The Anatomical Substratum of Pain
Evidence Derived from Morphometric Studies
on Peripheral Nerve

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SUMMARY Earlier theories as to the anatomical basis of pain postulated a direct 'pain pathway' from specific receptors in the periphery. Anatomical studies linked this with small myelinated and unmyelinated fibers in the peripheral nerves. Subsequently, hypotheses were advanced which postulated that pain depended upon particular spatial and temporal patterns of sensory input into the nervous system rather than upon specific sets of fibers.

More recent physiological studies have demonstrated the existence of peripheral receptors that respond exclusively to noxious stimuli and morphometric studies on peripheral neuropathies in man clearly implicate small myelinated and unmyelinated axons in the conduction of pain. Morphometric studies have also shown that spontaneous pain in neuropathies may be associated with a selective loss of small fibers. These observations therefore support the earlier concept of a specific nociceptive pathway involving small caliber fibers in the peripheral nerves. It is evident that this afferent pathway is capable of modification in the spinal cord both by peripheral inputs and by descending impulses. The notion of a 'pain pathway' as such is probably best avoided.

RÉSUMÉ: Des anciennes théories sur les fondements anatomiques de la douleur supposaient l'existence d'une voie-douleur ("pain Pathway") directe, reliée à des récepteurs périphériques spécifiques. D'après des études anatomiques, celle-ci était reliée à de petites fibres médullées et non médullées dans les nerfs périphériques. Des hypothèses subséquentes admirent que la douleur ne dépendait pas d'ensembles spécifiques de fibres, mais plutôt de configurations particulières spaciales et temporales de l'activité sensorielle dans le système nerveux.

Des études physiologiques plus récentes ont mis en évidence certains récepteurs périphériques qui répondent uniquement aux stimulations nociceptives; et des études morphométriques de neuropathies périphériques chez l'homme attribuent clairement aux petites fibres médullées et aux fibres non médullées un rôle dans la conduction de la douleur. Les études morphométriques ont démontré, d'autre part, une association vraissemblable de la douleur spontanée des neuropathies, à la perte sélective de patites fibres. Ces constatations appuient la thèse précédente de l'existence d'une voie nociceptive spécifique comprenant des fibres de calibre fin dans les nerfs pèriphériques. Il est évident que cette voie afférente est susceptible de modifications au niveau de la moëlle épinière, d'une part à cause d'apports énergétiques périphériques, et d'autre part à cause de pulsions descendantes. Il demeure probable qu'il faille abandonner la notion de voie-douleur (pain pathway) en tant que telle.

The singular status of pain in the spectrum of sensory experience has ensured that it has received particular attention from those describing the biological mechanisms of sensation. During the historical development of ideas related to cutaneous sensation, the earlier views associated in particular with the name of von Frey, were of modality-specific peripheral receptors and of specific neural pathways leading to defined 'centers' in the brain. As emphasized by Sinclair (1967), the most evident shortcoming of von Frey's approach was the inability to link end-organs with sensations: efforts to associate 'sensory spots' for particular sensations with defined anatomical endings consistently failed. Later (Henry Head, 1920), experimenting on the return of sensation to denervated areas of skin, postulated that his two forms of sensation, the primitive 'protopathic system' and the more discriminative 'epicritic system,' were both dependent upon anatomically different sets of fibers. The theory foundered because of the failure of others to repeat the Head and Rivers' observations, although in modified form, it continues to have its advocates, (Bishop, 1960, 1963). Walshe, in his extensive critical review in 1942, adhered to the view that there are four primary modes of cutaneous sensibility, with anatomically and physiologically specified endorgans and specific sensory pathways.

Part of the difficulty in discussing pain over the years has been the failure to distinguish between signals that transmit information about injury, and signals that give rise to

the sensation of pain. Tenderness and hyperesthesia require explanation as well as frank pain. The size of the fibers in the peripheral nerves that signal injurious stimuli was originally studied in animal experiments. Adrian (1931) showed in the frog that noxious stimuli excited fibers with slow conduction velocity, and in both amphibian and mammalian nerves the participation of unmyelinated C fibers was demonstrable. It was clear from reaction time experiments in man that pain is felt too quickly for it to be mediated exclusively by unmyelinated nerve fibers. Experiments in dogs (Zotterman, 1933) indicated that the reactions associated with pain occur whenever small myelinated nerve fibers are stimulated. However, attempts to detect significant numbers of myelinated nerve fibers that responded selectively to noxious stimuli in electrophysiological studies were unsuccessful. The failure to find such fibers was surprising, as activity in myelinated fibers is comparatively easy to examine.

Anatomical studies in man revealed that the peripheral receptors for pain consist of unencapsulated nerve terminals without morphological specialization (Woollard, Weddell and Harpman, 1940). In the skin, they were considered to be related to branching networks of nerve fibers.

Certain investigators in this field, notably Weddell and his collaborators, were reluctant to accept the concept of modality-specific nerve fibers. They had found that in the human cornea, where the sole innervation is by freely-ending unencapsulated nerve terminals, a wide range of sensory experiences could be evoked (Lele and Weddell, 1956). Moreover, in the cornea of the cat, they found single units that responded to multiple types of stimuli (Lele and Weddell, 1959). The concept was advanced that specific sensations depend upon various spatial and temporal patterns of impulses and not simply on a series of modality-specific endings (Weddell, 1963).

Information subsequently accrued which clearly indicated that small fibers were particularly implicated in the occurrence of pain. Collins, Nulsen and Randt (1960) made observations on humans undergoing chordotomy. The exposed sural nerve was stimulated electrically while recording from the nerve central to the site of stimulation. With increasing stimulus strengths it was possible to activate successively the various components of the A potential and finally the C potential. An unpleasant sensation was not reported until the gamma component of the A fiber group was stimulated, when a burning feeling was noted. When the delta component was added all subjects reported pain, which became 'unbearable' when the unmyelinated C fibers were stimulated. They concluded that the smaller fibers must be activated for the human subject to experience pain. This is likely to be the case, although such a strict conclusion cannot be drawn from their results, because at stimulus strengths required to activate the C fibers, repetitive firing of the A fibers also occurred. Further evidence also came from animal experiments when Burgess and Perl (1967) suc-

ceeded in detecting in the cat a significant population of cutaneous receptors which were activated exclusively by noxious stimuli.

The possibility of obtaining pertinent evidence from cases of selective pain loss in man was raised by Swanson, Buchan and Alvord (1965). They studied a twelve year-old boy suffering from congenital insensitivity to pain. A brother was similarly affected. There was a lifelong history of insensitivity to pain, defective temperature appreciation and an absence of sweating. At necropsy, a lack of small fibers in the dorsal roots, an absence of small dorsal root ganglion cells and of Lissauer's tract, and a reduction in the size of the spinal tract of the trigeminal nerve were observed.

More precise evidence from measurements of nerve fiber size distribution in human neuropathies is now available. Here it has been possible to correlate the predominant impairment of certain types of sensation with a preferential loss of fibers of a particular size range. Human sensory nerves such as the sural nerve at the ankle or the radial nerve at the wrist (O'Sullivan and Swallow, 1968) show a bimodal dis-
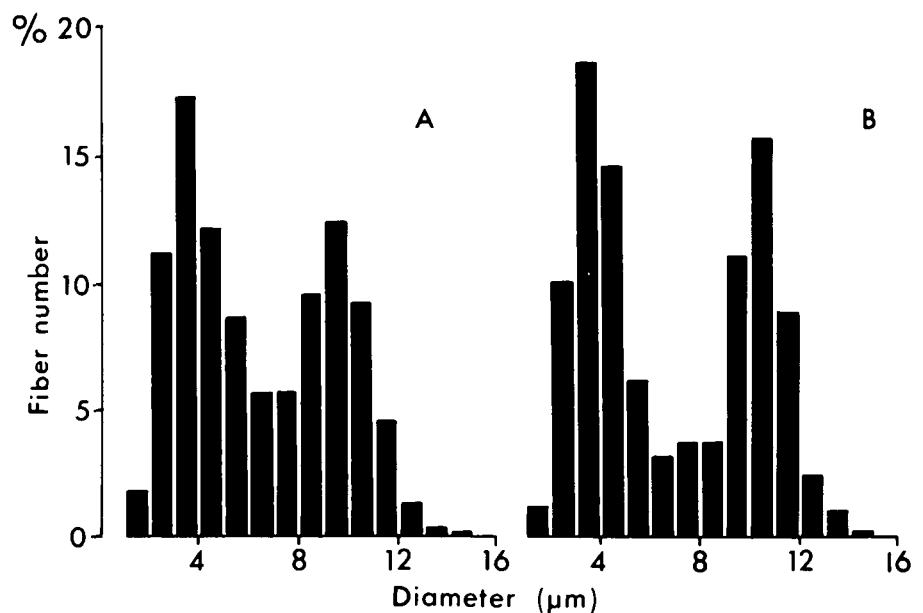

Figure 1. Percentage size-frequency distribution for myelinated fibers. A: In the radial nerve at the wrist from a 28-year-old subject. B: In the sural nerve at the ankle from a 30-year-old subject. Data from O'Sullivan and Swallow (1968).
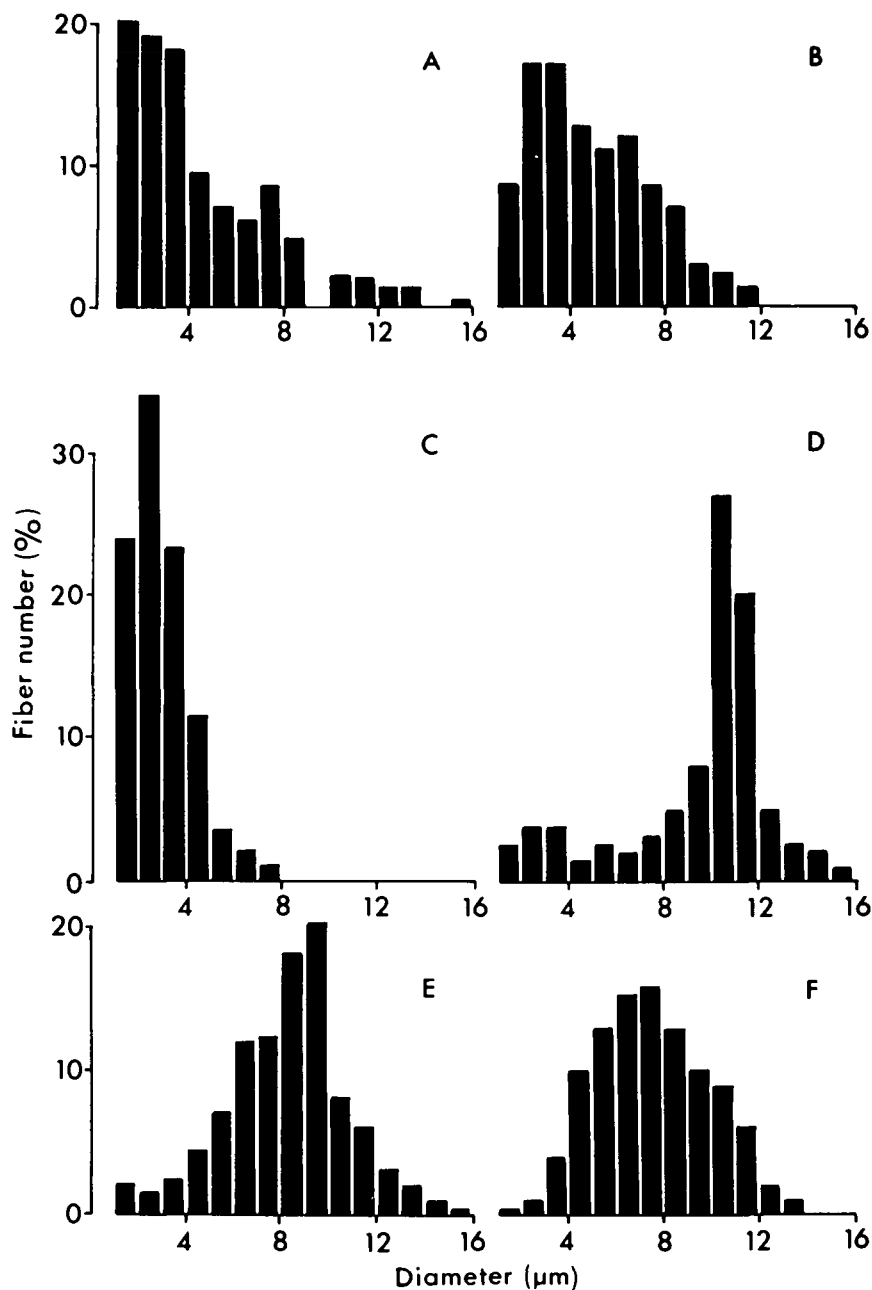
Figure 2. Percentage size-frequency distribution for myelinated nerve fibers. A-C: From sural nerve biopsies in three cases of uremic neuropathy (data from Thomas et al., 1971); D: Sural nerve biopsy from a case of amyloid neuropathy; E: Radial nerve biopsy from a case of Tangier disease (Kocen et al., 1973); F: Sural nerve biopsy from a case of Fabry's disease (Kocen and Thomas, 1970).

elinated axons. This has been confirmed in a personal case (Fig. 2D). From observations on excised nerve, Dyck and Lambert also demonstrated the loss of the A delta and C fiber elevations in the compound nerve action potential.

A further example of a peripheral neuropathy in which a dissociated loss of pain and temperature sensation occurs has recently been encountered in Tangier disease (hereditary high density lipoprotein deficiency). Two patients have been described with muscle wasting in the upper limbs, depression of tendon reflexes and a dissociated loss of pain and temperature sensation most marked on the head, trunk and the proximal parts of the limbs. Both cases were initially diagnosed as syringomyelia. A radial nerve biopsy from one of these patients, (Kocen, King, Thomas and Haas, 1973) showed a proportionately greater loss of the smaller myelinated fibers (Fig. 2E) and an almost total absence of unmyelinated fibers. Finally, in cases of dominantly inherited sensory neuropathy in which dissociated pain and temperature sensory loss is an early feature, Sluga (1974) has also found a predominant loss of small myelinated axons. Observations on these three different peripheral neuropathies have firmly linked preferential pain and temperature sensory impairment with depletion of small myelinated and unmyelinated fibers from the peripheral nerves.

In any discussion on the peripheral pathways involved in the sensation of pain, the connections made in the spinal cord obviously require consideration. The traditional view was that fibers subserving pain and temperature entered in the lateral division of the dorsal roots and joined the dorsolateral fasciculus or Lissauer's tract to synapse with cells in the substantia gelatinosa Rolandi. In a famous early experiment, Ranson and Billingsley (1916) claimed that selective section of the lateral division of the root in cats abolished pain responses. However, Earle (1952) was unable to confirm a

tribution of myelinated nerve fibers (Fig. 1) and an extensive population of unmyelinated axons (Ochoa and Mair, 1969). The first clear instance of a selective loss of fibers related to dissociated pain and temperature impairment came from observations on amyloid neuropathy. In primary amyloidosis, either in familial cases of the Portuguese type or in spor-

adic examples, a slowly progressive neuropathy may occur. This begins with a loss of pain and temperature sensation in the limbs, with relative preservation of other modalities, together with prominent autonomic symptoms. Dyck and Lambert (1969) demonstrated that in such cases there was a predominant loss of small myelinated and unmy-

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separate lateral division in the root, and Wall (1962) found that the Ranson and Billingsley results were produced by vascular damage which gave rise to ischemia of the dorsal horn.

On the positive side, a highly significant advance was the cytoarchitectonic analysis of the dorsal horn made by Rexed (1952). The dorsal horn was subdivided into six laminae containing different cell populations based on their cytological features and the pattern of their aggregation. The laminar organization of the dorsal horn was confirmed physiologically by Wall (1967). Lamina I caps the dorsal horn and has been shown to contain, among others, cells activated solely by myelinated afferents in the A delta group that respond to mechanical damage to the skin, and others activated both by A delta and C fibers that respond only to high threshold mechanical and thermal receptors (Christensen and Pearl, 1970). Lamina II corresponds to the substantia gelatinosa and is similar structurally to lamina III. Although Ralston (1965) failed to find evidence of dorsal root afferents terminating in this region, they were subsequently demonstrated by Heimer and Wall (1968). These layers also contain dendrites from deeper laminae and terminations from descending pathways.

The precise origin of the spinothalamic tract is still uncertain. This was studied electrophysiologically by Dilly, Wall and Webster (1968) who found that by the technique they employed, namely searching for antidromic spikes, the majority of the cells of origin were in laminae V and VI.

One of the most significant advances in sensory physiology made during recent years has been the demonstration of descending central influences on afferent activity. Although this has been studied more extensively for the posterior column-medial lemniscus system, it has also been established that neurons giving rise to the spinothalamic tract are subject to influences from supraspinal levels (Hagbarth and Kerr, 1954). Both postsynaptic and presynaptic inhibition are probably involved. The details of these terminations in the dorsal horns have not yet been established, but enough is known concerning the nociceptive afferents entering the spinal cord for it to be clear that the original concept of a simple relay in the substantia gelatinosa is no longer tenable.

A theory that has attracted considerable attention is the dorsal horn gate control system proposed by Melzack and Wall (1965). They postulated that the substantia gelatinosa functions as a gate control system modulating the afferent input before it influences transmission cells in the dorsal horn. These were considered to project centrally to activate a system responsible for perception and response. It was believed that vollies of impulses in large fibers are initially effective in activating the transmission cells, but with more prolonged stimulation, this effect diminishes because of a negative feedback mechanism involving the substantia gelatinosa. Vollies in small fibers were considered to inhibit this feedback mechanism.

Melzack and Wall proposed three features that characterized the afferent input and which they believed were involved in the origin of pain: first, the existence of continuous activity mainly in small myelinated and unmyelinated fibers, which sets the initial position of the gate; second, the activity evoked by the stimulus; and third, the relative balance between activity in the large and small fibers. A light pressure on the skin will activate the large fiber pathway which, in addition to activating the transmission cells, will tend to close the gate. With more vigorous stimulation, the small fiber input is increased, which will tend to counteract the large fiber effect on the substantia gelatinosa gate, so that the output of the transmission cells increases. On continued stimulation, adaptation takes place in the large fibers, resulting in a further opening of the gate and an enhanced output by the trans-

mission cells which is interpreted centrally as pain.

Although it has received criticism in terms of the physiological evidence on which it was based (Iggo, 1972; Schmidt, 1972), the Melzack and Wall gate theory stimulated interest and led to predictions that could be tested. Thus in situations where pain is occurring, activation of the large fiber system would be expected to reduce pain, and it is therefore of considerable importance that Wall and Sweet (1967) reported that in patients with chronic 'cutaneous pain,' this could be relieved by selective large fiber stimulation of peripheral nerves. This method of treatment still requires a full evaluation, but subsequent workers have also obtained encouraging results (Meyer and Fields, 1972).

A second prediction follows from the theory: that selective damage to the large fiber input might be expected to lead to opening of the gate and to the occurrence of pain. Attempts to relate cutaneous hyperesthesia to selective loss of large fibers with a preservation of small fibers in peripheral neuropathy date back to Wortis, Stein and Jolliffe (1942), and subsequently to studies by Weddell, Sinclair and Feindel (1948), Noordenbos (1959), Lourie and King (1966) and Ochoa (1970). In some of these reports, the small fibers may have represented regeneration from fibers of larger diameter, although this possibility was excluded in the study by Ochoa (1970). However, it is noteworthy that the selective large fiber loss in cutaneous sensory nerves in Friedreich's ataxia (Dyck, Lambert and Nichols, 1972) is unassociated either with hyperesthesia or with pain. The possibility that this is because of the very gradual development of the disorder, involving adaptive changes, is negated by the similar absence of pain and hyperesthesia in cases of uremic neuropathy with predominant large fiber loss in sensory nerves (Thomas, Hollinrake, Lascelles, O'Sullivan, Baillod, Moorhead and Mackenzie, 1971) (Fig. 2, A-C). Measurements of internodal length in teased fiber prep-

arations excluded the presence of significant numbers of regenerating fibers.

Conversely, it is of interest to establish whether there is any consistent pattern of fiber size loss in those chronic neuropathies in which pain is a prominent symptom. The distal aching pain in the limbs and the tabetic-like lightning pains of diabetic sensory neuropathy is an obvious instance, as is the nocturnal pain of ischemic neuropathy. However, both in diabetic neuropathy (Thomas and Lascelles, 1966) and in ischemic neuropathy (Eames and Lange, 1967), there is extensive segmental demyelination in peripheral sensory nerve trunks, making the interpretation of selective fiber loss difficult. Painful dysesthesiae and tenderness in the soles of the feet often accompany alcoholic neuropathy. In this disorder there is a loss of myelinated fibers affecting all size groups (Walsh and McLeod, 1970). The neuropathy associated with myelomatosis may be painful (Davis and Drachman, 1972). Walsh (1971) found that the fiber loss again affected myelinated fibers of all diameters, although in the cases that he investigated, pain was not a feature. Both in amyloid neuropathy and dominantly inherited sensory neuropathy, spontaneous pain may be a troublesome symptom. As has already been stated, in both these disorders, there is a predominant loss of small fibers, (Dyck and Lambert, 1969; Sluga 1974). Aching pain in the feet and lancinating pains in the legs occurred in the case of amyloid neuropathy whose sural nerve myelinated fiber size distribution is illustrated in Fig. 2A.

Perhaps the most significant condition in this context is Fabry's disease (angiokeratoma corporis diffusum). The affected hemizygous males may develop highly distressing pain in the hands and feet (Wise, Wallace and Jellinek 1962) sometimes of sufficient persistence and intensity to lead to suicide. A patient with pain in the hands and feet showed a selective loss of small myelinated fibers (Kocen and Thomas, 1970), (Fig.

2F). Degeneration of unmyelinated axons is known to occur in this disorder (Bischoff, Fierz, Regli and Ulrich, 1968). A similar case has since been examined, and the same pattern of fiber loss was evident (Kocen and Thomas 1973).

From these several studies, therefore, it can be concluded that predominant large fiber loss does not inevitably lead to the occurrence of pain, and that pain may be associated with predominant small fiber loss.

The physiological, anatomical and clinical observations reviewed here indicate that the earlier concept of specific nociceptive pathways has much to commend it. There is now good physiological evidence for peripheral receptors that respond selectively to noxious stimuli. This is the biophysical specificity of receptors. Such receptors are related to small myelinated and unmyelinated nerve fibers and represent specificity of nerve pathways. This is not to deny that there are also small myelinated fibers and C fibers that respond to other types of stimuli or to a range of stimuli. But the older concept of a direct 'pain pathway' must be replaced by something more sophisticated. Pain is a subjective attribute. As Melzack and Wall (1965) emphasized, stimuli that will be reported as pain under some circumstances may not be reported as pain under others in the same individual. Therefore as specificity of neural pathways in sensory terms is a difficult concept, it is probably unwise to speak of a pain pathway as such. The existence of descending supraspinal influences offers clear possibilities for the modification of ascending sensory information (Wall, 1967; Fetz, 1968), as do interactions between different afferent inputs into the dorsal horn (Taub, 1964; Hillman and Wall, 1969). Handwerker, Iggo and Zimmerman (1973) have recently produced evidence that cutaneous nociceptive afferents may be inhibited in the dorsal horn by interneurons activated by mechanoreceptor afferents and by descending axons.

Much further investigation is required before it will be possible to

explain why damage to fibers carrying nociceptive information results in spontaneous pain in some instances but not in others. This analysis of the relationship between the patterns of fiber loss in the peripheral nervous system and the presence or absence of pain in neuropathies directs attention towards the small myelinated and unmyelinated fibers and towards the secondary effects in the dorsal horn (and possibly more widely in the central nervous system) following their damage.

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