thus narrowing the intervertebral foramina. The disc most frequently affected in a large population study as judged by x-ray findings is the eighth thoracic in males (seventh in females). The pattern of distribution shows peaks also at the sixth cervical and third lumbar (Laurence 1977) (Fig. 87). These peaks do not correspond with those peaks responsible for the majority of spinal pain (C5–6, L4–5 and lumbosacral). Degeneration *per se* does not produce back pain but it makes the spine more vulnerable to injury. Osteophyte formation associated with facet joint arthritis and loss of disc height reduces the space available for the nerve roots so that the slightest alteration in the motion segment may

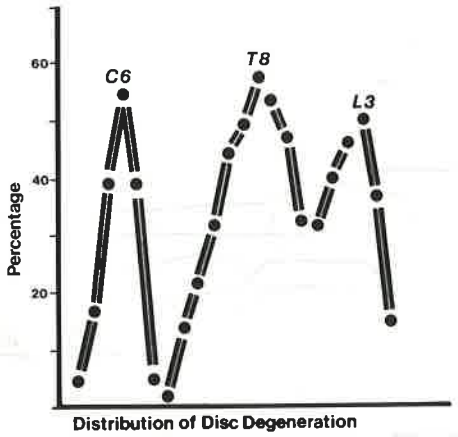


Fig. 87 Graph to demonstrate the distribution of disc degeneration from X-ray studies in epidemiological surveys. The male sex is represented here. Three significant peaks of disc degeneration are at C6, T8 and L3 levels. Note the poor correlation between levels of disc degeneration (C6, T8, L3) and most frequent painful segments (C5, L4, L5).

cause severe symptoms. This occurs in isolated disc resorption where a fall on the buttocks produces buttock and leg pain out of proportion to the injury despite absence of clinical signs (Crock 1976). Radial tears of the disc begin to appear in the early twenties and are probably a manifestation of degeneration and repeated trauma (Figs 88 and 89). They permit excessive mobility within the motion segment and lead to instability (Farfan & Kirkcaldy-Willis 1981, Van Akkerveeken et al 1979). Instability itself, like degeneration, is not necessarily a cause of pain but that motion segment is rendered more vulnerable to injury which will induce pain.

Increasing wear and tear ultimately implies that the corresponding facet joints are required to bear more of the transmitted body weight, and ultimately they are included in the motion segment failure. With their osteophyte formation and arthritic changes the facets become prone to minimal trauma and attacks of pain. It would appear that disc failure invariably precedes facet joint failure.

Osteophyte formation as in cervical spondylosis may narrow the spinal canal as well as the intervertebral foramen resulting in compression of the spinal cord. In the lumbar spine reduced space for the neural tissue leads to marked limitation of mobility because of low-back and limb pain from compression or ischaemia of the nerve roots — so called 'spinal stenosis'.

2. CAUSES OF SPINAL PAIN

a) A common cause of spinal pain is *trauma:* road accidents, injury at home such as falling downstairs, heavy falls onto the buttocks, accidents whilst lifting heavy weights, bending or repeated manual handling in heavy industry or special groups such as the nursing profession. *Post-operative backache,* not commonly recognised, is a very disabling problem (Jones & Lovett 1933). After a major operation the patient experiences a great deal of pain in the lumbar re-

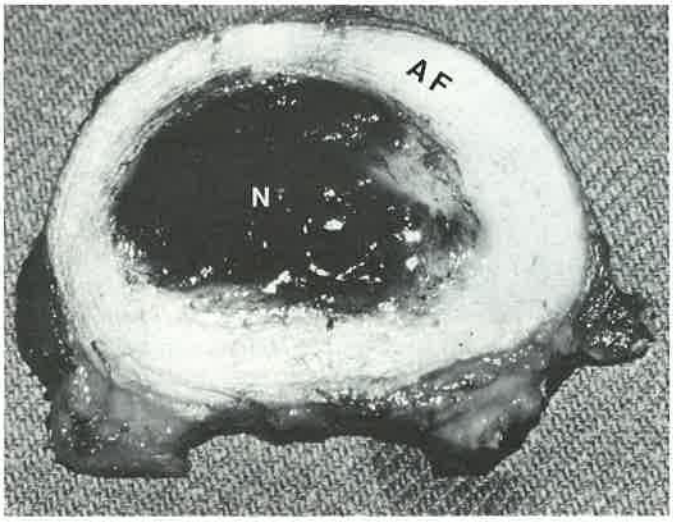


Fig. 88 Normal lumbar disc in which the nucleus (N) has been injected with methylene blue and the disc cut open. Specimen removed at autopsy from a young male. Note the integrity and thickness of the annulus fibrosus (AF), the outer half of which has a rich sensory innervation.

gion. It is probably due to rotational injury under anaesthesia during handling on and off the operating table. Particular risk occurs with use of the lithotomy position for urological and gynaecological surgery.

b) *Insidious onset* of pain often reveals, in discussion, a forgotten injury which was initially pain-free but which has suddenly become painful weeks or months later.

c) The cause of low-back pain was unknown in 79% of men and 89% of women presenting for the first time to their General Practitioners (Dillane et al 1966). In our present knowledge, low-back pain that has no definite aetiology (*idiopathic*) varies from 20% to approximately 85% of cases (Kelsey 1982).

3. SYNDROMES OF SPINAL PAIN

Structural considerations

The cervical and lumbar spine are the most mobile areas of the spine and therefore most likely to suffer mechanical failure. The thoracic spine is the least common site for vertebral pain which explains the paucity of literature on the subject. The thoracic motion segments are much more stable with their costovertebral joints providing added lateral stability, the amount of mobility of any one thoracic motion segment is only several degrees (White & Panjabi 1978). It is this stability of the thoracic spine which places added stresses on the mobile cervical and lumbar regions. Nonetheless the thoracic spine is the most common region for spinal deformities which frequently predispose to pain. Deformities do produce pain and the converse is also true: pain may produce deformity.

Spinal injuries

These are most commonly vertebral fractures and injuries to the motion segment. The spine is composed of two bony columns differing in structure and function; the anterior column, consisting of spongy vertebral bodies and the elastic intervertebral discs, is more compressible than the posterior column formed by the facet joints and neural arches. On compression the vertebral body always breaks before the disc gives way (Roaf 1960).

Vertebral fractures

Vertebral fractures are most common in the lower cervical segments and the thoraco-lumbar juntion. They are not so common in the larger and stronger vertebrae in the lumbar region, when the disc is more likely to fail with the injury. With an increasing number of high speed injuries, particu-

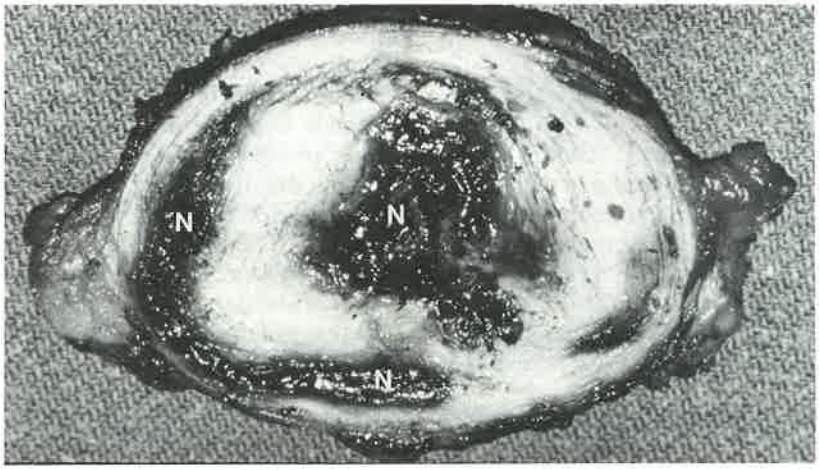


Fig. 89 Specimen of an abnormal lumbar disc. The nucleus has been injected with methylene blue similarly to Figure 88. The dye has escaped from the nucleus and fills extensive peripheral radial tears of the annulus fibrosus (N). Tears in the outer half of the annulus may produce disabling back and leg pain in the presence of a normal myelogram. They can only be demonstrated by discography. The annulus has no blood supply except for its most peripheral fibres. Continuing motion and avascularity singles out the disc as being the body's poorest-healing tissue.

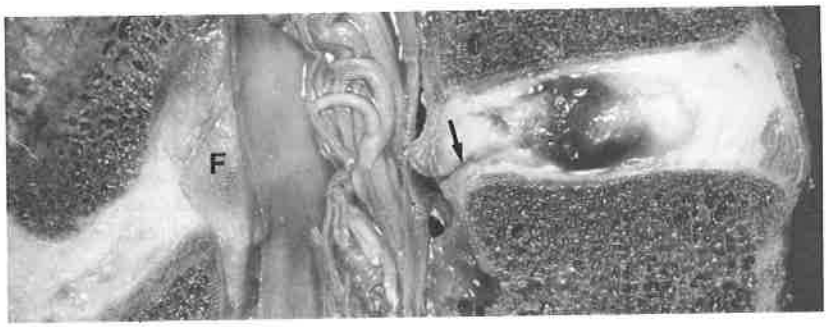


Fig. 90 Sagittal section of a lumbar motion segment. The nerve roots and dura are seen between the disc anteriorly and the facet joint (F) posteriorly. The interruption in the posterior annular fibres (arrow) demonstrates a tear of the posterior annulus, a lesion which can produce disabling back and leg pain following significant injury. It can only be demonstrated by discography and will usually be associated with a negative radiculogram.

larly road traffic accidents, cervical spine trauma is increasing, frequently associated with a spinal cord injury. Fractures of the vertebral body will produce a pain; characteristically beginning one or two segments below the injury and radiating a further two segments distal to that. Laterally the pain extends about 10 cm from the midline (Fairbank 1981). Sometimes compression fractures will escape immediate recognition and present with late onset of symptoms (Jones & Lovett 1933).

2. Injuries of the motion segment

Injuries of the motion segment are common and vary in their symptoms according to site and severity. They include:

a) Vertebral end-plate fracture
b) Internal disc disruption
c) Tears of the anterior and posterior annulus fibrosus
d) Herniation of the nucleus pulposus
e) Thoracic disc syndrome
f) Torsional injuries of the motion segment

Lesions a), b) and c) have the following features in common:

(i) They are produced by severe injury, usually in the cervical and lumbar region in the presence of normal or near normal radiographs.

(ii) They produce disabling pain with radiation, pain with movement, marked muscle spasm, restriction of motion and tenderness with pressure of the examining finger over the damaged segment. Extensive damage may produce pain radiating distally into the limb in the presence of a negative myelogram.

(iii) They can only be demonstrated by discography which will confirm the nature of the motion segment lesion and also reproduce or aggravate the pain suffered by the patient.

a) *Vertebral end-plate injuries* often remain undiagnosed. They occur most commonly in the cervical and upper lumbar regions where they can be missed because of an adjacent vertebral body fracture. They produce disabling pain which is confusing in the presence of a normal radiograph of the damaged motion segment (Crock 1976), the cartilage plate fractures permitting nuclear material to escape between the plates into the spongy vertebral body.

b) *Internal disc disruption* is seen in the lower cervical and the lower lumbar motion segments usually as a result of a severe accident, such as whiplash injury or injury during heavy lifting (Crock 1976). The diagnosis is obscure in the presence of severe pain radiating to the limb associated with a negative myelogram, and it is this combination of events that commonly leads to the diagnosis of psychological overlay. As with other injuries of the motion segment the pain and disability continue long after a soft-tissue injury should have healed.

c) *Tears of the anterior and posterior annulus fibrosus* (Fig. 90) Anterior annular tears are mostly seen in the thoracolumbar and upper lumbar spine. They are more prevalent and more severe in the older age group (Hilton et al 1980). However, posterior annular tears are more common in the lower cervical and the lower lumbar motion segments because the natural lordosis in these areas is associated with thinning of the posterior annular fibres which predispose them to tearing with compression and flexion injuries. Extensive tears of the annulus may avulse the cartilagenous end plate from the vertebral rim.

d) *Herniation of the nucleus pulposus*. With severe injury to the motion segment nuclear material may extravasate between annular fibres and cartilage plate or between avulsed cartilage plate and bony vertebral rim. It usually herniates posterolaterally in the lumbar region where the posterior annular fibres are thinnest.

Rupture of the cervical disc also occurs, but less frequently. In a large series of vertebral injuries Crock noted 15% of lumbar lesions were due to a prolapsed disc compared with only 2% of cervical spine lesions (Crock 1976). A prolapsed lumbar disc is the best known and most widely reported traumatic disc lesion but, in fact, accounts for only a small percentage of the total low-back pain problem.

Violent injury to the cervical or lower lumbar spine can produce a massive tear of the annulus with prolapse of the nucleus through the torn posterior fibres resulting in compression of the nerve root. It is more common to have repeated tears of the posterior annulus resulting in repeated

attacks of back pain over many years ultimately leading to severe leg pain when the outer fibres of the annulus posteriorly give way with further injury. The signs and symptoms will depend on the site and severity of the lesion and will be overshadowed by pain type C of dermatome distribution felt in the affected limb. The diagnosis is confirmed using radiculography.

e) *Thoracic disc syndrome*. In the lower thoracic motion segment there occurs an uncommon disc lesion often precipitated by injury which presents with deep pain and with lower limb spasticity. There is bulging of a calcific narrow disc into the spinal canal compressing the motor component of the spinal cord. The natural history of this syndrome is to progress and produce long tract signs with paraparesis

The early recognition of this syndrome is of paramount importance and its timely treatment by appropriate surgery. Laminectomy is notoriously prone to produce a complete paraplegia (Terry et al 1981). The calcified prolapsed disc should be removed surgically by an anterior or antero-lateral approach and the interbody defect replaced with bone graft (Gunn 1977).

f) *Torsional injury*. Many of the above mentioned lesions have in common compression as a major deforming force with involvement of the anterior column of either the vertebral body or the disc. With torsional injuries the posterior column is also injured, with radial tears of the annulus fibrosus and strain of the associated facet joint with buckling of the adjacent neural arch (Kirkaldy Willis & Farfan 1982). This is seen frequently at the L4–5 motion segment and is a major cause of chronic recurring back pain.

Syndromes of cervical pain — non-acute

a) Acute wry neck

Acute neck pain and torticollis which is present on waking in the morning is characterised by inability to move the neck because of painful muscle spasm. The clinical appearance suggests mechanical dysfunction, perhaps facet joint subluxation, and is usually an alarming phenomenon. It is often difficult to identify the involved motion segment by palpation because of diffuse muscle spasm. This syndrome usually settles spontaneously in several days but the time course can be shortened by gentle manipulation or traction. The lesion is benign and non-recurring, can occur at any age and does not seem to be related to cervical spondylosis.

b) Cervical spondylosis

Cervical spondylosis is most frequently seen at C5–6, the most mobile segment, less frequently at the C6–7 and C4–5 levels, whilst the other motion segments are not often involved. Radiculopathy (pain C) results from irritation of the nerve root in the intervertebral foramen by osteophytes from the adjacent facet joint or Lushka's joint. (The osteophyte is the dominant pathological entity in the neck and the disc in the lumbar spine.) The radiculopathy produces the characteristic pain C with a distribution in the region of the dermatome. There will be dullness or loss of sensation over the region of the dermatome (Fig. 84C and D). Muscle involvement will produce weakness and wasting of the affected muscles supplied by the nerve root and, in severe cases, frank paralysis.

Radicular pain due to nerve root compression is often sharp and aggravated by any neck movement. Compression of the head may aggravatee this pain whilst traction may relieve it (Hodgson 1969). Pain is felt in the region of the affected segment which, if intense, will radiate to the anterior chest wall, the interscapular region, the shoulder and upper limb. There is tenderness with palpation of the involved motion segment and restricted movement of the cervical spine. The muscle groups to which the pain is referred are tender with overlying hyperalgesia. This diffuse radiation causes confusion with other syndromes, in particular myocardial infarction, hiatal hernia, migraine, thoracic spondylosis, capsulitis of the shoulder, tennis elbow and carpal tunnel syndrome.

c) Cervical myelopathy

Posterior osteophytes which protrude into the spinal canal from the vertebral bodies may irritate the motor area of the cord with resulting spasticity and long tract signs. In a study conducted by Hughes, the most important measurement was the narrowest AP diameter of the cervical canal, the mean being 11.3 mm in cases with myelopathy (Hughes 1978). Evidence of cord compression is ominous because the natural history is for the osteophytes to increase in size and the cord myelopathy to progress with time.

d) Symptoms due to irritation of the cervical sympathetic system.

A rich plexus of sympathetic nerves is related to the vertebral artery in its bony foramen from the C2–C6 level. Irritation of this plexus by adjacent osteophytes may be the cause for a confusing group of symptoms often associated with cervical spondylosis. These include headaches, loss of balance, ocular symptoms, including migraine, ocular pain, blurred vision and photophobia. The headache often begins in the suboccipital region and extends above the ear into the temporal region.

Degenerative hypertrophic arthritis of the lumbar spine

This is gaining increasing attention, partly because of an ageing population. Large osteophytes on the facet joints and disc rim, together with narrowing of the motion segment, compress the nerve tissue and produce bilateral buttock and leg pain. These patients have a limited walking tolerance because this activity causes the worn motion segment to settle further and the frayed posterior annulus to compress even further posteriorly.

Their posture becomes more stooped during the day, and whilst their walking ability is severely and progressively restricted they can ride a bicycle for miles without symptoms. The spine is well flexed in this posture, assuming its widest antero-posterior diameter and thus accommodating the neural tissue more readily. Extensive laminectomy may

seem an attractive surgical solution for this syndrome of 'spinal stenosis'. In the presence of disc failure and gross instability forward shift with even more disabling symptoms may be precipitated by laminectomy. Surgery thus needs to be carefully planned and additional stabilisation by fusion added where indicated.

The facet joint syndrome

An irritable facet joint may occur anywhere in the spine, but has attracted most attention in the lumbar region. The original description by Ghormley fifty years ago (1933) was more recently clarified by Mooney & Robertson (1975); facet injections were performed using X-ray control; an irritant fluid in the joint intensified the pain which was relieved by local anaesthetic. Of 100 patients treated for back and leg pain one fifth gained long-term and one third short-term relief of pain. Limited straight-leg raising and diminished reflex signs in the legs were obliterated by injection thus confirming the non-specific nature of many neurological signs with back and leg pain syndromes.

Impingement syndrome

The interspinous ligaments and the muscles and soft tissues superficial to these may be a source of pain B from stretching or tearing which is felt locally with local tenderness to palpation. Another lesion is the impingement syndrome known as Baastrup's Disease (Baastrup 1933) in which an increase in lordosis or narrowing of the motion segment or both will produce approximation of the spinous processes. This can be an acute and painful lesion which is aggravated by extension, relieved by flexion and by infiltration of a small volume of local anaesthetic into the painful area.

4. TIME COURSE AND PROGNOSIS

a) Cervical pain

Whilst radiological changes in the cervical spine increase with age, symptoms will vary with each individual. In some cases, there will be an occasional ache in the neck which will settle with time, a collar, analgesics and heat. In the more severe variety there will be several bouts of acute neck and arm pain which may incapacitate the individual and prevent him working.

b) Thoracic pain

The prognosis with thoracic pain depends on the underlying pathology. Several factors tend to make thoracic pain syndromes less disabling than low-back pain. Firstly, the motion segments are stabilised bilaterally at most levels by costo-vertebral joints which restrict motion. Secondly, this area of the spine bears much less weight than lower down — 50% of body-weight is transmitted through the twelfth thoracic vertebra (White & Panjabi 1978). Many cases will respond to postural and manipulative therapy and rarely is surgery indicated. The thoracic disc syndrome is, however, an entirely different entity and requires anterior decompression and bone grafting.

c) Vertebral fractures

The healing potential of vertebral fractures is good, as for any cancellous bone, providing it does not involve the motion segment. Chronic pain complicating stable fractures of the thoracic and lumbar vertebral bodies has attracted little attention. In a series of 116 patients 75% were found to be suffering from continuing back symptoms (*49*). The mechanism for this chronic pain could be the result of unrecognised associated disc disruption, vertebral end plate fracture or subluxation of the corresponding facet joints.

d) Traumatic injuries to the disc

There is a high incidence of chronic recurring pain following significant disc injury. The intervertebral disc is avascular and its healing potential is therefore minimal, but it may heal in 1–2 years in the young individual. Because a tear does not heal does not necessarily mean it remains painful. It is difficult, if not impossible, for fractures of the cartilagenous end-plate to re-attach to the vertebral body because the segment is constantly moving.

A tear in the annulus fibrosus may heal by inferior scar which will disrupt with minimal trauma such as sneezing. In addition to this, the interposition of nuclear material between fractured cartilage plates or torn annular fibres allows no potential for healing. This situation is analogous to congenital pseudarthrosis of the tibia where the interposition of avascular scar tissue and constant motion prevents the bony ends from healing. Injuries involving the outer half of the annulus fibrosus, which has a rich sensory innervation, are likely to be associated with chronic recurring spinal pain.

e) Acute low back pain

70% of acute attacks of back pain settle within 3 weeks of the onset (whether treatment alters this course is not clear). 90% of sufferers will have settled within 8 weeks. After 6 months there are still 2–3% suffering (Nachemson 1982). Fairbank (Fairbank 1981, Fairbank et al 1981) has studied a group of patients suffering low-back pain for the first time. He could subdivide them into two distinct clinical groups according to their pain relief from an injection of local anaesthetic into the tender lower lumbar facet joint. Those who did not respond to the local block of the facet joint usually had an insidious onset of pain which very often extended down the leg.

f) Chronic recurring low-back pain

The prognosis for recovery in chronic low-back pain is impossible to give with real accuracy. The L4–5 disc is the largest avascular structure in the body and whilst small peripheral tears of the annulus fibrosus may heal, it is conceivable that larger clefts in the disc may take more than

a year to heal if they heal at all. The tendency to repeated attacks is due to poor healing of disc tears by inferior scar in avascular tissue which breaks down with minimal trauma in an area of the body constantly moving. There is a high incidence of recurrence when there has been a significant injury producing leg pain.

CONCLUSIONS

Injury and degeneration are the most frequent mechanisms responsible for spinal pain syndromes, which are widespread, frequently disabling and most commonly originating in the lower cervical and lower lumbar motion segments. Since the vertebral column and associated structures has a complex nerve supply resulting in a bewildering array of presentations of pain, identification of the anatomical pain source and the pathological mechanisms involved is essential to provide a scientific basis and to permit accurate diagnosis and management. The nerve supply of the outer half of the annulus fibrosus, which is frequently torn, should explain many cases of so-called 'idiopathic backache'.

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usually worse in the morning than later in the day. The condition is seen most often in young adult patients with poor posture, and is reported more frequently in women.

Palpation or percussion during examination may indicate tenderness of the brachial plexus. A confirming test for TOS is to have the patient assume the 'hold-up' position for 3 minutes while slowly opening and closing the hands. If radial pulses remain strong, but the patient experiences the usual symptoms, the test is positive for TOS. 'Hold up' position consists of sitting with both arms elevated to 90° abduction with external rotation. The elbows are maintained somewhat behind frontal plane.

Treatment course and prognosis. In so far as TOS may be related to poor posture, a conservative approach is to recommend posture-related therapy and mild exercise to strengthen shoulder muscles. If the problem can be associated with a particular type of activity or position during sleeping, these should be modified. Medication for muscle relaxation may be indicated. However, all of these measures are limited if the condition has progressed to the extent that only surgical procedures can provide decompression. Surgery will establish the presence of congenital fibromuscular bands, which could not be identified by X-ray. When these bands are present, they usually affect both sides of the body.

Peripheral neuropathies

Among the most puzzling pains of the extremity are the peripheral neuropathies (Fig. 93). The causes are obscure, and differential diagnosis is not easy, especially since cervical nerve root irritation must be considered. There is evidence that radiculitis increases the susceptibility of nerve entrapment (Upton & McComas 1973).

Any one of these syndromes can cause hand, forearm and shoulder pain which is not consistent in character. Generally, there is some local pain at the area of entrapment, but muscles distal to the entrapment may or may not have pain involvement. Frequently the pain experienced is intermittent, low-grade and worse at night. Scapulocostal irritation and myofascial disturbances tend to distort the pain patterns of peripheral nerve compression. Carpal tunnel syndrome is the most common of the nerve compression syndromes affecting the median nerve. Two other conditions

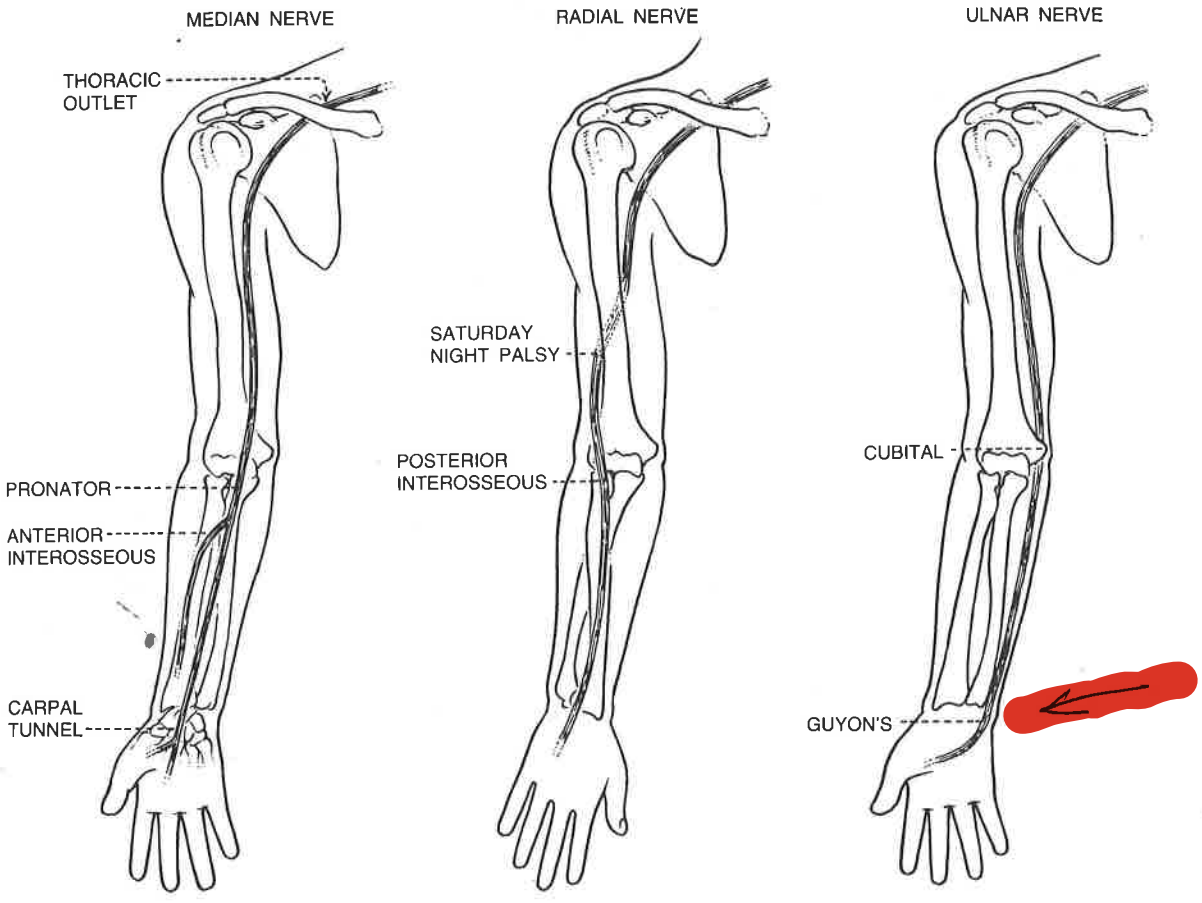

Fig. 93 Neurovascular and peripheral entrapment syndromes. There are four thoracic outlet syndromes: scalenus anticus, costoclavicular syndrome, cervical rib syndrome and hyperabduction syndrome. Peripheral entrapment syndromes affect the radial, ulnar or median nerves, and can cause pain at the area of entrapment and in muscles distal to the entrapment. These are often inconsistent or intermittent pains.

Olecranon bursa

Signs and symptoms The olecranon bursa, which lies over the bony olecranon process, is frequently injured by constant mechanical pressure. Clinically, the bursal sac area becomes red and swollen, warm to the touch and tender on palpation. Occasionally it may become infected. Patients who have gout and rheumatoid arthritis are prone to this disorder.

Treatment course and prognosis. Pain and swelling usually subside if a cushioning ring is used around the area of irritation to prevent further mechanical pressure. If pain persists, fluid can be aspirated from the bursal sac and examined for evidence of infection and/or to differentiate between aetiologies. If the condition is persistent or recurrent, surgical excision may be the treatment of choice.

Ligamental injuries

Signs and symptoms. Ligamental injuries are common at the wrist. Diagnosis is made on the basis of local pain and tenderness. The most frequent of these injuries is sprain of the ulnar collateral ligament, which is characterised by pain on radial deviation. When the radial ligament is sprained or torn, pain is present on ulnar deviation. The lunar-capitate sprain is also quite common. With flexion of the wrist, pain is felt at the dorsal aspect.

Treatment course and prognosis. Local management with steroid injection treatment is usually effective for ligamental injuries. Ruptures may require surgical intervention.

Ganglion cyst

Signs and symptoms. Ganglia are the most common tumours of the hand and wrist. They are most frequently found on the dorsal aspect of the wrist joint, and occasionally on the volar aspect of the wrist. The cystic swelling is found near, and often attached to, a tendon sheath, and it is believed that the cyst may be derived from these structures. Ganglia are often painless; however they can be locally tender and painful.

Treatment course and prognosis. Ganglia are known to disappear spontaneously. However, the usual treatment is puncture of the cyst and aspiration of its contents. Some clinicians inject a corticosteroid into the cyst after aspiration.

Dequervain's disease (constrictive tenosynovitis)

Sign and symptoms. Dequervain's disease may have slow onset or acute onset precipitated by an injury to the wrist which causes swelling in tendons thickened by the disease process. The patient will present with pain in the wrist and thumb area and weakness of grip. In the acute state, there may be local swelling with the symptoms similar to wrist sprain. Examination will reveal marked tenderness to pressure over the styloid process and over the tendons, abductor pollicis longus and extensor pollicis brevis.

The pain is related to thickening and stenosis of the sheath surrounding the tendons. It is most commonly seen in female workers doing heavy, hard work, such as cooks and dressmakers who lift heavy material. Diagnosis of Dequervain's Disease is affirmed by holding the patient's thumb in flexion and abducting the wrist. This will elicit a pain response.

Treatment course and prognosis. Immobilisation is recommended, and this area is injected with long-acting anesthetic. Injectable steroid therapy is also appropriate. In one study, symptoms of infectious arthritis was present in one-fourth of the patients with this condition.

Trigger finger

As result of injury, small tears in the flexor tendon curl into a ball and form a nodule, usually at the proximal end of the tendon sheath. This nodule inteferes with normal gliding motion, and abnormal tension is required to force it through the tendon sheath, causing the finger to snap in extension. Palpation of the tendon sheath will usually be painful.

Treatment is the same as Dequarvain's syndrome — immobilisation, steroid injection and surgical release if necessary.

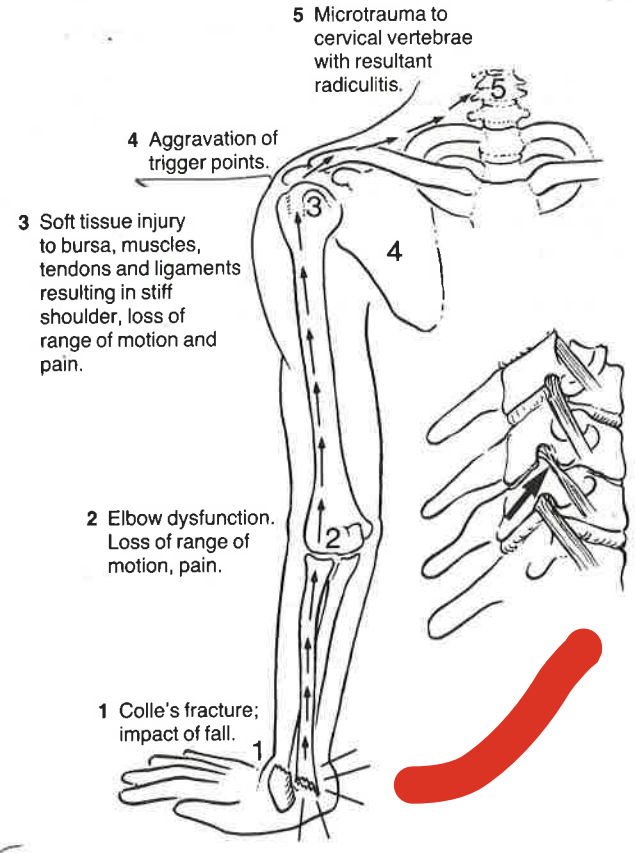

Fig. 94 Even a relatively minor force applied to a distal extremity can cause injury at any of these points on the shock pathway, or can cause flare-up of residual sequelae which were not identified at the time of an earlier injury. Minimal changes on EMG can reflect presence of radiculitis (Gunn 1980).

Combined lesions

One of the problems in managing upper-extremity pain is that several lesions may be contributing to it. This is particularly true in the case of a middle-aged or older patient who sustains an injury as result of a fall in which the first contact was made by his outstretched hand, an elbow or his shoulder (Fig. 94). The initial contact injury may be a fracture, contusion, ligamental sprain or muscle/soft-tissue injury. After successful treatment, the patient experiences residual pain, dysfunction or limitation of motion.

When this is the history, the first accessory injury to be considered is the cervical region, especially if cervical spondylosis is present. Slight injuries can occur at the nerve roots which involve nerve fibres in the root sleeves. When these are injured, they set up a radiculitis which continues to feed impulses to the original injury site. Unrelieved or persistent pain following seemingly satisfactory healing of the point of injury should always suggest further evaluation for potential cervical problems. In treating cervical radiculitis it is important to remember that it takes several months of treatment with traction and supportive physical therapy for recovery of damaged nerves.

Further assessment should also include examination of the shoulder for hypersensitive trigger points which, as stated before, may be perpetuating a pain cycle even though the initial stimulus has been negated. The elbow should be examined to rule out joint dysfunction and painful hypersensitive trigger points.

If cervical and myofascial pain sources have been eliminated, further evaluation of tendons, bursae, rotator cuff and joint capsule should be carried out to eliminate the possibility of undiagnosed injuries along the path of shock absorption. Any injury site has the potential for setting up a dystrophy-like syndrome, a possibility which must be recognised and prevented. An extremity which has residual sequelae from a previous injury is much more vulnerable for pain and dysfunction following another injury to the same extremity. It is unfortunate for the patient if the clinician overlooks these sequelae, since they can usually be treated effectively and the pain can be eliminated.

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pain syndromes are chronic, multiple and progressive, the patient rarely obtains lasting relief following initial specific myofascial therapy. Relief is temporary, only long enough to convince the sufferer that the pain is really of myofascial origin and treatable. Perpetuating factors must be resolved before the relief becomes lasting.

The following sections review first the specific technique of stretch-and-spray, then TP injection, followed by ischaemic compression. It concludes with the identification and management of a number of common perpetuating factors.

Stretch-and-spray

This treatment is generally preferred to injection as the first modality used, especially when multiple muscles are involved in a complex myofascial pain syndrome. For many muscles, it is a simple, relatively painless and rapid way to relieve a single-muscle syndrome. Additionally, it is useful immediately after injection to insure the inactivation of any remaining TPs in that group of muscles.

Purpose

In order to inactivate TPs by stretch, the involved muscle must reach its *full* stretch length. However, stretching alone causes pain and reflex spasm of the muscle, precluding further movement. The vapocoolant spray reduces the painfulness of the stretch tension, helping the patient to achieve complete relaxation. The spray also helps to block reflex muscle spasm initiated by autogenous stretch reflexes. Stretch is the ultimate goal of this technique, but is helped greatly by vapocooling, which suppresses the reactions that limit passive stretching.

Why chlorofluoromethane

Of the two vapocoolants available with nozzles that produce the jet-stream essential to this technique, chlorofluoromethane is much preferable to ethyl chloride.

Ethyl chloride is a potentially lethal general anaesthetic, flammable, explosive and colder than desirable. Freezing the skin with it has caused ulceration and cooling an underlying involved muscle aggravates its TPs; both should be avoided by applying chlorofluoromethane spray in parallel sweeps over adjacent skin areas.

Techniques

The parallel sweeps of vapocoolant are applied to the skin at a speed of about 10 cm (4 in) per second, from a distance of 50 cm (18 in). Unidirectional sweeps cover the muscle containing active TPs; the line of spray progresses in the same direction as the muscle fibres, toward the referred pain pattern. The operator pays special attention to cover the particular muscle fibres that are under maximum stretch tension, and also to cover the known pain reference zones. Spray patterns for individual muscles are illustrated comprehensively for the upper half of the body by Travell & Simons (1983) and summarised for all of the body by Simons (1983). Following stretch-and-spray, hot packs are applied at once to rewarm the skin. Then the patient moves the muscle actively through a full range of motion several times, avoiding heavy loading.

Injection

Precise TP injection with a suitable local anaesthetic can be depended on to inactivate at least temporarily those TPs that are encountered by the needle, but may not eliminate the ones that were missed.

Purpose

The primary objective of injection is to locate and disrupt individual TPs with the needle. A local anaesthetic shortens the painful period of the procedure and helps to interrupt the cycle of self-perpetuation demonstrated by many TPs.

Technique

The skin is cleansed with a suitable antiseptic, and a sterile technique is employed.

Skin pain is avoided by prespraying the area with vapocoolant for 4–5 s, or by thrusting the needle very rapidly through tightly-stretched skin, or more reliably by doing both. This application of spray is not bactericidal, but the spray itself was sterile when cultured. Frosting of the skin by the spray is always avoided; it may occur if the spray is directed at one spot for 6 s or longer.

The TP is localised and immobilised between the fingers of one hand; it is contacted with the needle of a 10 ml syringe that is filled with 0.5% procaine in isotonic saline. The syringe is held in the other hand. A few tenths of a millilitre of solution is deposited whenever a TP is impaled by the needle. Contact with a TP is identified by a local twitch response of the muscle (more often felt than seen) and/or by a pain reaction (jump sign) of the patient due to the flash of severe pain that is usually experienced when the needle encounters a TP. Travell & Simons (1983) have illustrated and described this technique in detail including caveats.

Following injection and application of pressure for haemostasis, hot packs are applied for a few minutes to reduce post-injection soreness, and then the muscle is passively stretched and actively moved through its full range of motion to fix its full functional capability in the patient's mind.

Other techniques

Ischaemic compression is also frequently effective, and is non-invasive. It may be used by itself as the primary method of therapy, and is also called myotherapy (Prudden 1980). It is similar in application to the *Shiatzu* thumb therapy of the Japanese (Irwin & Wagenvoord 1976). However, ischaemic compression and *Shiatzu* stem from quite different concepts; *Shiatzu* is applied to acupuncture points, ischaemic compression to myofascial TPs, although Melzack et al (1977) found that TPs and acupuncture points

for pain are frequently located close to each other.

To apply ischaemic compression, either the operator or the patient presses directly on the spot of greatest tenderness (the TP) with a steady, moderately painful pressure. As the pain then eases, increased pressure is added to maintain approximately the same level of discomfort. When the TP is no longer painful (or after one or two minutes of pressure), the pressure is released. After release, at first blanching and then reactive hyperaemia of the skin are evident. Any remaining nearby TPs should be similarly inactivated. Some operators prefer to apply less pressure for a shorter time, but repeatedly for several days, until the tenderness of the TP is relieved.

Dry needling of TPs without local anaesthesia is also known to be an effective mode of treatment (Lewit 1979).

The post-isometric relaxation technique (Lewit 1981) is related to the stretch of stretch-and-spray and to rhythmic stabilisation; it can be very effective when properly applied.

Rest, moist hot packs, deep massage of the involved muscles and ultrasound applied to the TPs are also sometimes used in various combinations to relieve myofascial pain (Travell & Simons 1983).

PERPETUATING FACTORS

Correction of perpetuating factors is *critically* important for lasting relief of pain in most patients with a *chronic* myofascial pain syndrome. This is a large topic that can be dealt with in only the barest outline form here, but has been covered in detail by Travell & Simons (1983).

Mechanical stresses

Mechanical stresses that overload muscles and perpetuate their TP activity are present in most patients with persistent myofascial pain syndromes. Among the most common are structural inadequacies of the body.

Structural inadequacies

A short leg, when standing, and a small hemipelvis, when sitting on a flat seat, cause the pelvis to tilt to one side. This produces a functional scoliosis and tilted pelvic and shoulder-girdle axes. Short upper arms also stress muscles.

Short leg. A short leg is measured functionally by adding pages of a pad or magazine under one heel of the standing patient (with feet together) until the pelvis is level, as determined by palpating the posterior superior iliac spines and the iliac crests. Most important, the spine should now be straight without any feeling of muscular strain by the patient. The shoulders are also levelled by the heel-lift. The shortness of one leg is confirmed by temporarily placing the lift under the other heel to double the discrepancy, which the patient almost always finds very unpleasant.

A permanent correction is added to the heel of the shoe on the short side, or a leather insert with the correction built into the heel is made to fit inside all of the patient's shoes that are suitable. If the shoes have high heels, the heel of the long side should be cut down. If the correction is a centimetre or more, it should be divided between the two shoes; half the correction is added to the heel of the shoe on the short side and half is removed from the other heel.

The strain caused by a short leg rarely activates TPs initially. However, once activated by back strain, quadratus lumborum TPs, and often TPs in shoulder-girdle and neck muscles, will persist despite treatment unless the discrepancy in leg length is corrected.

Small hemipelvis. The tilt due to a small hemipelvis when the patient is seated causes the same muscular strain as described above for a short leg when the patient stands. It is similarly measured and corrected by adding pages under the short side while the patient is seated on a firm, flat and level surface. Whenever seated, the patient must routinely use a 'butt-lift' such as a small magazine or paperback book. Soft seats require nearly double the correction under the ischial tuberosity that hard seats require.

Long second metatarsal bone. This feature of a Dudley J. Morton foot (Morton 1955) balances the weight of the body on a 'knife edge' during the stance phase of ambulation, which causes the foot to rock and the ankle to invert and/or evert. This often contributes to leg, knee and low-back pain by perpetuating TPs in the peroneus longus, vastus medialis and gluteus medius muscles (Travell 1975). The imbalance is corrected by placing a pad of Kiro Felt (Dr Scholl's Products) in the shoe under the head of *only* the first metatarsal bone. This distributes body-weight more evenly between the first and second metatarsal heads, checking the rocking of the foot (Morton 1955 and Travell 1975)

Poor posture

Furniture designed unphysiologically is a ubiquitous cause of poor posture. The failure of most chairs to provide adequate lumbar support encourages a slumped-forward, kyphotic posture that perpetuates TPs in the paraspinal, pectoral, posterior and anterior neck muscles. This defect of the chair is corrected by a roll of towelling or a narrow pillow placed in the small of the back, a correction that is particularly critical in a car when driving long distances. A similar stooped posture, when standing, is corrected by having the patient stand and walk tall with the weight shifted from the heels on to the *balls of the feet.* The head then automatically moves backward as a counterweight, to prevent falling forward.

Prolonged immobility

Leaving a muscle in a fully shortened position for a prolonged period of time, especially when sleeping, aggravates its TPs.

Nutritional inadequacies

As discussed in detail by Travell & Simons (1983), a remarkably high percentage of TPs in patients with chronic myofascial pain syndromes are perpetuated by inadequate levels of one or more B-complex vitamins, particularly B_1 B_6 B_{12} and folic acid. Many of these patients eat what is generally considered an adequate diet. A nutritional inadequacy is suspected whenever the serum vitamin value is in the

3.C.2

Sympathetic ganglion lesions

Peter Verrill

Blocking the function of the peripheral sympathetic nervous system often alleviates abnormal painful states, whether the causative lesion is central or peripheral (Loh et al 1981, Loh & Nathan 1978).

GENERAL ANATOMY OF THE SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system is the anatomically-identifiable part of the autonomic nervous system with two ganglionated chains extending from the base of the skull to the coccyx, three prevertebral plexuses (cardiac, coeliac and hypogastric) and numerous small intermediate and terminal ganglia.

The ganglia of the sympathetic chain lie on the anterolateral aspect of the vertebral column. In the neck they are anterior to the transverse processes, in the thorax anterior to the heads of the ribs, in the abdomen on the sides of the vertebral bodies, and in the pelvis in front of the sacrum. As a result of fusion there is not a ganglion for every segment but there are usually three pairs in the neck, twelve in the thorax, four in the lumbar region and four in the sacral.

Preganglionic fibres leave the thoracic and lumbar spinal cord via the anterior roots and form white rami which are connected to the ganglionated chains. Grey rami arising from these ganglia carry postganglionic fibres back to the spinal nerves, but other preganglionic fibres travel in the sympathetic chain to relay in higher or lower ganglia or pass through the ganglia to relay in the peripheral ganglia. Each spinal nerve contains postganglionic sympathetic fibres which are vasomotor or sudomotor, and are adrenergic and cholinergic respectively. Postganglionic fibres to the head are distributed along the arteries, but the abdominal viscera are supplied in a different way. The coeliac plexus receives preganglionic fibres in the splanchnic nerves and supplies postganglionic fibres to the upper abdominal viscera. The segmental distribution of sympathetic fibres is approximately as in Table 99. Afferent sympathetic fibres are carried in sympathetic nerves to terminate in the dorsal root ganglia. The sympathetic nervous system is also used by elements of the parasympathetic nervous system for distribution, e.g. the coeliac plexus receives a branch from the right vagus. The anatomical arrangement of the sympathetic nervous system allows for nerve-blocking procedures at three main sites; the stellate ganglion in the neck, the coeliac plexus in front of the first lumbar vertebra and the lumbar sympathetic chains. Although it is technically possible to block the thoracic sympathetic chain, its proximity to the pleura and the risk of pneumothorax deters most practitioners.

STELLATE GANGLION BLOCK

The sympathetic supply to the head, neck and arm can be interrupted at the stellate ganglion.

Regional anatomy

The sympathetic chains originating from the upper thoracic segments extend through the neck as far as the base of the skull. The cervical chain has no white rami and usually only three ganglia, a superior, middle and lower. The lower ganglion is usually fused with the first thoracic ganglion to form the stellate ganglion. This usually lies over the neck of the first rib. Grey rami leave the stellate and middle cervical ganglia to provide the sympathetic supply to the arm via the brachial plexus. Postganglionic fibres are also distributed to the subclavian artery and the vertebral artery and their branches. From the superior cervical ganglion grey rami form plexuses around the external carotid artery and its branches. Stellate ganglion block is achieved by the injection of a sufficient volume of local anaesthetic into the correct tissue plane. A small volume will produce sympathetic block of the head and neck but a larger volume will be necessary to produce sympathetic denervation of the upper limb.

The sympathetic chain lies anterior to the fascia covering the prevertebral muscles. These are thin sheets covering the

Table 99

Region	Segments
Head and neck	T1–T2
Upper limb	T2–T7
Thoracic viscera	T1–T4
Abdominal viscera	T4–L2
Lower limb	T11–L2

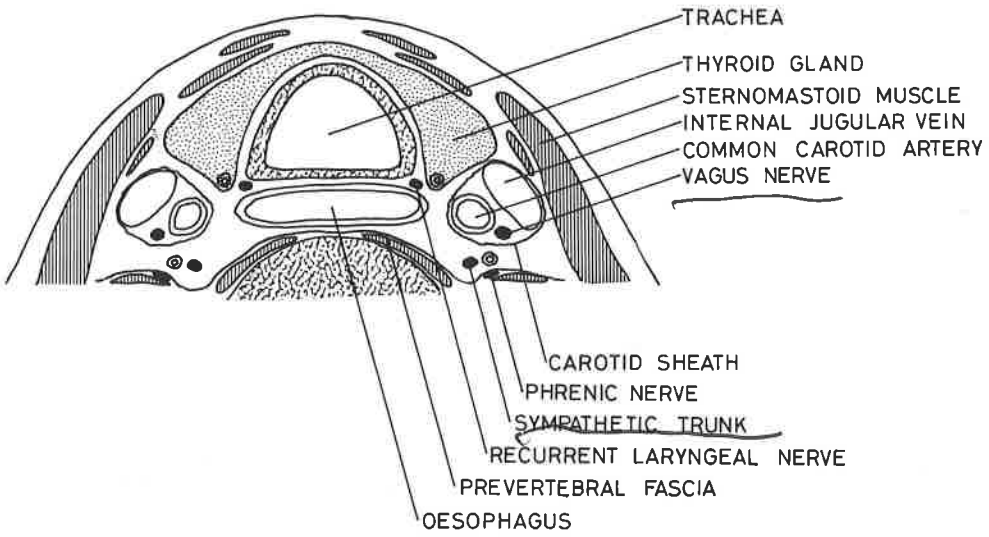

Fig. 175 Transverse section through the lower part of the neck to show the position of the sympathetic trunks

transverse processes of the cervical vertebrae. The upper six transverse processes have well developed anterior tubercles but there is no anterior tubercle on the seventh cervical vertebra. The sixth anterior tubercle is particularly prominent, is known as Chassaignac's tubercle and is easily palpated in the neck at the level of the cricoid cartilage. The vertebral artery runs upward in foramina in the transverse processes and the cervical spinal nerves pass out between them in long dural sleeves. Anterior to the sympathetic chain lies the carotid sheath and medially the pharynx and larynx with the recurrent laryngeal nerve between them (Fig. 175) Inferior to the stellate ganglion lies the dome of the pleura. Many of the complications of stellate ganglion block are related to its proximity to important anatomical structures.

Moore (1954) has described 16 possible approaches to the cervical sympathetic chain. These are variations of anterior lateral and posterior approaches. The anterior approach is most commonly used and the objective is to place a needle in the correct plane well above the pleura and to inject a volume of anaesthetic which will bathe the cervical and upper thoracic sympathetic chains, Smith (1951) described such an approach at the level of the seventh cervical transverse process but more recently Lofstrom (1969) and Carron & Litwiller (1975) have described an anterior paratracheal approach at C6 and this is the method used by the author. It has the advantages of needle placement well above the dome of the pleura and well anterior to the plane of the roots of the brachial plexus.

Technique

The patient lies supine with the head slightly raised and extended on a flat pillow. A finger between the sternomastoid and the trachea feels for the most prominent transverse process which should be the sixth, at or slightly above the level of the cricoid cartilage. Palpation may be facilitated by a slight opening of the patient's mouth. A skin weal is made at this point. The essential manoeuvre in this technique is using the middle and index fingers of the operator's left hand to compress the groove between the sternomastoid and the trachea and to gently hook the carotid sheath and its contents laterally (Fig. 176). This has the effect of making the anterior tubercle of C6 almost subcutaneous so that it can be reached with a 2.5 cm 20 gauge needle attached to a 10 ml syringe. If the palpating fingers of the left hand are separated slightly they can straddle the transverse process of C6 and the needle can be inserted at right angles to the skin to contact the anterior aspect of the transverse process. It should be possible to dance the needle lightly on the bone and demonstrate the sensation to an observer. If bone is not contacted the needle may have passed between the transverse processes and could penetrate the vertebral artery or a dural sleeve. It is vitally important not to inject local anaesthetic unless the operator is confident of being anterior to the transverse process. Passage of a needle between the

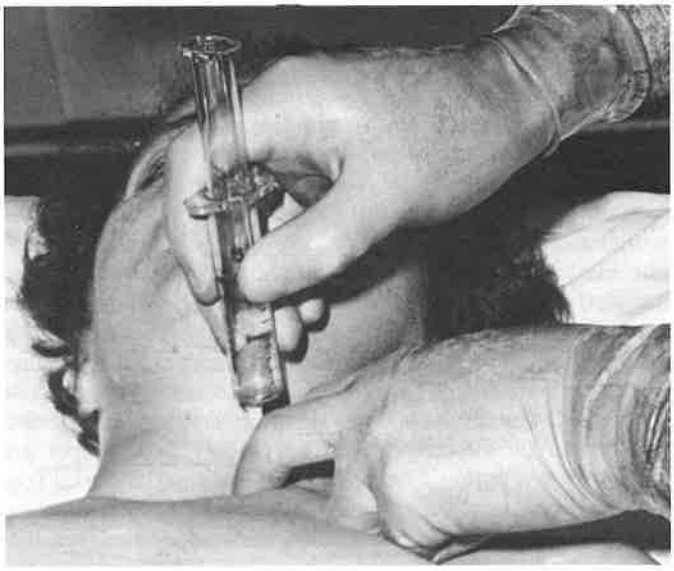

Fig. 176 Left stellate ganglion block. The index and middle fingers are being used to hook the carotid sheath laterally.

transverse processes usually meets a fibrous resistance and causes a dull, aching pain.

When the needle rests securely on the transverse process the palpating fingers can be moved to hold the hub of the needle after which the needle should be withdrawn 2–3 mm and fixed with the left hand. After careful aspiration the injection is made with the right hand. 10 ml of 0.25% plain bupivicaine is then injected and the needle withdrawn.

If the patient is allowed to sit up at this stage gravity will accelerate the development of ptosis on the injected side. Often the first sign of a correctly-placed injection is a moistening of the conjunctiva and this is followed by the classical triad first described by Horner (1869) ptosis or drooping of the eyelid, enophthalmos and myosis or constriction of the pupil. If the light is restricted it will be seen that the affected pupil does not dilate. An additional eye sign is suffusion of the conjunctiva. Within the next few minutes other signs develop. The nose may become blocked on the injected side and the face may become flushed and dry. The development of Horner's syndrome and the other associated signs described above does not necessarily imply that sympathetic blockade of the arm has been achieved but it is confirmation that the anaesthetic solution has been injected into the correct tissue plane and if a significant volume has been used it will spread to affect the sympathetic outflow to the arm and lead to subjective warmth before it is obvious to the physician.

Complications

Incorrectly-performed stellate ganglion block can produce some alarming complications. If the injection is made too low the pleura may be penetrated; for this reason a full syringe should be kept attached to the needle and if needle insertion produces coughing it should be withdrawn and a chest X-ray should be carried out subsequently. Injection of local anaesthetic drugs into the vertebral artery may lead to dizziness, convulsions and unconsciousness. Injection into the dura will produce high spinal anaesthesia and possible respiratory arrest and circulatory collapse. Injection too medially may puncture the pharynx and produce an unpleasant sensation of taste. The recurrent laryngeal nerve becomes anaesthetised in about 10% of cases with resulting hoarseness for several hours. The brachial plexus may also be affected resulting in temporary loss of sensation in the arm. Haematomata are not uncommon in such a vascular region but can be minimised by the use of fine needles. With careful attention to asepsis, infection is uncommon but osteitis and mediastinitis have been reported. It is generally advised that stellate ganglion block should be carried out one side at a time and that when bilateral blocks are indicated these should be carried out on alternate days. It is possible that simultaneous bilateral blockade could result in bradycardia and bilateral recurrent laryngeal palsy can cause acute respiratory obstruction due to adduction of the vocal cords.

INDICATIONS

In the past, stellate ganglion blockade has been used for a wide variety of conditions, but the two main indications have been vascular insufficiency and pain. Acute vascular occlusions lead to spasm and pain which may be relieved by stellate ganglion block and the method has been used to treat arterial spasm following embolectomy and at one time was used in the early treatment of cerebrovascular occlusions. Sudden deafness may respond to sympathetic block by relief of arterial spasm and remissions are occasionally produced in Menière's disease. The accidental intra-arterial injection of drugs such as thiopentone leads to intense spasm which may be relieved by sympathetic block. The commonest vascular disorder to be treated by stellate ganglion block has been Raynaud's disease or phenomenon and severe cases showing gangrene of the finger tips have responded well to alternate daily blocks.

Causalgia, reflex sympathetic dystrophy and Sudeck's atrophy are the major painful indications for cervical sympathetic block but a number of other painful peripheral states may benefit, particularly when the pain is accompanied by hyperpathia (Loh & Nathan 1978). These conditions include post-herpetic neuralgia, post-amputation pain, painful scars, pain due to carcinoma and Paget's disease. In some cases of pain due to lesions of the central nervous system, pain and hyperpathia are temporarily relieved by sympathetic block (Loh & et al 1981).

It is unusual for pain relief to be permanent after a single stellate ganglion block, but with repeated blocks on alternate days relief often becomes more prolonged and many experts regard a course of five to eight injections as normal. Neurolytic blocks of the stellate ganglion require accurate localisation with X-ray control and have been used in the treatment of intractable angina (Lipton 1979) but even with X-ray control there is a high risk of complications due to spread of the neurolytic solution to affect neighbouring structures.

The intravenous regional sympathetic block with guanethidine (Hannington Kiff 1974) has proved a very useful technique. Where pain or vascular insufficiency is confined to the arm it is as effective as stellate ganglion blockade. In the authors experience a series of three guanethidine blocks carried out on alternate days will often alleviate Raynaud's phenomenon for as long as 4 months, and the method has been shown to be as effective as a series of stellate ganglion blocks in a number of painful states (Loh & Nathan 1978). Occasionally, when pain is not relieved by guanethidine block it is relieved by stellate ganglion block, so that if a series of at least two guanethidine blocks fails to produce relief one stellate ganglion block should be carried out before deciding that sympathetic blockade is not helpful.

Surgical sympathectomy has been in use for over 50 years and was frequently used in the treatment of Raynaud's phenomenon. It is more likely to be helpful in primary Raynaud's phenomenon than when the condition is associated with collagen disorders, but there is a tendency for symptoms to return within 6 months – 2 years (Gillespie 1975). Surgical sympathectomy has also been used in the treatment of painful conditions which have been relieved by diagnostic stellate ganglion block. Surgery carries the risk of producing a permanent Horner's syndrome, and in many

cases pain and hyperpathia return within a year. In the arm there is a tendency for sympathetic activity to return in a relatively short time (Barcroft & Hamilton 1948), but when this occurs guanethidine block is often effective in reinforcing and prolonging the effect of sympathectomy. Guanethidine has been shown to produce axon retraction in newborn rat sympathetic cultures (Burnstock 1974) and it may be that in man regenerating sympathetic fibres are particularly sensitive to guanethidine.

LUMBAR SYMPATHETIC BLOCK

Regional anatomy

In the lumbar region the sympathetic ganglia lie on the antero-lateral surfaces of the lumbar vertebrae along the medial margin of the psoas muscle. There are usually four ganglia but their arrangement is variable: adjacent ganglia may be fused but almost always there is a large ganglion on the second lumbar vertebra. The first, second and sometimes the third lumbar nerves send white rami communicates to the corresponding ganglia; these are long rami and accompany the lumbar arteries around the sides of the bodies of the vertebrae. The psoas muscle takes origin from the sides of the lumbar vertebrae and part of its origin is a series of tendinous arches across the waists of the bodies of the lumbar vertebrae. These arches pass over the white rami. Grey rami pass from the ganglia to the lumbar spinal nerves which lie in the posterior part of the psoas muscle. The genito femoral nerve arises from the first and second lumbar nerves and passes through the psoas to emerge near its medial border opposite the third or fourth lumbar vertebra. On the right the sympathetic chain lies behind the inferior vena cava (Fig. 177). On the left the aorta is well forward and medial to the chain. The kidneys form an important posterior relation. Their surface markings extend from the eleventh thoracic to third lumbar spines between two vertical lines drawn 2.5 and 9.5 cm from the midline with the hilum opposite the lower border of the first lumbar spine. The position of the lumbar sympathetic chains in relation to the lumbar vertebrae allows very accurate needle placement with radiological assistance and their separation from other important anatomical structures permits the injection of neurolytic solutions to produce relatively permanent effects with a low incidence of complications. Furthermore the chains occupy a fascial compartment between the vertebrae, the psoas muscle and the retro-peritoneal fascia so that solutions deposited in this compartment will spread up and down to bathe the chain.

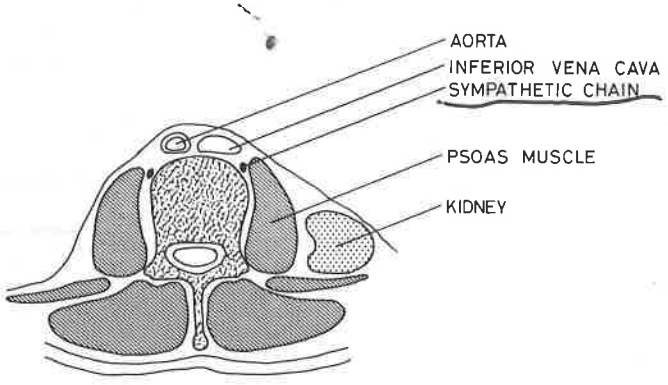

Fig. 177 Transverse section of the paravertebral region at the level of L3 to show the position of the sympathetic chains

(Mandl 1926) first described a technique for blocking the lumbar sympathetic chain and later studied the effects of Phenol on the sympathetic chain of cats (Mandl 1947). Reid et al (1970) described their experiences with over 5000 injections. They used a posterior paravertebral approach to L3 and L4 from points 10–12 cm lateral to the midline. Other writers have recommended three or four needle insertions from L1 to L4 varying from 5–13 cm from the midline. Other points at issue are how far the needles should be inserted and whether X-rays should be used.

L2 is probably the most important level at which to aim since the pre-ganglionic outflow to the sympathetic chain usually ends here (Carron 1976) but as long as at least one needle enters the correct tissue plane, injection will produce effective blockade. For this reason the author inserts two needles, one at L2 and one at L3. Too lateral an approach risks injury to the kidney and it is wise not to stray further than 10 cm from the midline at the L2–L3 level, but rather than apply one measurement to patients of all sizes it is preferable to use the lateral edge of the paravertebral muscle mass as the guide. When diagnostic block is being performed only one needle need be inserted at any level between L2, L3 and L4 and the injection of 15–20 ml of solution is very likely to produce effective sympathetic blockade. When neurolytic agents are being used precision is essential and this can only be provided with the help of X-rays.

Technique of chemical sympathectomy

The patient is placed prone and the twelfth rib iliac crest and lumbar spines marked on the skin. After skin preparation skin weals and deeper infiltrations of local anaesthetic are made at the lateral edge of the paravertebral muscles opposite the spine of L2 and L3. 18 gauge needles are used to approach the bodies of L2 and L3 (Fig. 178). Using this fairly lateral approach the first bone encountered is often the vertebral body. Bony encounters at a fairly superficial level are usually with tips of transverse processes and these can usually be passed by cephalad angulation. The use of 18 gauge needles allows easier directional alterations and a brisk flow of blood or cerebrospinal fluid, without aspiration, in the event of malplacement. Following the insertion of the first needle it is helpful to check its level radiographically so that the second needle can be placed above or below it. Viewed antero-posteriorly the points of the needles should appear to lie inside the vertebral bodies (Fig. 179). A lateral radiograph is then taken and the needles advanced until their tips are almost at the anterior borders of the lumbar vertebrae. It is important to advance the needles sufficiently to emerge from the psoas muscle and a loss of resistance may then be experienced. If injection is carried out with the needle still in the substance of the psoas, sympathetic blockade will usually result, but there is an increased risk of genito-femoral neuritis. Once the position

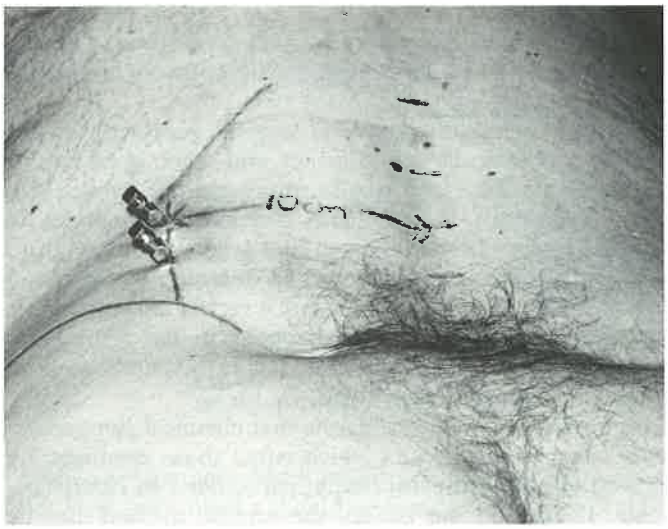

Fig. 178 Lumbar sympathetic block in a large male. The patient is prone and two needles have been inserted 10 cm from the midline at levels L2 and L3.

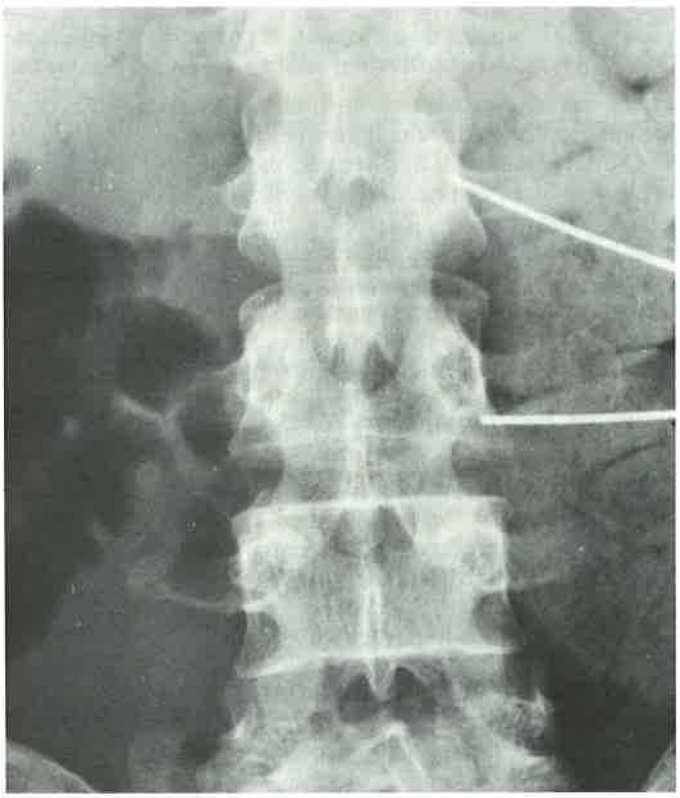

Fig. 179 Lumbar sympathetic block. Antero-posterior X-ray. The tips of the needles appear to be just inside the bodies of the second and third lumbar vertebrae.

of the needle is satisfactory gentle aspiration should be attempted. If blood is withdrawn from either needle it should not be used. The injection of 1 ml of contrast medium should reveal a spread limited to the anterolateral aspect of the lumbar vertebrae and not widely within the psoas muscle (Fig. 180). Many experts rely on X-ray appearances without the use of contrast medium and there is some risk that the contrast material will dilute the neurolytic solution and reduce its effect.

The neurolytic solution most commonly used is 6% phenol in aqueous solution and this has the advantage of not causing pain but is thought by some to produce less permanent results than the use of absolute alcohol. If absolute alcohol is used a brief period of general anaesthesia is necessary. The author injects 3 ml of absolute alcohol through each needle and increases the volume to 4 ml if only one needle can be used. Use of this volume through a single, accurately-placed needle has frequently produced satisfactory blockade. The use of a second needle merely increases the chances of technical success.

Complications

These are usually minor and confined to bruising and stiffness in the back due to the passage of the needles. If a little air is injected to clear the needles before they are withdrawn following neurolytic injections this reduces the incidence of local irritation and neuritis due to alcohol or phenol follow-

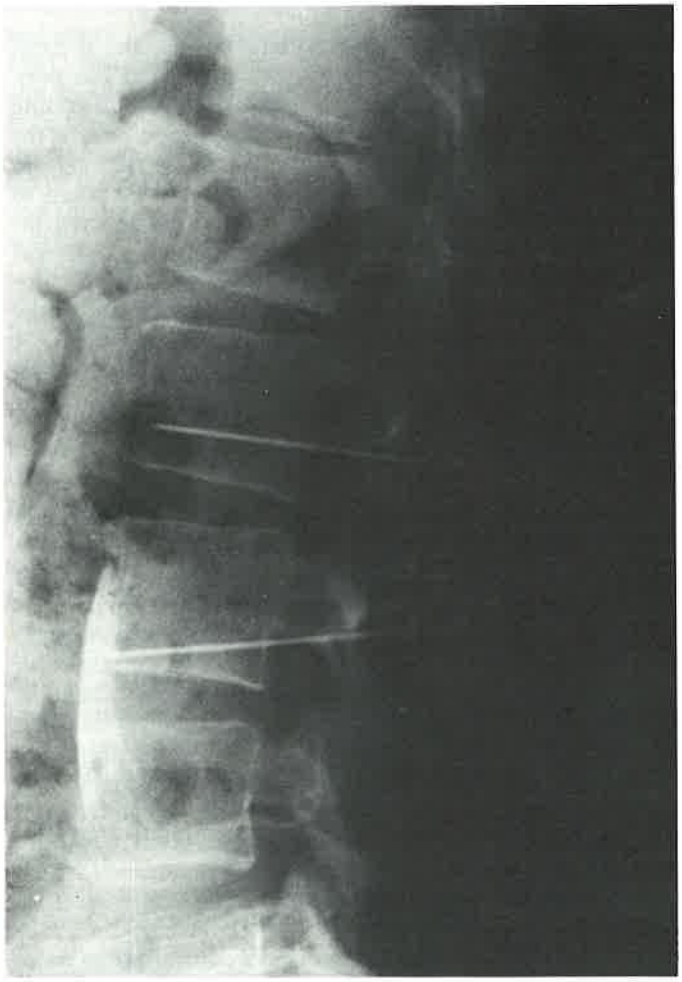

Fig. 180 Lumbar sympathetic block. Lateral X-ray. The tips of the needles have been advanced almost to the anterior borders of the bodies of the second and third lumbar vertebrae. 1 ml of contrast medium has been injected through the lower needle and its spread is confined to the anterolateral aspects of the vertebrae.

ing the track of the needles. Should this occur infiltration of local anaesthetic and steroid is very helpful.

In up to 20% of cases post-sympathectomy sympathalgia develops. This complication, which is just as frequent after surgical as after chemical sympathectomy was well described by Tracey & Crockett (1957). After a latent period of 10–17 days the patient develops pain over the anterior aspect of the thigh, as far as the knee. It is worse at night and hyperaesthesia is a prominent feature. Spontaneous remission occurs in a matter of weeks. This complication occurs sufficiently frequently that patients should be forewarned, particularly as it usually develops after they have left hospital. The condition is alleviated by simple analgesics but if insufficient relief is produced epidural analgesia should be considered. Genito-femoral neuritis due to spread of neurolytic solution usually presents fairly early with pain and dysaesthesia or with anaesthesia over the front of the thigh.

Major neurological deficit due to injection of neurolytic agents into the intervertebral foramina should be avoided by the use of X-rays, but there is a remote risk of major neurological deficit resulting from damage to the arterial supply of the spinal cord.

Lumbar veins cross the sympathetic chains, and if damaged may lead to extravasation of blood behind the peritoneum and this may lead to paralytic ileus. Bleeding within the psoas muscle may cause backache and pain in the groin; sympathetic blocks should not be carried out in patients receiving anticoagulants. Care should be taken to avoid intravascular injection. When alcohol is injected intravenously it usually provokes a fit of coughing, whereas phenol may produce convulsions (Benzon 1979).

A needle placed too laterally may pass through the cortex of the kidney and this may be followed by haematuria. A needle moving up and down with respiration, on screening gives warning of this possibility.

Indications

By far the commonest indication for lumbar sympathetic block is arterial disease of the lower limbs. It is most likely to be useful, when the foot is ischaemic in a limb not suitable for direct arterial surgery or when the patient is judged unfit for prolonged general anaesthesia and surgery. Many of the patients in this group have ischaemic rest pain, ulceration and threatened gangrene. Successful chemical sympathectomy relieves rest pain in the majority of these patients and this often precedes any demonstrable improvement in the circulation. The best results are achieved in non diabetic patients over the age of 60 (Hughes-Davies & Redman 1976). Chemical sympathectomy is often added to reconstructive arterial surgery in the lower limb.

It is doubtful whether intermittent claudication can be reliably alleviated by sympathectomy (Fyfe & Quin 1975) since improvement in blood flow is more to skin than muscle. Feldman & Yeung (1975) have described the use of paravertebral block with phenol for the relief of this condition. It may be that on the occasions when lumbar sympathetic block relieves intermittent claudication, it is due to neurolysis of afferent sympathetic fibres within the psoas muscle.

Other vasospastic conditions where sympathetic block is useful include frostbite, erythromelalgia, severe chilblains and thrombophlebitis.

Chemical sympathectomy is usually reserved for the treatment of vascular insufficiency and when good results are produced these are usually prolonged (Gillespie 1960, Lynn & Barcroft 1950). There is a maximal increase in blood flow after 2 days followed by a gradual decline but in most cases there is a long standing doubling of the blood flow. A minority of cases show much return of sympathetic function in contrast to what happens in the arm. Post-sympathectomy escape when it occurs responds well to intravenous guanethidine block.

Increasing experience suggests that chemical sympathectomy can produce results which equal those produced by surgical lumbar sympathectomy, particularly in elderly patients. In the younger patient the surgical method may be preferred as a long segment of the chain can be reliably removed and the risk of genito femoral neuritis avoided, but the risk of post sympathectomy sympathalgia is not reduced.

Pain and sympathetic block

There are three main groups of neurological disorders accompanied by pain which may be relieved by sympathetic block, post-traumatic dystrophies, painful peripheral states and pain due to central nervous system lesions.

The pain produced by injury to peripheral nerves has been known as causalgia since Weir Mitchell introduced the term in 1864. Although it occurs in less than 5% of injuries and more often in the upper limb it is notorious for its resistance to treatment once well-established. The pain is characteristically burning in quality and the affected region shows alterations in sweating and temperature regulation and loss of motor function. Pain is intensified by light cutaneous stimulation.

The term algodystrophy has been introduced to include most conditions hitherto described as minor sympathetic dystrophies. There are three essential diagnostic features, intense ill defined pain and hyperaesthesia, vasomotor changes and sweating disturbances and osteoporosis. Most of these syndromes follow minor trauma or surgery. Once well established treatment is often unsuccessful but sympathetic block is most likely to be useful if introduced at an early stage.

In the leg as in the arm a number of painful peripheral states are sometimes alleviated by sympathetic block and include, post amputation pain, post herpetic neuralgia, painful scars, carcinomatous invasion of nerves and occasionally pain due to lesions of the central nervous system may be improved. The combination of burning pain and hyperpathia should lead to a trial of sympathetic block.

There is some evidence that the sympathetic nervous system influences receptors, afferent nerve fibres and posterior root ganglia but it seems clear that blocking the sympathetic fibres and preventing noradrenaline release stops the hyperaesthesia, hyperpathia and pain in certain painful states.

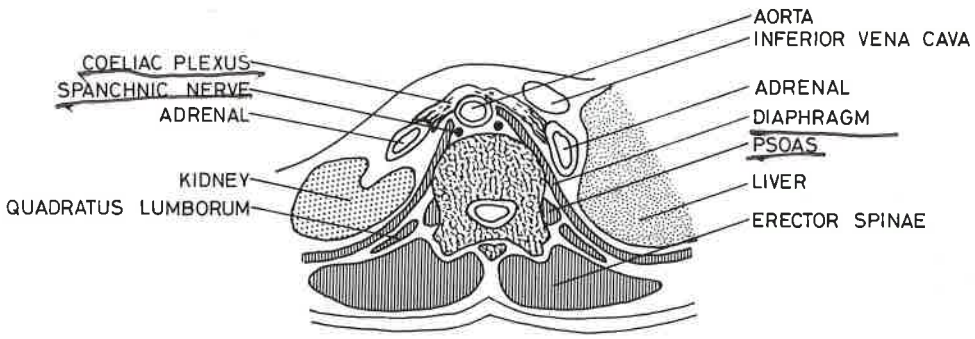

Fig. 181 Transverse section of the paravertebral region at the level of L1 to show the position of the coeliac plexus and the splanchnic nerves

When sympathetic block relieves pain in the leg, a series of at least three blocks should be completed and pain relief may thereby be prolonged. Guanethidine block may be equally as effective as paravertebral sympathetic block, but whereas in the arm guanethidine block is a more trivial procedure than stellate ganglion block it is a more formidable procedure in the leg, necessitating a high pressure tourniquet and twice the dose of guanethidine. Intravenous sedation is necessary and the patient needs to stay in hospital overnight.

Paravertebral sympathetic block with local anaesthesia is a simpler procedure which can be carried out on an outpatient basis but if the patient refuses a series of blocks or prolongation of relief does not occur with successive blocks, intravenous regional sympathetic block should be tried (Benzon et al 1980).

COELIAC PLEXUS BLOCK

Coeliac plexus block is the single most effective neurolytic nerve block (Thompson et al 1977).

Anatomy

The coeliac plexus is the upper part of the plexus of autonomic nerves around the aorta. It surrounds the coeliac artery at the level of the upper part of the first lumbar vertebra. There are two large coeliac ganglia one on each side of the midline in front of the crura of the diaphragm (Fig. 181). The plexus contains preganglionic parasympathetic fibres, preganglionic and postganglionic sympathetic fibres and afferent fibres. Preganglionic sympathetic fibres reach the coeliac plexus in the greater and lesser splanchnic nerves. The plexus also receives branches from the right vagus. Numerous secondary plexuses pass from the coeliac plexus along the arteries supplying the abdominal viscera. Organs supplied include the stomach, liver, gallbladder, pancreas, kidneys and the gut as far as the transverse colon.

Technical considerations

The coeliac plexus is a large structure of variable anatomy. The size and vertebral level of each ganglion can vary appreciably and the presence of malignant tumours, whether primary or secondary can interfere with the spread of anaesthetic and neurolytic solutions. Classical methods relied on bony landmarks for needle placement and this produced a wide range of results, with success rates varying from 33% to 94% (Thompson et al 1977). The use of X-rays and more recently computerised tomography (Moore et al 1981) has clarified some important technical points. The aim should be to pass one needle on each side paravertebrally to the front of the first lumbar vertebra without impaling the kidneys. Maximum spread of solution occurs when the tip of the needle on the left is immediately behind the aorta and the tip of the right needle is adjacent to the side of the aorta.

Anatomical studies during autopsies on 20 adults (Ward et al 1979) suggest that the left needle should have its tip at the junction of the middle and lower thirds of the first lumbar vertebra with the needle on the right 1 cm higher (Ward et al 1979) but radiography and computerised tomography show that needles placed anterior to the first lumbar vertebra are behind and above the crura of the diaphragm and solution injected here spreads mainly cephalad along the sides and anterior to the vertebrae. To bathe the coeliac plexus itself the solution must pass through the aortic hiatus in the diaphragm and this may be obstructed by tumour but pain relief is probably produced by solution bathing the splanchnic nerves behind and above the diaphragm. A volume of 25 ml through each needle is necessary. To avoid the kidneys the needles should not be inserted further than 7.5 cm from the midline (Fig. 182).

It is usually desirable to perform a diagnostic block with local anaesthesia before carrying out neurolytic injection. This discovers the extent of the pain relief which can be produced and prolonged by neurolysis and may reveal the possibility of serious complications e.g. profound hypotension. Although diagnostic block is commonly carried out without X-ray control it has some advantages in that if substantial pain relief develops with needles in known positions efforts can be made to place neurolytic injections by means of identical needle positions. The only serious disadvantage of diagnostic block is that if a large haematoma is produced this may interfere with a subsequent attempt at neurolytic block.

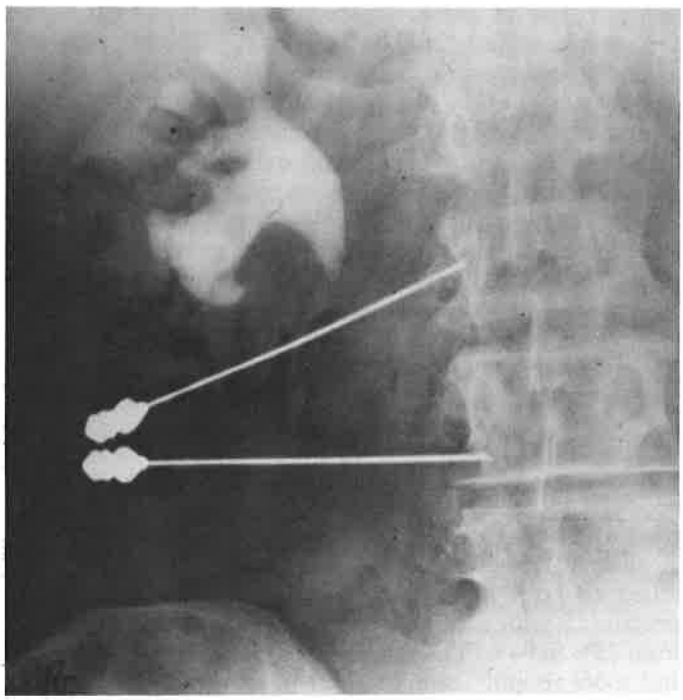

Fig. 182 Antero-posterior X-ray of the lumbar spine with needles positioned for chemical sympathectomy. The patient has a large renal calculus and it can be appreciated that a needle inserted to reach the first lumbar vertebral body risks injury to the kidney and should not be inserted too far laterally.

Technique

The patient should be placed prone and the arms raised alongside the head or allowed to hang down alongside the table. Sedation is often necessary; intravenous diazepam provides this and the addition of an analgesic either as premedication or intravenously may be helpful; an intravenous infusion should be established.

It is essential to identify the important landmarks and mark these on the skin. These are the twelfth ribs, the upper lumbar spines and a vertical line 7 cm from the midline. The transverse process of the twelfth rib is rather shorter than that of the lumbar vertebrae and this permits needle insertion nearer the midline than in lumbar sympathetic block. Needles of 15 cm should be enough to reach the coeliac plexus in most cases and should be 18 or 20 gauge with stilettes. It is an advantage to screen the patient before introducing the needles in order to discover the angulation of the twelfth ribs and any abnormalities of the lumbar vertebrae such as a sixth vertebra. A large kidney outline may suggest a more medial approach.

After appropriate skin preparation and local anaesthetic infiltration of the skin and subcutaneous tissues the blocking needles are introduced where the vertical line crosses the twelfth rib and angled cephalad at an angle suggested by the screening. Care should be taken that the needle is not passed at too shallow an angle from the skin or it may enter an intervertebral foramen.

Often the first bony encounter is with the body of the first lumbar vertebra and the needle can be walked off it anteriorly. Anteroposterior screening at this stage should show the needle appearing to be within the outline of the first lumbar vertebra and heading for its upper border (Fig. 183). Needles need to be advanced well in front of this vertebra as shown by a lateral X-ray and a distance of about 1.5 cm is likely to be satisfactory. On the left this may result in aortic pulsations being transmitted to the needle in which case the needle should be withdrawn about 3 mm from this valuable landmark. The right needle is introduced as on the left to the same depth. It can then be advanced a further 1 cm to bring its tip lateral to the aorta. Stilettes can now be removed and the needles aspirated for blood. If either needle is moving with respiration, renal puncture should be suspected, the needle withdrawn completely and reinserted more medially.

Once the needles are satisfactorily placed a small injection of contrast should be given to check that neither needle is in a blood vessel. If the block is diagnostic, 25 ml of 0.25% bupivicaine with adrenaline 1 in 200 000 is injected taking about 30 seconds for each injection. For neurolytic injections 25 ml of 0.5% bupivicaine is mixed with 25 ml of absolute alcohol. A test injection of 5 ml should be given through each needle and after a few minutes careful observation the injection completed.

Complications

Postural hypotension is very likely, so the circulating blood volume should be increased by the intravenous infusion of 1–2 litres of crystalloid and the patient kept flat initially and allowed to sit up only after careful observation of blood pressure. Younger patients accomodate fairly rapidly to the widespread sympathetic block but older patients may suffer from postural hypotension for several days.

Irritation of somatic nerves by alcohol can be avoided by clearing the needles with air before withdrawal, but when the complication occurs local infiltration with local anaesthetic and steroid is very helpful. Major neurological complications should be avoided by checking that needle tips are not positioned in the locality of the intervertebral fora-

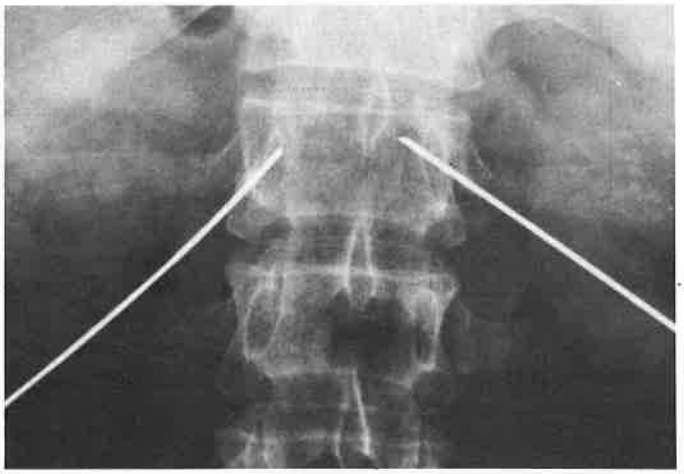

Fig. 183 Coeliac plexus block. Antero-posterior X-ray. The tips of the needles are heading towards the upper border of the first lumbar vertebra.

mina on the lateral X-ray. Galizia & Lahiri (1974) describe a case of paraplegia following coeliac plexus block with phenol when only 6 ml were injected and postulate that this was due to intravascular injection, but no X-rays had been taken. A particularly important artery supplying the spinal cord is the artery of Adamkiewicz. It occurs on the left side in about 80% of cases somewhere between T7 and L4 but most often between T9 and T11 (Dommisse 1980), so may be at risk during coeliac plexus block. Radiography and the test injection of a small amount of contrast should minimise the risk.

After neurolytic injection many patients experience backache and increased pain in the upper abdomen for a day or two but will begin to feel the benefit of the block after this. Gut motility is often increased dramatically and previously constipated patients may welcome this.

The widespread sympathetic block produced by coeliac plexus block may lead to loss of ejaculatory reflexes in the male, but potency may not be affected. Patients should be warned of this possibility. The theoretical possibility that splanchnic block could produce a dangerously silent abdomen does not seem to have resulted in any potential problems and the innervation of the parietal peritoneum coming from the somatic nerves remains intact.

Indications

Carcinoma of the pancreas remains the main indication for coeliac plexus block (Jones & Gough 1977, Thompson et al 1977) and good results can be expected in over 90% of cases. Other upper abdominal cancers are less reliably relieved and diagnostic blocks should always precede neurolysis. Some of the symptoms may be due to parietal peritoneal involvement.

In recent years chronic pancreatitis has been an increasingly common cause of upper abdominal and paraspinal pain. It is frequently associated with alcohol abuse. Coeliac plexus block is often effective in relieving this pain though less so than in carcinoma (Bell et al 1980) but since these patients have a longer life expectancy, pain recurs sooner or later probably due to regeneration of sympathetic fibres. Coeliac block can then be repeated, but is often less successful and the author is reluctant to carry out a series of neurolytic blocks unless good relief is produced for a period of at least 6 months. In carcinoma of the pancreas few patients survive more than a few months but survival times are increasing and it is occasionally necessary to consider repeat blocks in these patients, but recurrence of pain is often due to extension of tumour to involve the parietal peritoneum or the development of metastases, and successful neurolytic block is then unlikely; careful assessment should be made of the patients general condition together with his response to diagnostic block.

If the abdomen is opened surgically it may be possible to divide the splanchnic nerves or infiltrate the coeliac plexus with neurolytic agents but these structures are often obscured by tumour and the posterior approach used for coeliac plexus plexus block is more likely to be successful.

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the mean volume was almost the same (2.09 ml).

These studies all indicate that the average volume of disc tissue removed by discectomy represents only 6–8% of the total disc volume, and apparently it is not easy to excise disc tissue with the instruments usually applied for this purpose — rongeur and curette — unless the disc is already in a certain condition of degeneration and fragmentation.

The 'combined operation'

Since 1940 it became increasingly common to advocate concomitant discectomy and some type of fusion operation as a standard procedure in an attempt to improve the results of disc surgery. Arthrodesis of the spine — or fusion — was already an established and approved operation, based on the principles of Albee and Hibbs, in the treatment of an unstable spine. As compared to simple discectomy, fusion is a surgical procedure of considerable magnitude with prolonged convalescence and more serious post-operative complications.

Most studies comparing discectomy with and without concomitant fusion indicate that the results after the 'combination operation' are 5–10% better than after simple discectomy (Nachlas 1952, Hoytema & Oostrom 1961, White 1966). The issue is still controversial, but the dominating conclusion has been that the advantage of the 'combined operation' is too small to warrant the use of this method as a routine in patients with typical lumbar disc herniations. The surgical indications for discectomy and spine fusion are different, and the decision to recommend a fusion depends on many factors. The special indications for this procedure should be considered separately in the individual case, when disc surgery is planned (Symposium 1981).

Re-operation after discectomy

The rate of re-operations after a first disc operation is usually reported at 10–15%, and the risk of acquiring a new disc herniation is probably considerably increased in patients with a verified herniation in their medical history.

Recurrences occur both on the same side and level and at others, but rarely within the first year after a discectomy. The mean interval between the first and a second operation for true disc herniation is 5–6 years in our experience, but a true recurrence from the same disc may occur more than 20 years after the 1st operation.

The pathological process, which in some patients results in a true disc herniation, tends to begin at the lumbo-sacral level and proceed in the cranial direction with age. The mean age at operation for verified ruptures at the level L5–S1 was found to be 38 years, at the level L4–L5 42 years, and in the unusual herniations at the three higher levels (L1–L4) 47 years (Spangfort 1972). Simultaneous complete ruptures of two different discs were never found during the same operation in this series, and seem to be very rare.

Thus, symptoms of a recurrent disc herniation may be expected with a certain degree of probability approximately 5 years after a first operation, although not necessarily severe enough to motivate a re-operation. In this situation there is no reason to classify the first operation as a failure.

In patients without relief of pain for at least 6 months after a 1st operation, the operation has usually been an outright failure — in some cases caused by technical errors during the operation, e.g. failure to locate an offending fragment or exposure at a wrong level, but in the majority caused by an incomplete or wrong pre-operative diagnosis: another type of operation should have been performed, or the patient should not have been exposed to surgical treatment at all. In the latter group the probability of a successful re-operation with the same technique is low. If the first operation was a negative exploration, the risk of a second negative exploration is about 50%.

The results of re-operations are generally less favourable than those of first operations. This is partly due to a somewhat higher rate of surgical complications at re-operations, but the main reason is diagnostic difficulties in patients assessed for repeat surgery — resulting in high rates of negative explorations in this group. When the degree of herniation found by re-operation is considered, the results are, however, almost as good.

In my study of the disc operation, the rate of excellent results — i.e. complete relief of both low-back pain and sciatica — decreased from 62.0% after first operations to 43.1% after second operations and 28.6% after third operations.

If a disc herniation was found by re-operation (161 cases) the rate of excellent results was still 53.4%, but if the re-operation was a negative exploration (69 cases) the rate was as low as 14.5%. Again, the pre-operative diagnosis is crucial for the result of operation. Proper selection of patients for re-operation is, however, often a difficult task even for the experienced low-back specialist.

The multi-operated low-back patient with a 'failed back-surgery syndrome', who seldom achieves satisfactory relief of pain by any combination of measures, should be carefully examined by a qualified investigation, preferably in a centre specialising in assessing these highly complicated patients, before further 'salvage surgery' is attempted — 'no matter how severe or how intractable the pain, it can always be made worse by surgery' (Finneson 1978).

Epidural scar formation

The prevalent pathological condition found in re-operations for recurrent pain after disc surgery is often a dense fibrous scar formation strangling the dura and nerve roots. This scar formation is considered a major cause of recurrent symptoms after discectomy; it also complicates correct diagnosis and re-operation of a true recurrent disc herniation. Excision of the scar tissue — neurolysis — is difficult and the results of dissection usually poor.

LaRocca & MacNab (1974) called this excessive fibrosis 'the laminectomy membrane', and showed that the main source is fibrous tissue from traumatised surrounding muscles.

Langenskiöld & Kiviluoto (1976) reported efficient prevention of epidural scar formation by the use of free grafts of subcutaneous fat tissue placed on the denuded dura.

It has been confirmed that covering raw bone and mus-

cles with fat grafts before the wound is closed impressively reduces the formation of epidural scar formation.

Urgent disc surgery

The only indication for immediate disc surgery is acute compression of the cauda equina by a large herniation causing a sacral syndrome with neurological signs referable to the second and lower sacral roots — i.e. dysfunction of the bladder and bowel with loss of sphincter control, impairment of sexual functions and saddle-shaped loss of sensation in the sacral dermatomes. In most cases the herniation is large, situated in the midline and ruptured. The condition is rare, probably less than one case per year in a population of 200 000.

In patients with symptoms of acute cauda equina compression a qualified examination — including cystometry and myelography — is urgent. Dysfunction of the bladder is, however, a common symptom in patients with severe low-back pain and not necessarily caused by a large disc herniation.

Immediate surgical decompression is generally considered mandatory, when an acute disc herniation is identified as the cause of the syndrome.

Severe impairment of bladder function, bilateral saddle anesthesia, and a pre-operative duration of more than two days appear to imply a poor prognosis for satisfactory neurological recovery after surgical decompression (Aho et al 1969).

SURGICAL INDICATIONS AND SELECTION OF PATIENTS

Except for the rare cases of acute cauda equina syndrome, the purpose of discectomy is relief of pain, in particular severe sciatic pain, caused by a disc herniation, i.e. by dislocated — protruding or extruded — disc tissue.

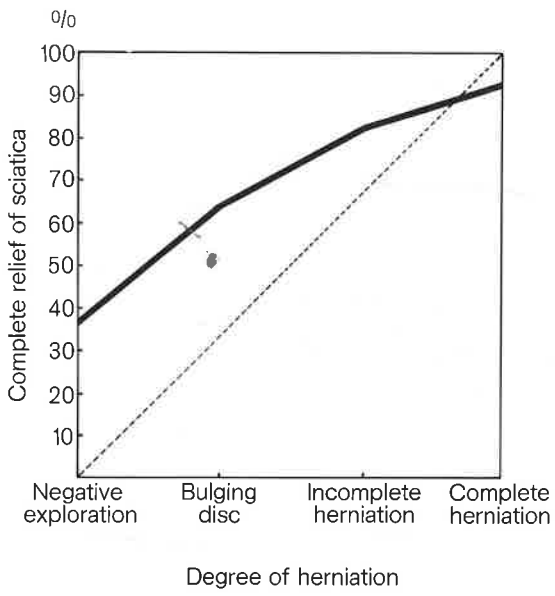

Fig. 192 The correlation between complete relief of sciatica and the degree of herniation in 2503 operations (from Spangfort 1972)

The disc herniation is a special lesion occurring sometimes in the course of disc degeneration — but disc degeneration, in itself, is not an indication for discectomy.

Complete relief of sciatic pain after discectomy is correlated almost exclusively and completely to the degree of herniation (Fig. 192). The rate of complete relief is excellent in patients with high-grade herniations, and the ideal indications for discectomy are recently ruptured herniations and large incomplete herniations in the process of rupturing, or dissecting beneath the posterior longitudinal ligament.

Only by meticulous selection of patients with high-grade herniations is it possible to improve the results of discectomy and avoid a growing number of disastrous failures.

Disc surgery is pain surgery — and the first condition for considering the possibility of discectomy, is that the pain is severe enough to motivate surgical treatment. The next condition is that the pain is caused predominantly by a high-grade herniation. These conditions must be strictly respected.

The point is to establish the presence and location of an offending disc herniation, and — unfortunately — surgical exposure is still the only way to do so with complete certainty.

The decision to advise discectomy must, therefore, be based on a systematic and comprehensive diagnostic investigation, comprised a detailed history, and an adequate analysis of the pain syndrome — disentangling in each case: the debut and duration of pain, the temporal pattern, activities and circumstances affecting the pain, the anatomical and topographical patterns, the sensory modalities and an assessment of the intensity of the pain. Furthermore, a complete physical examination is necessary — including the recording of posture and gait, degree of lordosis, range and pattern of spinal motion, the pattern of pain by rest, motion and weight-bearing and a neurological examination — as well as psychological assessment, routine laboratory tests and plain radiographs of the spine and pelvis.

In the detailed analysis of the pain syndrome — particularly of the topographical pattern and the sensory modalities, which are of fundamental importance in the diagnosis of a disc herniation — we have found diagnostic thermography of little value. To gain this information, in our experience, a pain drawing-method is definitely superior — and even cheap and convenient. Our present pain drawing system (Fig. 193) was developed from the model published by Ransford et al (1976), and has become indispensable in our pre-operative investigation.

We use metrizamide myelography as a routine examination to support the clinical diagnosis and localise the herniation accurately, but we do not consider a positive myelogram, in itself, sufficient indication for surgical treatment. Occasionally we advise discectomy in spite of a negative myelography, if the clinical diagnosis is clear. In such cases computerised tomography is now reducing the diagnostic confusion caused by a 'false negative' myelography.

Epidural venography may be of value in some cases, but we do not consider a discogram helpful in the decision of

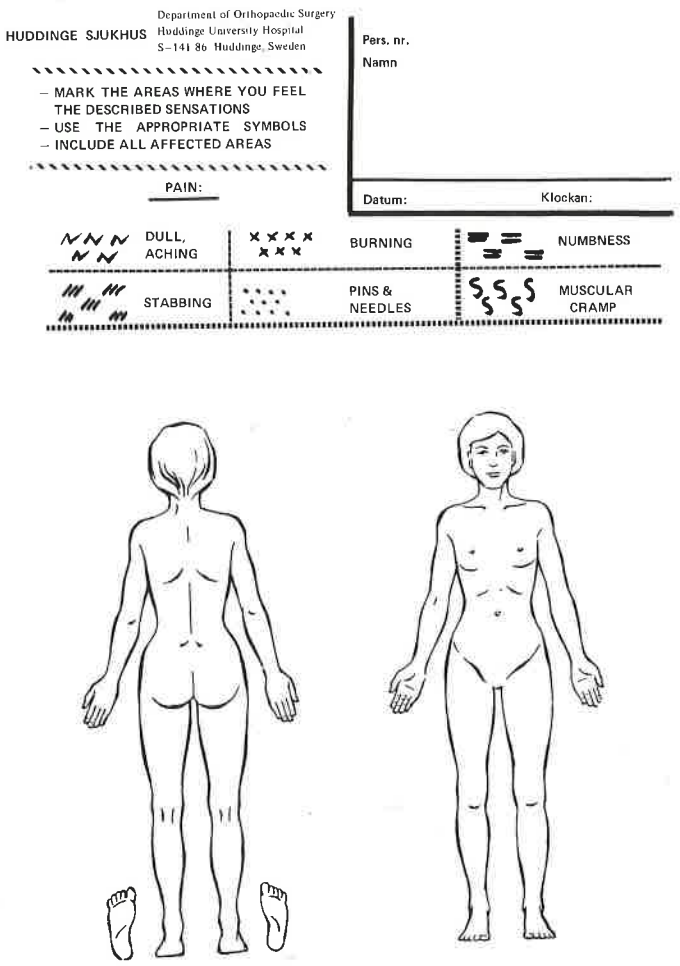

Fig. 193 Main form for Pain Drawing used for patients with low-back pain (modified from Ransford et al 1976)

whether or not to recommend a discectomy.

Electrodiagnostic examination may add information to the diagnosis, but there is no single test that measures all aspects of nerve root function, and there is no test measuring sciatic pain — which may be present in the absence of nerve root pathology.

Progressive neurological deficits are usually listed as an indication for disc surgery. Strictly speaking, we do not agree with this — we consider neurological deficits important diagnostic signs, but not an independent indication for discectomy, as surgical treatment has not been shown to improve the average prognosis of peripheral neurological deficits.

If surgical treatment of a disc herniation cures neurological deficits — which is still most likely in some cases — we still cannot identify the subgroup of patients who will benefit from discectomy in this respect.

The rupture of a disc herniation into the spinal canal is an anatomical disaster, and surgical measures against it are widely independent of the patient's general psychological status. Certainly, the individual psychological experience of pain and suffering is the main indication for discectomy, and inappropriate or incomprehensible description of the symptoms and unusual or pathological pain behaviour may seriously complicate the objective diagnostic interpretation and assessment, but in the case of an unequivocal diagnosis of disabling disc herniation we do not deny the patient surgical relief for psychological reasons. The emotionally unstable patient may, indeed, be in greater need of immediate pain relief than the stable one.

The situation is somewhat different in other types of low-back surgery, especially 'salvage surgery', in which the psychological variables apparently play a more dominating role in the surgical management.

It is generally recognised that, with the rare exceptions already mentioned, surgical treatment of a disc herniation should be advised only if the pain is unrelieved or worse after due trial of conservative management.

A reasonable trial period is 2–3 months in many cases, but we hesitate to accept rigid rules in this respect, as a wide variety of circumstances necessitates individual evaluation and decision in each case.

CONSERVATIVE VERSUS SURGICAL TREATMENT

So far, it has not been possible to design a clinical trial of the differences between conservative and surgical treatment of disc herniations, which completely fulfills scientific criteria.

One problem is that a disc herniation can be definitely confirmed and classified only by surgical exposure. Another obstacle is the fact that, when patients with a convincing clinical diagnosis of disc herniation are allocated at random to comparable groups for one of the two treatment modalities, there are always some patients, allocated for conservative treatment, in whom the pain becomes so excruciating that they cannot reasonably be denied surgical relief. This group is therefore lost for comparison.

A few studies in which it is possible to draw tentative conclusions (e.g. Hakelius 1970, Nashold & Hrubec 1971, Hasue & Fujiwara 1979) do, however, indicate that surgical treatment does not improve the prognosis in the long term — either as regards pain, or the risk of persistent neurologic deficits.

Weber (1983), in his controlled, prospective study, allocated 126 patient with questionable indications for discectomy to either operation or physiotherapy, and then compared the groups for 10 years. After 1 year the results were significantly better after surgical treatment than after conservative treatment. After 4 years the operated patients still showed better results, but the difference was no longer significant. Only minor changes occurred throughout the last 6 years of observation.

After 10 years no patients in the two groups complained of sciatic pain, and the rate of persistent low-back pain was equal in the groups. The severity of low-back pain decreased substantially the last 6 years — in both groups.

If the clinical situation allows a choice between conservative and surgical treatment, the patient should be informed that the benefit expected from the operation is immediate relief of sciatic pain, and not an improvement of the long-range prognosis — which is fairly good anyway.

COMPLICATIONS OF DISC SURGERY

The mortality rate

The mortality rate associated with disc surgery is low. In a survey of 54 reports from the period 1937–1972 with a total of 25 392 operations the mean rate was 0.3% (72 cases), and constantly decreasing the last 35 years. Pulmonary embolism and post-operative infections were the most frequent causes of death (Spangfort 1972).

Injury to vessels and viscera

Injury to abdominal vessels and viscera is an uncommon but extremely dangerous complication to disc surgery. Not all cases are reported in the literature, but an estimated incidence of this complication is less than 1 case in 2000 operations (DeSaussure 1959, Birkeland & Taylor 1969).

The disaster occurs when the instrument used for evacuation of tissue from the interior of the disc space accidentally and without awareness of the surgeon passes through a fissure in the anterior wall of the disc. The major vessels — the abdominal aorta, the inferior vena cava, and the common iliac vessels — are in close proximity to the anterior surface of the lumbar discs and easily within the range of the biting rongeur (Nilsonne & Hakelius 1965). Laceration of these vessels may cause a dramatic retroperitoneal haemorrhage, which is detectable in the surgical field in only half of the cases — the first warning of a vascular catastrophe may be symptoms of severe hypovolaemic shock during or after the operation. Immediate laparotomy and repair of the injured vessel is imperative.

Arteriovenous fistula is another type of vascular injury, which may produce complex circulatory impairment and cardiac failure. The diagnosis is often delayed for months or years, but the mortality rate is lower.

Injuries to the bowel, the ureter, and the sympathetic trunk may occur by the same mechanism, but are less commonly reported in literature.

In 95% of all disc operations the total loss of blood is less than 500 ml. Damage to the epidural veins is the usual cause of more extensive bleeding, and although this type of haemorrhage is almost always well within safe limits, the bleeding may cause troublesome difficulties, at least in the narrow field exposed by the interlaminar approach.

Injuries to neural structures

Injuries to the nerve roots, and even to the cauda equina, may occur during the operation in spite of a careful surgical technique. Surgical damage to nerve roots is reported by the surgeons in 0.5–3% of all operations — in re-operations the rate is two or three times higher. Verified damage to a nerve root is not always followed by significant clinical symptoms. Motor weakness in the leg, obviously caused by the operation, occurs in at least 5% of all operations, but in the majority the paresis is partial and recovers satisfactorily with time.

Dura lesions

Minor surgical lesions to the dura are not uncommon and are often revealed by the occurrence of a cerebrospinal fluid leakage during the operation. If the lesion is located and closed with fine sutures, the complication is usually harmless. In rare cases a dura lesion results in the formation of an extradural pseudocyst or a fistula leaking cerebrospinal fluid, which requires secondary surgery.

Thrombo-embolism

Post-operative thrombo-embolism is reported at an average of 2% in the literature. The complication is usually diagnosed between the fourth and twelfth day after the operation, and is rare in patients below 40 years. A period of immobilisation before the operation is probably a pathogenetic factor.

Post-operative infections

With modern surgical technique and facilities, the mean rate of post-operative wound infections after discectomy should not exceed a total of 2–3%, with severe infections accounting for less than 0.5%.

Septic meningitis, epidural abscess and frank pyogenic spondylitis are rare and major complications.

Post-operative discitis

This condition — caused by a low-grade infection of the disc space, and first described by Turnbull in 1953 — is now recognised as a complication to disc surgery. The true incidence is unknown, but probably does not exceed 2% at present.

The most typical symptom, almost pathognomonic, is violent, spasmodic pain in the back precipitated by the slightest movement, and in most cases appearing during the second week, after an otherwise uneventful postoperative course. The pain is referred to the lower abdomen, the groins, hips or upper thighs. True root pain is unusual, and the patient often describes the pain as a new and terrible experience.

Systemic reactions are scarce. Some patients have moderate fever reaction and/or infection of the surgical wound. The sedimentation rate (ESR) is always elevated, and a second rise of the post-operative ESR, which normally reaches its peak 3 days after the operation, is a significant warning. Needle aspiration from the disc space results in a positive culture in less than 50%, and is not necessary in typical cases.

Early radiological changes may appear 3–4 weeks after the onset of pain, and the main features are: fuzziness and irregular defects of the end-plates, cavitations into one or both of the adjacent vertebrae, marked narrowing of the intervertebral disc space and vertebral sclerosis. Later in the course there is abundant new bone formation, which often results in solid bony fusion.

The acute pain syndrome lasts between 6 and 12 weeks in most cases, and complete immobilisation is the most efficient treatment. Antibiotics are usually recommended, but the effect is still questioned in some reports. There is no indication for surgical intervention when the clinical picture

is typical. The course is always prolonged, and the pain may be a frightened experience to the patient, but the prognosis is good.

Spinal arachnoiditis

An association between lumbar disc disease and arachnoiditis — a progressive inflammatory reaction of the pia arachnoid — was suspected long ago (French 1946), but the condition is difficult to diagnose, the more so because intradural exploration is seldom performed during a disc operation, and the complication has been considered rare. Recent studies indicate, however, that some degree of arachnoiditis is common, at least in patients presenting with severe pain and disability secondary to disc surgery. Arachnoiditis may be clinically silent, and the correlation between the pathology and pain is still poorly defined (Symposium 1978).

Many aetiological factors are apparently involved in the development of arachnoiditis: injection of contrast media, anaesthetics and other agents into the subarachnoid space, infection, the presence of blood, trauma, disc lesions and spinal stenosis, surgical injuries, and unknown individual factors (Ransford & Harries 1972).

Symptoms vary considerably, and mild cases are probably often overlooked. In severe cases, the condition is extremely distressing. The pain is constant in the back and radiates to one or both legs, often in a well-defined distribution of more than one root. The pain is described as burning or cramping — painful muscle cramps and violent spasms of the legs are usual. The cauda equina may be involved. Pain is unrelieved by rest and poorly correlated to weight-bearing and motion.

Treatment of this neuralgic pain syndrome is extremely difficult, but the condition is not inevitably progressive — a slow recovery over the years occurs in some patients. Severe psychological complications in response to the constant torturing pain are, however, the rule.

Structural impairment

It has not been established that simple discectomy — without removal of the articular facets or the pedicles — is associated with an increased risk of disc degeneration, recurrent herniations, segmental instability or arthrosis of the intervertebral joints.

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3.E.2

Vertebral manipulation

James Cyriax

Manipulation consists of a passive movement performed by the hands with therapeutic intent. It is the purposefulness of the movement that transforms it into a manipulation. Vertebral manipulation has lain under a cloud all this century — understandably so, for most doctors do not manipulate the spinal joints at all, while most lay manipulators (of whom Britain contains 3000) manipulate almost all comers. Both these policies are mistaken and smack of bigotry. The proper attitude lies midway between these two illogical extremes.

Manipulation of the spine is important for three reasons:

1. It is the only method of treatment required in the doctor's daily work that he was taught nothing of as a student.
2. The lesions that respond, though restricted in number, occur very commonly and provide the most frequent reason for a fit man being off work.
3. Every time a patient in pain which is relievable by spinal manipulation visits his doctor and this is not done, a gratuitous advertisement is afforded to lay manipulators. We all know that some of these men claim to cure disorders that no manipulation could possibly affect, but this justified scepticism should not blind us to the fact that some of their patients are greatly benefited. It behoves doctors to study not their failures, but their successes. We must avoid forcing patients to look beyond the medical profession for relief either by manipulating them ourselves, or (as has been my policy for the last 30 years) handing them over to physiotherapists trained in spinal manipulation.

PURPOSES OF MANIPULATION

Manipulation of joints has three purposes (no mention will be made of reduction of fractures, dislocations, hernias, etc., since no controversy exists there).

1. *To break adhesions.* Minor adherent scars may form when a sprained ligament unites, restricting its mobility. They can be ruptured by a sharp jerk in the direction of the limitation. Major adhesions severely restrict movement at the joint after, say, immobilisation in plaster after fracture. These require rupture by a strong stretch under anaesthesia.
2. *To stretch out a contracture.* Both congenital and acquired contractures need elongation by gradual, increasing sustained pressure. Congenital torticollis and talipes equinovarus are obvious examples; arthritis at the shoulder and hip represent acquired capsular contracture.
3. *To reduce an intra-articular displacement.* Here lies the main object but, curiously enough, also the most controversial aspect of manipulation. In general, a physician's first thought when a displacement is found to be present is the feasibility of reduction. In fracture, dislocation, hernia or breech presentation, or indeed a subluxated meniscus at the knee or jaw joint, the advisability is considered at once. But manipulative reduction appears scarcely to figure in medical thought when a fragment of disc is found out of position at an intervertebral joint. Before 1929, when Dandy (1929) first ascribed sciatica to a disc-protrusion, the disorder was regarded as 'sciatic neuritis', for which manipulation would have been absurd. Until 1945, when I (Cyriax, 1945) put forward the concept of postero-central displacement of a fragment of disc as the cause of lumbago, this had been regarded as the result of spontaneous inflammation of muscle, which manipulation could only aggravate. Now, however, when the pathological concepts that were advanced have been accepted everywhere, reason surely demands logical treatment based on this mechanical aetiology.

By no means all disc lesions will respond to manipulation. Suitability is based on the size, duration, position and consistency of the displacement. Moreover, the patient's age, occupation and sensitivity to pain must all be taken into account. In the lumbar region, my experience is that two-thirds of all cases of backache, but only one-third of all sciaticas, prove to be reducible. Reduction of a fracture or of a dislocation is ascertainable objectively. By contrast, at a spinal joint, it is a subjective event. It is only with the patient's co-operation that the operator can tell when all the spinal movements have become free, or straight-leg raising has become painless at full range. The patient is examined immediately before the session starts and after each manoeuvre. The immediate result is ascertained, as well as which measure has the best effect. All this knowledge is denied to the manipulator under anaesthesia, who cannot even tell if he is making the patient better or worse, let alone when to go on and when to stop. Since so much spinal manipulation is carried out in Britain either under anaesthe-

sia or by untrained persons, it occasions little surprise that many medical men regard it as dangerous or useless.

CERVICAL DISC LESIONS

These present themselves in five different ways and, to add to the confusion, have been given names that distract attention from the actual lesion. Acute torticollis, scapular fibrositis, brachial neuritis, acroparaesthesia and postero-lateral sclerosis disguise the fact that there are different stages in the progression of a cervical disc lesion.

Clinical examination

This has five purposes. The function is assessed of:

1. *The joints*. The partial articular pattern indicates internal derangement. Of the six movements, for example, two, three or four may hurt, while four, three or two do not. Moreover, the pain is usually unilateral.
2. *The cervical muscles*. Movement, attempted against such resistance that none of the joints move, discloses the state of each muscle group in turn.
3. *The cervical nerve roots*. Monoradicular palsy indicates a disc protrusion. Neuralgic amyotrophy, neuroma, secondary neoplasm, neuritis and pulmonary sulcus tumour each set up weaknesses in wholly different patterns.
4. *The spinal cord*. Whether the pyramidal deficit is caused by a disc protrusion or not, objective signs of spinal cord involvement wholly contraindicate manipulation.
5. *The upper limb*. This may well contain a separate lesion causing pain in the arm.

Radiography

None of this vital information is obtainable by inspection of radiographs. A displaced fragment of disc within an osteoarthritic joint is often just as reducible by manipulation as one in a radiographically normal joint. Every time a physician pays excessive attention to a few harmless osteophytes, he is creating one more opportunity for nonmedical manipulators to score. The only reliable basis for a decision on whether to manipulate or not rests on careful and informed evaluation of clinical data. By contrast, normal radiographic appearances must not be allowed to lull the manipulator into a false sense of security, since chordoma, myeloma, neuroma and early secondary neoplasm do not show up at first.

Some of the major manipulations described in the text below are illustrated in the plates at the end of this chapter.

Clinical types of disc lesion

Acute torticollis

This is the analogue at a cervical joint of lumbago. The young patient wakes with his neck fixed in a posture of gross deformity. Marked limitation of one rotation and one side-flexion movement is present.

Reduction is secured in patients under 30 by manipulating during strong traction only in the direction of full range. When this measure has secured as much improvement as possible, the patient lies down and his head is pushed over more and more in the direction of limited range. It may well be 1–2 hours before full range is restored by this means. In patients over 30, manipulation during traction, first in the painless direction, then in the painful, suffices.

'Scapular fibrositis'

This is the unfortunate name that has been given to cervical disc lesions causing, as they usually do, pain felt in the muscles about the scapula. The lesion is neither scapular nor is it caused by inflammation of fibrous tissue. Clinical examination shows that the passive, but not the resisted movements of the cervical spine bring on the pain, thus showing its cervical articular origin, and that the resisted movements of the scapula are neither weak nor painful, thus exculpating the structures about the scapula. In other words, positive signs at a joint of the neck are corroborated by negative signs from the circumscapular tissues.

Physicians are accustomed to cervical lesions causing scapular pain and accept this extrasegmental reference. Reference to the pectoral area is rare. When it does occur diagnoses like pseudo-angina may be reached. When a lay manipulator now manipulates the neck and relieves this symptom, both he and the patient may well imagine that the manipulation has cured some obscure form of heart disease. Physicians must be on the look-out for such cases, for they strengthen the assiduously-fostered idea that manipulation by laymen cures visceral disease.

Manipulation during traction is simple and usually completely successful in one or two sessions. The distraction relieves the pain, thus enabling the patient to relax; it doubles the width of the joint (Cyriax 1954), thus giving the fragment room to move. It also exerts centripetal force on the displacement both by suction and by tautening the posterior longitudinal ligament. In addition, it disengages the facet joints which then allow more movement. Manual traction can be used early in cases of basilar ischaemia (but not during anticoagulant therapy).

Lay manipulators inexplicably avoid adequate traction; in fact they squeeze the vertebrae together. Naturally, such compression militates against a successful result, and this type of 'adjustment' (locking the facets) may require many sessions or may fail altogether. Also, judging by the literature, it tends to be dangerous.

Between each manipulative attempt the patient sits up and states the effect on his pain, and the painfulness or not of each movement. The manipulator assesses range of motion. The session continues until, as a rule, painless movement has been secured in each direction.

'Brachial neuritis'

There are many reasons for pain and paraesthesia in the upper limb, but a common cause is a disc protrusion compressing a cervical nerve root; if so, the lesion is neither brachial nor a neuritis.

If no root palsy is present when the upper limb is ex-

amined and the spinal cord conducts normally, reduction of pain is often still possible provided that unilateral radiation to the arm has lasted less than 2 months. If a root palsy has supervened and muscle weakness is apparent, manipulation always fails and spontaneous recovery from pain (3 –4 months since the brachial pain, not the scapular pain, started), and from the muscle paresis (6–8 months) must be awaited. Manipulation is also apt to fail when one or more of the neck movements provoke the pain down the upper limb, and when the symptoms appear in the reverse of the usual order, i.e. paraesthesia in the hand, then aching in the limb, then scapular pain.

Physicians often fail to recognize the importance of the temporal sequence of events. In cervical root compression, the pain in the scapula and arm may go on getting worse for 2–3 weeks. During this time, the patient's physician prescribes him ever stronger analgesics. By the third or fourth week the pain is at its worst, and lack of progress leads to reference to hospital. There examination reveals the root palsy, confirmed by electromyography. Physiotherapy, traction or a collar are employed, all in vain. At the end of 2 months, just when the symptoms are about to wane, the despairing patient takes himself off to a lay manipulator. Since his treatment starts at the same moment as spontaneous subsidence of the pain, manipulation twice a week for, say, 6 weeks coincides in time with the advent of spontaneous recovery. Again, both the lay manipulator and the patient mistakenly ascribe recovery to the manipulations.

Acroparaesthesia

Bilateral root pressure may set up pins and needles in both hands, together with a vague aching in the upper limbs. (Differentiation between the thoracic outlet syndrome and a bilateral carpal tunnel syndrome may present difficulty). Manipulation may help. Often the disorder proves intractable, but the symptoms are never severe. Wearing a collar for, say, 6 months may help.

Posterolateral sclerosis

Evidence of pressure on the spinal cord contraindicates manipulation. Pins and needles in the hands and feet (or postural vertigo indicating basilar ischaemia) are not an absolute bar, provided the methods of lay manipulators are avoided; these are dangerous and death has sometimes resulted. Strong traction without rotation may succeed and no lasting harm has resulted from such measures. If the apex of the spur compressing the spinal cord consists of a fragment of cartilage, manipulating during strong traction can still shift it. If the point is osseous, manipulation must fail and the only prevention of paraplegia due to compression of the anterior spinal artery is now laminectomy.

Prevention of cord pressure is feasible. The osteophyte arises in the first place by traction on the posterior longitudinal ligament from a posterocentral bulging of the disc. The periosteum at the edge of the vertebral body is elevated and bone grows to reach its limiting membrane. The prophylaxis of an osteophyte which increasingly menaces the spinal cord is to have carried out manipulative reduction years earlier.

HEADACHE

There is one type of headache that physicians often fail to recognise — that arising from the ligaments about the occipito-atlantoid and atlanto-axial joints. These joints are developed within the first and second cervical segments and therefore refer pain along the relevant dermatomes in the usual way — i.e. to the back of the head (C1) and the forehead (C2). The patient is typically an elderly man (women are almost immune) who describes occipito-frontal headache every day on waking. At first it has eased by midday, later by the afternoon; it never lasts all day. At his age, some elevation of blood pressure may be found present. The headache is attributed to that, the more so since the radiographs of the upper neck show no more osteophytosis than anyone that age often has. One session of manipulation of the neck during traction nearly always affords full relief lasting at least a couple of years. The lay manipulator may cure this type of headache. If so, again both he and the patient understandably, but mistakenly, take for granted that high blood pressure has been relieved. This not uncommon misdiagnosis provides lay manipulators with renewed 'evidence' that they can cure visceral disease.

THORACIC DISC LESIONS

These also present under misleading names, such as fibrositis of the chest wall, muscle-strain, pleurodynia (because a deep breath hurts), intercostal neuritis. Diagnosis is not difficult if thoracic disc lesions are kept in mind. The influence of posture and exertion on the pain is elicited in the history and the spinal movements are therefore tested.

The difficult cases are those with a primary posterolateral onset, the root pain felt in the anterior thorax or abdomen coming on without previous backache. Exhaustive examination of the visceral junction naturally reveals no abnormality, and such patients are often dismissed as neurotic, or alternatively, some vague label such as gastritis or chronic cholecystitis is applied. A.T. Still, the founder of osteopathy, describes how he had pain in the region of his heart, which ceased with a click during pressure at his mid-thoracic vertebrae. In this type of case, pain exists that the lay manipulator can easily abolish; however, it is instead wrongly ascribed to some vague visceral disorder. Obviously, vertebral manipulation relieves, not visceral disease, but those pains actually of spinal origin that have been mistakenly ascribed to a viscus. Neither patient nor lay manipulator realises that, nor would it suit the latter's book if he did have doubts.

Examination

This comprises eliciting:

1. Articular signs. The partial articular pattern indicates internal derangement. Some, but not all, of the six move-

ments prove painful.

2. *Dural signs*. Neck flexion and scapular approximation draw the dura upwards and increase the thoracic pain.

3. *Root signs*. Though root pain felt as a rule along the lower costal margin is common, neurological deficit is rare and suggests a neuroma rather than a disc lesion.

4. *Cord signs*. If evidence of pyramidal pressure exists, manipulation is wholly barred; laminectomy should be considered.

Articular signs accompanied by dural signs clearly indicate a posterior disc displacement, since the dura mater lies behind the joint. Manipulative reduction during traction is usually very easy.

LUMBAR DISC LESIONS

Here, too, the situation is obscured by many different names for the same disorder — pulled muscle, lumbago, sciatica, sacro-iliac strain, sprung back, lumbar or gluteal fibrositis, spinal arthritis or spondylosis. The same phenomenon as is so conspicuous at the neck — extra-segmental reference from the dura mater with a secondary localised tender spot within the painful area — occurs also in lumbar disc lesions. Since a postero-central disc protrusion bulges the posterior ligament out far enough to compress the dura mater, remarkable areas of reference are reported by sufferers from acute lumbago — e.g. to one or both groins, to the lower abdomen, up to the lower posterior thorax. When the referred pain overshadows local pain, it is not unknown for a low lumbar disc lesion to be mistaken for chronic appendicitis, since the way the dura mater refers pain misleadingly is not recognised by most doctors. Clearly, spinal manipulation may well relieve such a pain in the iliac fossa, and the mistaken notion of lay manipulation curing visceral disease is once more strengthened.

Detailed diagnosis is most important, for it is by no means enough to know that a lumbar disc lesion is present. The lesion's duration, size, position, consistency and stability all have to be correlated with the patient's occupation, age and sensitiveness. A small cartilaginous displacement should be reduced by manipulation; a small nuclear protrusion should be reduced by daily traction. If the protrusion is large, neither method is applicable and the desensitisation of the nerve root at the point of impact by the induction of epidural local anaesthesia is the treatment of choice.

Four data are sought:

Articular signs. These comprise: 1. visible deviation; 2. limitation of movement in some directions but not in others. In early disc lesions a painful arc, usually on trunk flexion, is often present. The partial articular pattern indicates internal derangement.

Dural signs. A cough hurts. Lumbar pain produced by neck flexion and bilateral limitation of straight-leg raising indicate that the mobility of the dura mater is impaired on stretching from above or below. When, in sciatica, the straight leg is raised as far as possible, neck flexion causes added root pain, again as the result of pulling on the tense nerve root via the dura mater.

Nerve root mobility. At the third root, this is tested by prone-lying knee flexion. At the fourth and fifth lumbar and first and second sacral levels, the mobility of the dural sheath of the roots L4–S2 is assessed by straight-leg raising.

Nerve root conduction. Muscle weakness, impaired reflex, cutaneous analgesia indicate a degree of protrusion too great for manipulation or traction to help.

Manipulative reduction

Choice of treatment in disc lesions rests on what is found when these four essential elements in clinical evaluation are correlated. None of these findings emerges from inspection of a straight radiograph nor is appreciable help afforded by positive or negative myelographic appearances.

Manipulative reduction should form the physician's first approach, and be performed forthwith unless clinical examination has disclosed a contraindication.

The patient lies on a low couch and rotation of the pelvis and the thorax in opposite directions is carried out. Strong distraction is applied while the patient lies on his painless side. Rotation pressure is now added. The final overpressure is administered by rotation of the manipulator's thorax, whereby further distraction and rotation is effected by means of his straight arms. This is done first in one direction then the other. A click is often felt. Should that not suffice, greater force can be imparted to the movement by using the femur to rotate the pelvis while the patient lies supine. Should that not suffice, particularly in the elderly, forced extension with the patient prone follows. Pressure is applied at the affected level until full passive extension has been reached, whereupon the manipulator suddenly bends his trunk forwards transmitting overpressure via his straight arms. This is effected centrally and to each side, and a click is often felt as the fragment moves.

If these manoeuvres fail, traction is substituted, since it is probable that the lesion consists of nuclear material.

Contraindications to manipulation

The contraindications are:

1. *Danger to the fourth sacral root*. Any complaint of weakness of bladder or rectum or of perineal, testicular or saddle paraesthesia suggests severe stretching of the posterior longitudinal ligament. If this should rupture during manipulation, massive protrusion of the whole disc may result, leading to severe bilateral sciatica and damage, possibly permanent, to the innervation of the bladder. In such cases laminectomy is urgently required.

2. *Hyperacute lumbago*. Most cases of lumbago respond very well to manipulation. However, in a few cases the patient is so fixed that the slightest movement provokes such sharp stabs of pain that the attempt becomes unthinkable. If so, epidural local anaesthesia is induced, whereupon the displacement impinges against the now-insensitive dura mater and all pain ceases for the time being. Spontaneous reduction is aided during the period of painless mobility if the patient lies prone for as long as the anaesthesia lasts.

3. *Pregnancy*. During the last month manipulation is impracticable. During the first 4 months, prone pressures

as well as the rotation manipulations are quite safe.

4. Neurosis. Very nervous patients, or those who, owing to a legal suit pending, have to maintain disablement are not suited to manipulation.

Anaesthesia should not be used during most manipulations. Anaesthesia leaves the manipulator in the dark. Has any particular manoeuvre proved successful? Is one technique helping more than another? Is the displacement getting larger or smaller? Which manipulation offers the best chance of success? Should he go on, or stop? Anaesthesia deprives the operator of all the information that he requires for proper selection of method and the exercise of due care; it is therefore strongly contraindicated. Moreover, in my experience, recurrent intra-articular subluxations that have been previously reduced under general anaesthesia prove quite easy to reduce without anaesthesia; conversely, those that cannot be reduced while the patient is conscious nearly always defy attempts at reduction under anaesthesia.

Manipulation useless but not harmful

1. Too large. Reduction is impossible when the protrusion is larger than the aperture whereby it emerged. Sciatica with a marked lumbar lateral deviation, or signs in the lower limb of impaired conduction at the nerve root (muscle paresis, loss of reflex, cutaneous analgesia) show that this is the situation.

2. Too long. When root pain has lasted 6 months or more in a patient under 60 years of age, the attempt is almost sure to fail.

3. Too soft. Nuclear protrusions require 1–3 weeks' daily traction for 30 to 45 minutes, at a distracting force of 80 pounds (minimum for a frail woman) to 200 pounds (for a large, strong man). The treatment is entirely painless (Cyriax 1950). It should never be used for acute lumbago with twinges, which is made much worse.

LUMBAR MANIPULATION

Manipulative technique is not difficult to master. The patient lies on a low couch (40 cm high) and pressure on his lumbar spine, accompanied by a jerk, is applied as he lies prone, or rotation of the pelvis on the thorax is secured while he lies on his side or supine. Patients who present with much lumbar deviation do best on the rotational manoeuvres.

The family doctor should be prepared to carry out these manoeuvres as soon as the patient presents; for he sees the case early and thus offers treatment at the most favourable moment. Alternatively, he should instruct a physiotherapist of his choice to carry out these measures at once. This ensures that the patient remains under medical supervision throughout, and is treated by trained personnel. I found this policy welcomed in England, and wherever my graduates have gone, including the USA and Canada, they have been esteemed by physicians and patients for their skill (Cyriax 1980).

SUMMARY

In my experience, the only good reason for spinal manipulation between the third cervical and fifth lumbar vertebra is an endeavour to reduce a displacement of a small fragment of disc. This is what lay manipulators, without realising it, have been doing for the past 100 years and have gained much kudos thereby. Their successes have led to untenable hypotheses. An attempt is made to substitute a valid anatomical explanation.

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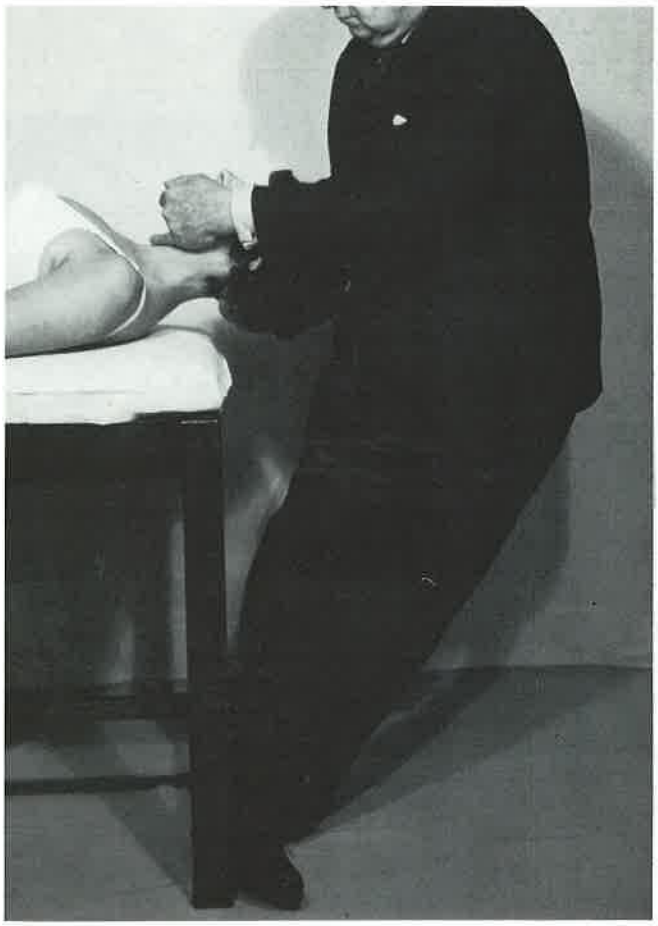

Fig. 230 Position for traction on neck. An assistant holds the patient's feet.