Delayed onset and resolution of pain
Some observations and implications

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Summary
Occasionally, pain after disease or trauma develops only after a prolonged interval. Examples include late-onset pains which first occur months or years following a stroke, spinal cord lesion or amputation of a limb; a previously experienced pain that is recalled years later; and latent pain triggered for the first time by a further insult in the same area. Late-onset pains may develop gradually or suddenly, and may be brief or long standing. Pains which develop after an innocuous insult may be associated with slowly evolving sensory changes. However, even long-standing pains, particularly those of nociceptive origin, may resolve sometimes after many years. Resolution, which again can occur gradually or suddenly, may be spontaneous or follow development of another disorder or after therapeutic intervention. The duration of this pain relief can range from minutes to an indefinite period. These clinical phenomena, and the mechanisms, including genetic factors, subserving them, have been little studied. It is postulated that mechanisms implicated in acute pain may not be the same as those that subserve pain that develops after a long interval. Those late-onset pains which develop slowly after innocuous lesions may be associated with a variety of slow anatomical, physiological and biochemical changes. In late-onset pains that follow a painful insult, however, memory of the former pain and threshold triggering factors may be particularly important. Further studies of these neglected conditions may lead to understanding of as yet unknown processes subserving pain and to novel approaches to treatment.

Keywords: delayed; onset; resolution; pain

Introduction
Les cicatrices nerveuses gardent une potentialité évolutive. Pour elles, la notion de temps ne compte pas... Le calme clinique ne signifie pas que tout est fini. Le temps n’existe pas pour nos tissus.

Leriche, 1951

We recognize that acute illness and damage to the nervous system often give rise to pain acutely, and we expect that the pain will gradually subside. We also recognize that occasionally acute pain fails to subside, with the result that chronic pain ensues. Yet surprisingly, pain sometimes only develops a long time after the causative event and, equally surprisingly, even chronic pain can subside after a long time. What is a long time? Clearly a pain that develops or resolves 30 years after an insult is of late onset, but whether onset of pain after 10, 5 or 1 year, or 1 month, is ‘late onset’ remains as arbitrary as defining post-herpetic neuralgia.

Not only are the temporal aspects very variable, but the manner in which late-onset pain develops or subsides is also very variable. Sometimes pain occurs suddenly, even within minutes, yet sometimes development takes place over weeks; similarly, freedom from pain can occur suddenly or gradually and may prove evanescent or long lasting, if not permanent.

These temporal phenomena, which are difficult to explain by extrapolation from the processes currently thought to subserve acute and early onset chronic pains, raise issues that are rarely addressed about how pain is generated, maintained or resolves over long periods of time. The aim of this review is to draw attention to the unusual time course of certain painful conditions in man. Brief reference will first be made to a few illustrative examples of delayed onset and delayed resolution of chronic and, in particular, neuropathic pains. Some implications of these conditions for understanding long-term mechanisms subserving pain will then be considered.
The delayed appearance of chronic neuropathic pain

Delayed development of pain after stroke or spinal cord lesions

It is well recognized that pain first develops in some patients many months or even years after a stroke or spinal cord injury. These two conditions are of importance since the precise time of onset of the initiating insult is known. Whilst central post-stroke pain usually develops immediately or within the first few weeks of the stroke, occasionally the pain may only occur after months or even years (Garcin, 1968; Boivie and Leijon, 1991), and Leijon and colleagues (Leijon et al., 1989) found that three of their 27 patients only developed pain between 2 and 3 years after the stroke (Fig. 1). Spinal cord injury patients present considerable difficulties when trying to correlate pain and its onset in relation to the injury because of the various nociceptive and neuropathic components that often co-exist. Nevertheless, in specific painful disorders such as the central dysaesthetic syndrome, pain onset is often delayed for many months (Berić et al., 1988). Other rarer, acute-onset spinal cord disorders may also be associated with long-delayed onset of pain. Thus, following vascular cord insults such as the acute anterior spinal artery syndrome, painful dysaesthesias may be delayed for 6–7 months (Triggs and Berić, 1992), and a similar phenomenon may be seen after cordotomy (Nathan and Smith, 1984). Even in reports which include patients with unselected spinal lesions from a variety of causes, delay in onset of pain is common. For example, Tasker and colleagues (Tasker et al., 1992) noted delay in onset of pain for over a year in 26% of their 127 patients with intractable pain due to spinal cord lesions of traumatic and other causes.

In the absence of additional damage as might occur following a further stroke, or the development of post-traumatic syringomyelia or of a double lesion syndrome (Berić et al., 1987), the pain that develops late presumably must have been generated as a consequence of the original lesion.

Particularly striking in these cerebral and spinal pains of late onset is that their development sometimes coincides with alteration in sensation, including improvement in sensory loss and the development of dysaesthesias (Boivie and Leijon, 1991), or return of dorsal column function in spinal cord injury patients (Berić et al., 1988). Also striking is that, in comparison with many of the other conditions discussed below, these pains often develop slowly over weeks or months.

Perhaps the most unusual observation is that delayed-onset ipsilateral central post-stroke pain can occur (Kim, 1998). Recently, six patients were described who developed typical, early-onset central post-stroke pain contralateral to the ischaemic lesion. As the pain worsened, mild ipsilateral pain in a mirror distribution started to appear, with an interval that ranged from 6 to 24 months after the stroke. There was no evidence to suggest a new ischaemic lesion had developed, and a relationship between the early-onset contralateral pain and the delayed-onset ipsilateral pain seems likely.

Delayed onset of phantom pain

Delayed onset of phantom pain is another well-recognized phenomenon. In 10–33% of patients, delay of onset of pain is longer than a year, and individual cases with onset as long as 13, 25 and 30 years after amputation have been reported (for references, see Sunderland, 1978, p. 437). Late-onset phantom pain may develop suddenly or gradually (see Sherman, 1997), and the pain may be long lasting or fluctuate, and may or may not gradually subside or be liable to reactivation at a future time.

Apart from fluctuating emotional states, phantom pain can sometimes be reactivated or worsened by various specific factors such as benign and malignant spinal diseases, spinal cord injury and spinal anaesthesia, and phantom pain can increase even after 24 years when an additional disease develops (see Chang et al., 1997). Rare examples have also been reported of a previous phantom pain being reactivated years later by an unrelated pain. For instance, Wilson and colleagues described the recurrence of left upper limb phantom limb pain following left D2 herpes zoster infection (Wilson et al., 1978), and a ‘flare-up’ of phantom limb pain coinciding with acute appendicitis has also been reported (Crue et al., 1964). These cases illustrate the influence on phantom pain of intercurrent illness, either at the same segmental level or at a remote site.

There are also patients whose amputation stump pain (e.g. Moore, 1946) or painful leg phantom (e.g. Sellick, 1985) has been transiently induced by spinal anaesthesia, presumably due to temporary loss of inhibition. The opposite phenomenon, however, may also occur. Thus phantom leg pain transiently resolved when the patient developed cervical cord compression from a disc, the phantom reappearing after removal of the disc (Brihaye, 1958), and the abolition of
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for example, an 80-year-old woman developed shingles affecting the first and second divisions of the right trigeminal nerve which resolved within 3 weeks. Ten years later, she developed intractable burning pain in the distribution of the previous rash within 24 h of an uneventful right cataract operation (Schott, 1998). Thus an unrelated traumatic event in the previously affected neural segment had induced delayed-onset post-herpetic neuralgia, probably due to the threshold for pain appreciation now being exceeded rather than to evocation of a former pain.

Fig. 2 Duration of post-herpetic neuralgia by age of patient. From Hope-Simpson, 1975. Reproduced with permission of the Journal of the Royal College of General Practitioners.

chronic pain which disappears after a long interval

Gradual resolution of long-standing neuropathic pain

Long-standing central pains that resolve, often do so slowly. Thus, reminiscent of the slow onset of chronic pain some years after a stroke referred to above, the converse can be seen when on rare occasions chronic central post-stroke pain gradually subsides even after prolonged periods. Patients with post-herpetic neuralgia may become pain free after many years and without specific treatment, and Hope-Simpson (Hope-Simpson, 1975) reported resolution of post-herpetic neuralgia of even 10 years’ duration (Fig. 2). Phantom limb pain too may subside. For example, in a prospective study of 58 patients undergoing amputation for vascular disease, the incidence of phantom pain dropped from 72 to 59% over 2 years (Jensen et al., 1985). However, phantom pain may also subside unpredictably after long periods (cited in Sunderland, 1978, p. 438), and a phantom sensation has been reported to disappear after 40 years when a diabetic sensory neuropathy developed (Sacks, 1984).

Peripheral neuropathic pain, even when severe, can slowly resolve. For example, Sunderland and Kelly reported that in three of 34 patients with pain due to peripheral nerve injury, which was sometimes causalgic in nature, the pain resolved in 1–2 years (Sunderland and Kelly, 1948), and spontaneous relief of causalgia after 3 years has been described (Slessor, 1948). Such observations led Sunderland (1978, p. 385) to conclude ‘In most cases the pain subsides to become bearable within 4 to 5 months, and it rarely lasts more than a year’. This view, however, remains contentious (Bonica, 1979), and whilst causalgia can certainly subside spontaneously over years, it remains uncertain how frequently such resolution occurs.

Rapid resolution of long-standing pain

In many chronic nociceptive conditions, pain can be abolished even after it has been present for many years. Examples include the relief of long-standing arthritic hip pain following joint replacement or of chronic facial pain after removal of a chronically impacted wisdom tooth, the resolution of the

phantom pain after stroke or electroconvulsive therapy is referred to below.

Pain memories

Different from these phantom pains which may first occur after a prolonged interval are the occasional reports of patients who have experienced a major painful event in the past and in whom this pain, together with its emotional accompaniments, is evoked years later by an unrelated painful stimulus.

particularly vivid examples have been described; for example, the patient with a left above-knee amputation reported by Nathan. The day after a series of saline injections into the stump, the patient had been woken during the night by phantom limb pain, ‘...but this was not the pain I [Nathan] had been inducing. He told me that a few years before his amputation he had been playing ice-hockey in Canada, had fallen, and one of the players had skated over the outside of his leg, the skate cutting open the skin and damaging the muscles. What he felt during the night were the identical sensations in his leg that he had had five years before. It was not that he remembered having such sensations; the sensations were present once again’ (Nathan, 1985).

Of note was not that the patient developed a delayed painful phantom but that his previous pain had been rekindled. Previous pains, unrelated to the pain of a phantom or stump, may have been first experienced anything from 2 weeks to 35 years earlier, and the rekindling can be very sudden. Contrasting with persistence of pain prior to amputation of a limb, this evocation of an earlier pain has been termed a somatosensory memory of a former pain, and ~20 cases following amputation have been reported in the literature (Katz and Melzack, 1990; Katz, 1997).

Delayed pain triggered by a further insult at the segmental level

These examples differ again from the triggering of post-herpetic neuralgia for the first time, sometimes many years after an initial, short-lived attack of shingles. For example,
Orthopaedic surgeons have reported other examples of rapid pain relief following surgery on damaged nerves. Examples of such pain-relieving interventions include repair of painful accessory nerve lesions even long after the initial nerve trauma (Nakamichi and Tachibana, 1998), and surgical repair of brachial plexus injuries many months after the massive nerve injuries have been sustained (Berman et al., 1996).

A bizarre example of the unexpected abolition of neuropathic pain is the report of rapid pain relief following nerve biopsy in diabetic patients with proximal peripheral neuropathy (Said et al., 1997). Not unexpectedly, nerve biopsy may be followed by the development of pain; the converse occurrence is remarkable and inexplicable. Another commonly encountered example, but of a paroxysmal neuropathic pain that can resolve extremely quickly, is trigeminal neuralgia. Whilst acknowledging that spontaneous resolution of pain can occur, it is striking that, despite extremely severe bouts of pain that may have continued for months or years, the patient is typically pain-free immediately following an interventional procedure such as radiofrequency thermocoagulation (Zakrzewska, 1995, p. 140).

Yet another instance of rapid pain relief is that following surgical removal of an osteoid osteoma. Although perhaps more nociceptive than neuropathic in origin, the pain from this benign bony tumour, which can sometimes spread to affect the whole limb and which can be so severe as to suggest causalgia, has usually disappeared by the time the patient wakes from surgery. One might have expected that the free unmyelinated nerve endings, for years embedded persistently sensitized, if not damaged, and that permanent livingstone.

Central pains that have been present for years can also disappear suddenly, either temporarily or permanently. Intriguingly, both peripheral and central neuropathic pains that have been present for years can disappear suddenly. This disappearance can happen spontaneously or following a particular event, and various examples are discussed below.

A striking example of long-delayed resolution of a peripheral neuropathic pain is reported by Sir Herbert Seddon (Seddon, 1972). In his classic textbook Surgical Disorders of the Peripheral Nerves, the operative findings in a patient with the carpal tunnel syndrome are illustrated, the photograph demonstrating a grossly damaged median nerve (Fig. 3). Although pain had been present for 20 years, a simple decompressive procedure resulted in cure. Abolition of chronic pain resulting from gross structural nerve damage sustained over so many years is difficult to explain by current views on the major and extensive peripheral and central somatosensory changes thought to occur after peripheral nerve lesions.

Fig. 3 The compressed median nerve found at surgery on a patient with painful carpal tunnel syndrome of 20 years duration. From Seddon, 1972. Reproduced with permission of Churchill Livingstone.
free episode might be attributed to chance, or to physiological changes related to altitude or to attentional factors related to the stress of travel, a similar observation was reported by Livingston who described an American marine with severe causalgia affecting the right leg due to a bullet wound sustained during World War II. Spontaneous pain relief only occurred during the aircraft flight from Hawaii to the mainland (Livingston, 1966). These accounts are also reminiscent of the anecdotal improvement in parkinsonian symptoms during an aircraft flight (Stern, 1994).

Some general conclusions can be drawn from these various clinical observations. (i) Pain sometimes occurs only after an interval of months or years following the initiating event, when presumably the acute damage to the nervous system or to the affected part has resolved. The duration of the pain ranges from extremely brief to long lasting. (ii) The initiating event may or may not have been painful. (iii) Pain resolution, too, may occur after these long time intervals. (iv) Changes may occur suddenly or gradually. (v) Late-onset pain relief is seen with pains of both neuropathic and, more commonly, nociceptive origin.

Discussion
As a preface, it should be acknowledged that nearly all the clinical reports referred to above are retrospective and often anecdotal. Anecdotal accounts are necessarily limited but, as here, may be particularly valuable when reporting uncommon phenomena (Nathan, 1967). Further understanding of these phenomena can only be achieved by means of very long-term prospective studies on patients with clearly defined and potentially painful disorders such as diabetic peripheral neuropathy, shingles or stroke. With rare exceptions (e.g. Hope-Simpson, 1975; Helgason et al., 2000), such studies have yet to be done, and the remarks that follow inevitably reflect the paucity of information available.

A second prefatory consideration is that delayed-onset pain may result from mechanical causes. Some of the patients with conditions referred to above have disabilities resulting in abnormal use of a limb, and disturbances of tone and posture. Patients may also develop structural complications such as joint disorders, contractures, foot deformity and scoliosis. These sequelae can all give rise to delayed-onset pain which is predominantly nociceptive in type. Whilst patients can have nociceptive, neuropathic or both types of pain, discussion here does not include those more readily explicable late-onset nociceptive pains attributable to musculoskeletal factors.

Are mechanisms mediating acute pain different from those mediating late-onset pain?
Although there are examples of changes that occur in the acute phase that may be prolonged, such as the surprisingly long-term inflammatory changes reported in post-herpetic neuralgia (Watson et al., 1991), it seems improbable that mechanisms implicated in acute pain can usually account for pain that develops after a prolonged period. Processes that mediate acute pain occur rapidly and are followed by a cascade of events that take place within minutes, hours and days, and affect widespread regions of the nervous system (Wall, 1984). It seems implausible that in the majority of painful conditions those molecular changes that ensue in the wake of acute damage and inflammation (for reviews, see Zimmermann and Herdegen, 1996; Woolf and Costigan, 1999), or the development of physiological phenomena such as central sensitization (for a review, see Li et al., 1999), could develop de novo months or years after the initiating event.

What happens to the acute-phase processes during the long pain-free interval is unknown. Late-onset pain seems to have its origin in, but is separate from, mechanisms associated with a noxious or even an innocuous insult, a view that accords with the concept of the nervous system that becomes changed after it has been ‘primed’ by a damaging event and which can now produce stimulus-independent responses (Woolf and Decosterd, 1999). Yet major nerve damage itself cannot be the critical factor since rapid relief of long-standing pain of nociceptive origin not uncommonly occurs. Explanations, therefore, must presumably implicate the response of the nervous system to damage and disease. Late-onset pains are heterogeneous. This suggests that there are different, but not necessarily mutually exclusive, responses of the nervous system to the innocuous or noxious acute, initiating event.

Late-onset pain after an innocuous event
In some patients, pain develops following a previously painless insult to the nervous system. Examples include delayed onset of pains after stroke and spinal cord injury, and these pains tend to come on gradually. The interval before pain develops varies considerably between different patients. This suggests that, rather than there being distinct types of pains which develop at different times, there is a continuous although reducing liability to develop pain. Figure 1 illustrates the continuous, albeit diminishing, tendency to develop pain after a stroke, and an illustration showing the same phenomenon in patients with pain after spinal cord injury has also been presented (Widerström-Noga et al., 1999).

Pain that only slowly develops (or resolves) could be subserved by slow anatomical or biochemical changes. Such anatomical changes could include axonal sprouting, regrowth and collateral sprouting (see, for example, Goldberger and Murray, 1988); effects induced by apoptosis and other forms of slowly developing cell death (see, for example, Charriaut-Marlangue et al., 1996); and gradual use of alternative pathways and unmasking of pre-existing connections (for a review, see Waxman, 1988). At spinal cord level, considerable information is available from animal studies concerning structural reorganization of central connections and the
physiological and biochemical changes that develop after injury (see Woolf and Decosterd, 1999). The chemical accompaniments of slow changes may comprise, for instance, slowly evolving depletion of acetylcholine and activation of NMDA (N-methyl-D-aspartate) receptors (Cusick, 1996).

That the nervous system is indeed changing slowly can be witnessed clinically in the slowly evolving sensory state that sometimes accompanies the development of pain after stroke and spinal cord injury, and after cordotomy (White and Sweet, 1979). There is also experimental evidence confirming slow, pain-related, metabolic changes in the nervous system, as shown in the recent SPECT (single photon emission computed tomography) study of the metabolic changes in the thalamus contralateral to a limb affected by reflex sympathetic dystrophy (Fukumoto et al., 1999). The authors investigated 10 patients whose illnesses were of different durations, and found that there was gradual evolution in thalamic perfusion from initial hyperperfusion to hypoperfusion over the course of 1 year (Fig. 4).

**Fig. 4** SPECT (single photon emission computed tomography) study findings showing the correlation between contralateral thalamic uptake index and time since onset of reflex sympathetic dystrophy. From Fukumoto et al., 1999. Reproduced with permission of The Lancet.

**Late-onset pain after a noxious event**

Several examples have been cited above in which pain has resolved but then recurred, sometimes after an interval of several decades. The return of pain, which can be very sudden, may occur spontaneously or be evoked, and evocation may be a result of noxious or innocuous input at the segmental or non-segmental level, and may be triggered by sensory or by psychological and attentional factors. Two particular questions arise in this group of patients: what is the nature of the memory of the preceding pain; and what triggers the onset of pain?

**Is there always a memory of previously experienced pain?**

In pains which are recalled, some memory of that pain must have been ‘stored’ in the nervous system and, at least in some instances, this memory appears to be permanent. The memory must have been laid down early if not immediately after the causative event, and it could be that injury and disease *always* generate biochemical and physiological changes that lead to permanent changes in the nervous system.

Experimental observations in man indeed demonstrate the lasting effect of previous painful experiences. In infancy, for example, the neonate who has received necessary though painful procedures retains a persistently lowered flexion reflex threshold (see Chiswick, 2000), consistent with the observation that neonatal circumcision leads to a baby having enhanced pain behaviour at inoculation several months later (Taddio et al., 1997). In adults, electrical stimulation of the CNS is more likely to evoke pain in patients suffering from chronic pain than in pain-free patients suffering from movement disorders (for references, see Lenz et al., 1993).

The nature of learning and memory in pain pathways has been reviewed recently (Sandkühler, 2000). Long-term, activity-dependent changes in synaptic strength leading to various forms of long-term potentiation and depression are important for phenomena such as central sensitization and wind-up, and involve glutamate-gated and voltage-gated calcium channels. However, ‘long-term’ in the context of animal experiments lasting minutes, hours or days is of uncertain relevance to human pain with onset delayed for months or years. It has been postulated that memory of pain might be subserved by alterations in distributed neural networks comprised within that entity that Melzack termed the ‘neuromatrix’ (Melzack, 1990). Whilst such a notion remains hypothetical, many of the conditions referred to above support the idea that the nervous system may never ‘forget’ a pain, i.e. memory of pain is persistent and presumably retains its ‘potentialité évolutive’ (Leriche, 1951).

**Triggering of late-onset occurrence, recurrence or resolution of pain: what is the contribution of threshold changes?**

Particularly in those patients who have already experienced an episode of pain and in whom therefore the neural network has already been ‘primed’, changes in threshold for experiencing pain might be crucial both for triggering and inhibiting late-onset pain. There is experimental evidence that, independent of morphological changes, changes could be mediated by physiological mechanisms such as alterations in cells’ receptive fields (Wall, 1988).

In the clinical context, threshold changes could be triggered by any one of numerous factors, both somatosensory and affective, and the effects may be either brief or long lasting. Several examples of triggered, late-onset pains have been cited above. Other examples of factors which in man
selectively trigger short-lived painful conditions range from transient alterations in voltage-gated calcium ion channel function in hemiplegic migraine (see Ptáček, 1998), to innocuous cutaneous triggering of shoots of pain in trigeminal neuralgia, intermittent pressure transduction affecting peripheral nerve endings in patients with painful callouses on the feet, emotional factors that exacerbate causalgia (e.g. Kirklin et al., 1947) and possibly even changes in the weather that might influence chronic rheumatological pain (Jamison et al., 1995). Long-lasting pain too can be triggered, sometimes very rapidly, e.g. as seen following amputation or spinal anaesthesia that uncovers a previous pain, or following a further peripheral insult that generates post-herpetic neuralgia for the first time months or years after shingles.

Perhaps once a potential pain state has been generated, it is the ceaseless interplay between excitation and inhibition that determines whether or not pain is experienced (see Wall, 1988). Such subtle interplay has been demonstrated experimentally in the alteration in pain and area of anaesthetic or analgesic skin in patients with surgically induced areas of sensory loss who receive medication with l-dopa or methyldopa (Hodge and King, 1976). l-Dopa administration increased pain and the area of denervated skin, and with methyldopa the subjective and objective changes were the opposite. Such patients demonstrate that pain and sensory loss can be modified presumably simply by altering central catecholamine levels.

Genetic factors
Genetic factors are likely to be important in a number of painful conditions (for a review, see Mogil, 1999), although the contribution of these factors to delayed pain phenomena remains to be studied. The example of hemiplegic migraine, however, illustrates that though the disorder is presumably lifelong, the symptoms are not only brief but may only become manifest after several years. In contrast, in certain hereditary painful neuropathies, the pain again only develops later in life but tends to be persistent (Dyck, 1993). In the former example, transient membrane threshold changes mediated by ion channel phenomena are likely to be relevant to the generation of transient pain, whereas in the latter example slowly progressive and persistent changes in peripheral nerve function presumably underlie the persistent, late-onset pain.

Late-onset resolution of pain
Phenomena associated with late-onset pain relief appear to mirror the phenomena seen in the development of late-onset pain. For example, relief can develop quickly or slowly, may be brief or long lasting, and can occur spontaneously or following interventions, including drugs and pain-relieving procedures as well as psychophysical methods ranging from behavioural therapy to use of mirrors for phantom pain (Ramachandran and Hirstein, 1998).

It is unclear whether pain relief develops through the same processes that can be used to pre-empt or alleviate acute or early-onset chronic pain. It is also unclear how long-standing pain can sometimes, but unpredictably, be alleviated, since it could be envisaged that, just as chronic pain is so often entrenched, changes in the nervous system following injury and disease might be irreversible. Yet local anaesthetics and opiates are sometimes effective even for long-standing pains. Furthermore, pain relief occurs within minutes of removal of a prostaglandin-containing osteoid osteoma or of a glomus tumour that had caused pain for several years. Again, pain associated with brachial plexus lesions can be improved following surgery at intervals ranging from 4 to 580 days after the trauma (Berman et al., 1998). These and several examples cited above demonstrate, therefore, that pain, however great its severity and long its duration, and whether associated or not with major nerve injury, still has the potential for rapid alleviation.

Just as late-onset pain has its origin in the acute event, mechanisms subserving late-onset pain resolution could also have their origins at the time of the acute event and could be long standing. Abolition of diffuse inhibitory noxious control mechanisms has been observed in paraplegic patients whose injuries had occurred from 3 to 13 months previously (Roby-Brami et al., 1987), and whether in humans long-term changes occur, e.g. in other inhibitory physiological processes subserving descending inhibition, endogenous opioids, and attentional and other psychological factors, is unclear. In some instances, threshold phenomena are likely to be as important for inhibition as for pain development, and perhaps even a ‘memory’ of the pain-free state can be recalled by psychological means.

Delayed-onset and relief of chronic pain: an example of a general biological phenomenon?
Many of the clinical phenomena discussed above, some of which might be viewed as neuroplastic phenomena related to pain (Melzack et al., 1999), occur in conditions entirely unrelated to pain. Examples of delayed-onset neurological disorders include delayed-onset dystonia (Burke et al., 1980), post-traumatic epilepsy (Jennett, 1975) and perhaps the late weakness seen in the post-polio myelitis syndrome (Dalakas et al., 1986). There is also evidence for retained memories of non-painful experiences, e.g. those memories that can be evoked by cortical stimulation (Penfield and Jasper, 1954). There is even evidence for retained memories of a phantom limb; thus thalamic microstimulation can give rise to phantom limb sensations apparently selectively in those patients who already have had spontaneous phantom limb sensations (Dodrovsky, 1999). Psychological experiences too may have delayed-onset sequelae; examples include the psychological consequences in adult life of events occurring in childhood,
and the experience of flashbacks that can follow trauma many years earlier.

There are also further examples that illustrate the combination of late-onset triggering with a previously induced ‘trace’ in the nervous system, such as the tendency for paralytic poliomyelitis to affect a limb that had been the site of an earlier injection (Anon., 1992), and perhaps for the predilection for various neurological conditions to develop at the site of previous trauma (for references, see Schott, 1985).

That these phenomena are not even confined to the nervous system is evident from the intriguing observation that skin lesions may develop in a site previously affected by a different skin disorder. This observation led to the comment of considerable relevance to the present discussion: ‘The skin does not quickly forget its previous injuries, no matter how normal it looks. Skin ‘memory’ may last a lifetime’ (Wolf et al., 1995). The same comment could apply to immunologically mediated ‘memory’ and numerous other biological phenomena.

**Conclusion**

Much is known about the physiological and biochemical changes that occur in the acute and early stages of patients’ experiences of pain. What processes occur, however, when pain develops or resolves after months and years are unknown. Almost certainly different mechanisms subserve the heterogeneous temporal phenomena seen in clinical practice.

If a single theme permeates this subject it is, as Leriche noted half a century ago (Leriche, 1951), that nothing appears to be forgotten by the nervous system, that time counts for nothing and that after neural damage there is always the potential for pain to occur and, perhaps, to resolve. The phenomena discussed here are probably not unique to the sensory and affective components which comprise pain. Rather, pain is but one, eloquent form of expression of processes which are relevant to diverse biological conditions. Studies of these hitherto neglected delayed pain-related conditions may provide clues to as yet unknown pain-suberving mechanisms and lead to novel approaches to treatment.

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