Phantom limb pain

L. Nikolajsen[1 3]* and T. S. Jensen[2 3]

Departments of [1]Anaesthesiology, [2]Neurology and [3]Danish Pain Research Centre, Aarhus University Hospital, DK-8000 Aarhus C, Denmark

**Corresponding author*

Br J Anaesth 2001; **87**: 107–16

Keywords: pain, phantom limb

The first medical description of post-amputation sensation was given by Ambroise Paré (1510–1590), a French military surgeon, who noticed that patients may complain of severe pain in the missing limb following amputation. In his 'Haquebusses and other guns', Paré characterized the post-amputation syndrome and proposed different models to explain the pain.[45] Subsequent studies by Charles Bell (1830), Magendie (1833), Rhone (1842), Guéniot (1861) and others provided detailed descriptions of the phenomenon and, in 1871, Mitchell coined the term 'phantom limb'.[26 57 98]

In modern times, traumatic amputations originating from World War I and II, Vietnam and Israeli wars and from landmine explosions all over the world are a tragic cause of phantom pain in otherwise healthy people. Other major reasons for amputation and phantom pain are peripheral vascular disease and neoplasms. Today, it is common knowledge that virtually all amputees experience phantom sensations, painful or not, after limb amputation. Non-painful phantom sensations rarely pose a clinical problem. However, in some amputees, the phantom becomes the site of severe pain, which may be exceedingly difficult to treat. A large number of different treatments have been suggested but the vast majority of studies concerning the treatment of phantom pain are based on small groups with no controls. A clear and rational treatment regimen is difficult to establish as long as the underlying patophysiology is not fully known. The development of animal models mimicking neuropathic pain, together with research in other neuropathic pain conditions, have contributed significantly to our understanding of phantom pain. It is now clear that nerve injury is followed by a series of changes in the peripheral and the central nervous system and that these changes may play a role in the induction and maintenance of chronic phantom pain. Although phantom pains may occur following amputation of body parts other than limbs,[27 49 66] the present review will focus on clinical characteristics, mechanisms, treatment, and possible preventive measures of phantom pain after limb amputation. The phantom complex includes three different elements.

- *Phantom limb pain:* Painful sensations referred to the absent limb.
- *Phantom limb sensation:* Any sensation in the absent limb, except pain.
- *Stump pain:* Pain localized in the stump.

These elements often coexist in each patient and may be difficult to separate.

Clinical aspects

Incidence

Early literature suggested that the incidence of phantom pain was as low as 2%. However, more recent studies report incidences of 60–80% (Table 1). The discrepancy in reported frequencies mainly occurred because early studies based prevalence rates on patients' request for pain treatment. This will substantially underestimate the problem of phantom pain as many amputees, at least in the past, were reluctant to report pain to health care providers. Sherman and Sherman (1983) reported that, although 61% of amputees with phantom pain had discussed the problem with their doctor, only 17% were offered treatment and a large proportion of the rest were told that they were mentally disturbed.[80]

The occurrence of phantom pain seems to be independent of age in adults, gender and level, or side of amputation.[37 46 54 59 80] Phantom pain is less frequent in young children and congenital amputees. In a recent study of 60 child and adolescent amputees who were missing a limb because of congenital limb deficiency (n=27) or surgery/trauma (n=33), the incidence of phantom pain was 3.7% in the congenital group and 48.5% in the surgical group.[99] Some authors have suggested a relationship between

Table 1 Incidence of phantom pain as reported in different studies

Year, authors	Patients (*n*)	Incidence (%)
1941, Riddoch	?	50
1948, Henderson and Smyth	300	4
1969, Appenzeller and Bicknell	34	56
1973, Parkes	46	61
1978, Carlen and colleagues	73	67
1983, Jensen and colleagues	58	72
1983, Sherman and Sherman	764	85
1985, Wall and colleagues	25	88
1991, Pohjolainen	124	59
1994, Houghton and colleagues	176	78
1995, Krane and Heller	24	83
1997, Wartan and colleagues	526	55
1997, Montoya and colleagues	32	50
1997, Nikolajsen and colleagues	56	75
1998, Wilkins and colleagues.	33	49
2000, Kooijman and colleagues	72	51

phantom limb pain and the aetiology of the amputation.[30 67 96] In a study of 92 lower limb amputees, Weiss and Lindell found that patients with a history of gangrene and/or infection had higher pain levels.[96] However, most studies have found no relationship between the amputees health status and incidence of phantom pain. It is also generally agreed that the incidence of pain is similar following civilian or military accidents.[32 37 59 81]

Onset and duration

Onset of pain is early. Several studies have show that 75% of patients develop pain within the first few days after amputation.[9 37 48 59 67] However, phantom pain may be delayed for months or years. Rajbhandari and colleagues described a 58-yr-old man, who had undergone left below knee amputation at the age of 13. Eight months before a diagnosis of diabetes, he began to complain of typical diabetic neuropathy pain in the phantom leg, which was followed by a similar pain complaint in the intact limb.[72]

At least three prospective studies have examined the duration of phantom pain. Parkes found that 85% of 46 amputees experienced phantom pain immediately post-amputation. One year later, 61% still had some pain.[67] Jensen and colleagues (1985) studied 58 amputees and found that the incidence of phantom pain was 72, 65 and 59% after 1 week, 6 months and 2 yr, respectively.[38] In a recent study by Nikolajsen and coworkers (1997) 56 patients who underwent amputation of the lower limb (mainly because of peripheral vascular disease) were questioned about phantom pain 1 week, and 3 and 6 months after the operation. Although the incidence and intensity of pain remained constant during follow-up, both frequency and duration of pain attacks decreased significantly.[59] Similar results have been found in retrospective studies based on questionnaires. Houghton and collaborators asked 176 amputees to specify on a scale of 0 to 10 the degree of phantom pain at 6 months, 1, 2 and 5 yr after amputation. The median phantom pain score decreased from 4 (moderate) immediately after amputation to 1 (slight), 5 yr post-operatively.[32] In a survey of 526 veterans with longstanding amputations, phantom pain had disappeared in 16%, decreased markedly in 37%, remained similar in 44% and increased in 3% of respondents reporting phantom pain.[93]

Character and localization

Phantom pain is usually intermittent; only a few patients are in constant pain.[46 59 93] Kooijman and colleagues studied 99 upper limb amputees of which 37 experienced phantom pain. Nine amputees were in constant pain, nine had attacks of pain a few times per day and the rest only experienced phantom pain weekly or less.[46] Phantom pain is described as shooting, stabbing, boring, squeezing, throbbing, and burning. A few patients more vivid and colourful descriptions.[9 37 38 42 54 59 93]

Phantom pain is primarily localized in distal parts of the missing limb (fingers and palms in upper limb amputees and toes, instep, top of the foot and ankle in lower limb amputees).[38 59]

Pre-amputation pain and phantom pain

Several retrospective studies—but not all[29 46 92]—have pointed to pre-amputation pain as a risk factor for post-operative phantom pain.[3 32 42 75] In paediatric amputees, Krane and Heller found that most children with phantom pain also experienced pre-operative pain.[48] In the study by Houghton and colleagues there was a significant relationship, in vascular amputees, between pre-amputation pain and phantom pain in the first 2 yr after amputation. In traumatic amputees phantom pain was only related to pre-amputation pain immediately after the amputation.[32] Similar findings have been described in prospective studies.[38 59] In the recent study of mostly vascular amputees by Nikolajsen and colleagues, a relationship was found between pre-operative pain and incidence of phantom pain 1 week and 3 months after amputation, but not after 6 months. However, as can be seen from Figure 1, the relation is not simple. Some patients with severe pre-amputation pain never developed phantom pain while others with only modest pre-operative pain developed intense phantom pain.[59]

Another issue concerns the possible persistence or revival of pain experienced before amputation. Striking case reports show that phantom pain may mimick pre-amputation pain both in quality and in location.[5 29 31 42 56 59] A recent study describes a woman who had her left leg amputated because of recurrent wound infection over a period of 2 yr. The most distressing pre-operative pain was invoked by the treatment carried out on the open drainage site on the calf, which required cleaning and re-packing twice daily. Immediately after amputation the patient experienced phantom pain

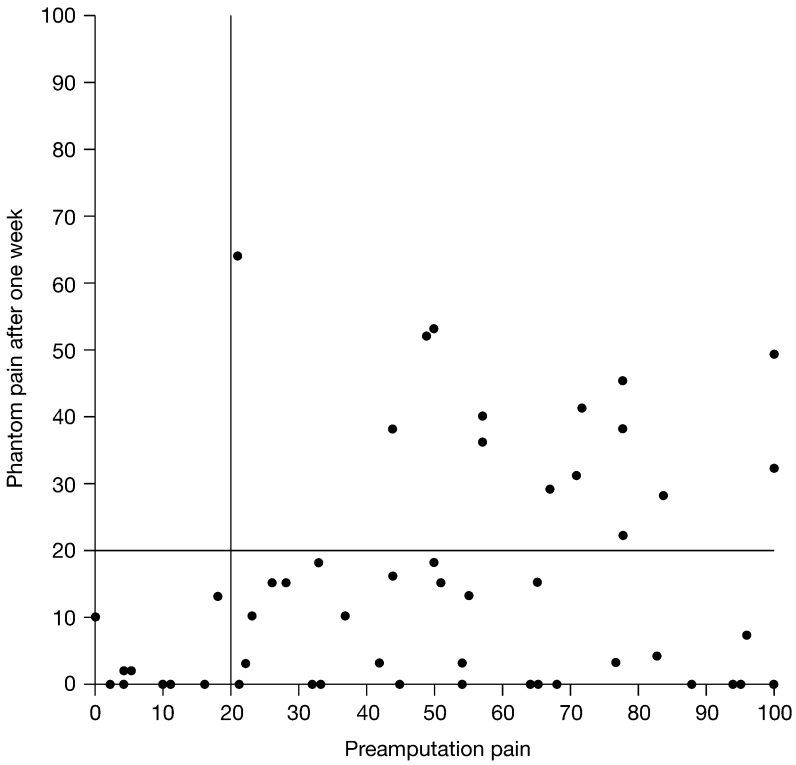

Fig 1 Pre-amputation pain ⩾20 increases the risk of phantom pain ⩾20 after 1 week and 3 months (on a VAS, 0–100). Data from the 1 week interview are shown. Each dot represents one patient, n=54. P=0.04, Fishers' exact test. (From Nikolajsen and colleagues 1997, with permission).

localized to the open drainage site, which was no longer there. The patient continued to suffer from episodes of phantom pain similar to the pain experienced pre-operatively for several years after the amputation.[31]

In a retrospective study by Katz and Melzack, 68 amputees were questioned about pre-amputation and phantom pain from 20 days to 46 yr after amputation. Fifty-seven of those who had experienced pre-amputation pain claimed that their phantom pain resembled the pain they had before amputation.[42] Jensen and colleagues prospectively examined the incidence of pre-amputation pain persisting as phantom pain. A similarity between pre-amputation pain and phantom pain, with respect to both character and location, was found in one-third of patients after 8 days, but only in 10% of patients after 6 months and 2 yr.[38] In another, more detailed prospective study by Nikolajsen and colleagues, patients were requested to describe pain and its localization before amputation. This was done using different word descriptors, the McGill Pain Questionnaire and their own words. After amputation, 42% of those who experienced phantom pain felt that the pain was similar to the pain they had experienced before amputation. However, when comparing preoperative and postoperative pain descriptions, the incidence of *actual* similarity was not higher in patients who claimed similarity than in those who found their phantom pain did not resemble pain experienced preoperatively. This indicates that patients memory of their pain does not always reflect the truth.[59] So, while a few case reports suggest that pre-amputation may persist as post-amputation pain, this is not the case in the vast majority of amputees.

Stump pain

Not surprisingly, stump pain is common in the early post-amputation period but, in most patients, it subsides with healing. However, in 5–10%, stump pain persists and may even get worse with time. Stump and phantom pain are interrelated phenomena and several authors have reported a higher prevalence of phantom pain among amputees with coexistent stump pain compared with amputees without stump pain.[9 37 38 46 59 80] Examination of the stump frequently reveals factors that may be related to pain. These include obvious pathology such as infection, bone spurs, neuromas and adherent and wrinkled scars. Further examination may reveal reduction in pain threshold (hyperalgesia), evocation of pain by non-noxious stimuli (allodynia) and pain elicited by repeated pricking stimuli ('wind-up' like pain).[9 37 38 62 71] Persistent stump pain may be very difficult to treat and it often interferes with prosthetic use and rehabilitation.

Phantom sensation

Phantom sensation is experienced by almost everyone who undergoes limb amputation, but it is rarely a clinical

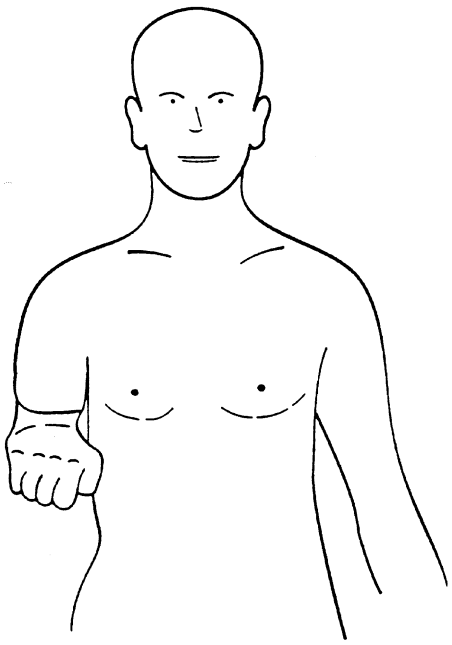

Fig 2 Telescoping. The phantom hand gradually approaches the residual limb and eventually becomes located inside the stump.

problem. Immediately after amputation, the phantom limb often resembles the pre-amputation limb in shape, length, and volume. The sensation can be very vivid and often includes feelings of posture and movement. Over time, the phantom sensation may fade. In some patients, a phenomenon called 'telescoping' occurs when the distal part of the phantom is gradually felt to approach the residual limb and, in the end, it may even be experienced within the stump.[37 38 46 54 93] An example of telescoping is shown in Figure 2. Phantom sensation and phantom pain are interrelated. In a recent study by Kooijman and colleagues, phantom pain was present in 36 of 37 patients experiencing phantom sensation but only in one of 17 who did not experience phantom sensations. Stump pain is also more frequent in patients with coexistent phantom sensation.[46]

Other factors

Evidence is growing that the individual's genetic predisposition to develop neuropathic pain may be important.[53] However, an inherited component is not always a feature of phantom pain. Schott described an interesting case in which five members of a family sustained traumatic amputations of their limbs. The development of phantom pain was unpredictable.[77]

It has been claimed that severe phantom pain may recur in lower-limb amputees undergoing spinal anaesthesia. Tessler and Kleiman prospectively investigated 23 spinal anaesthetics in 17 patients. Only one patient developed phantom pain, which resolved in 10 min.[88]

Phantom phenomena may be modulated be several other internal and external factors, such as stress, attention, urination, stump massage, and weather change. In a group of upper extremity amputees, Weiss and colleagues found that phantom pain was decreased by the use of a prosthesis, which allowed extensive use of the affected limb. A cosmetic prosthesis had no effect.[97] Successful rehabilitation may reduce the amount of pain.[69] A list of modulating factors is shown in Table 2.

Table 2 Factors that may modulate the experience of phantom pain

Internal factors	Genetic predisposition
	Anxiety/emotional distress
	Attention/distraction
	Urination/defaecation
	Other disease (cerebral haemorrhage, prolapsed intervertebral disc)
External factors	Weather change
	Touching the stump
	Use of prosthesis
	Spinal anaesthesia
	Rehabilitation
	Treatment

Mechanisms of phantom pain

The mechanisms underlying phantom pain have not been clarified completely. However, experimental and, to some extent, also clinical studies have contributed to our understanding of phantom pain after amputation. There is now evidence for peripheral and central contributions to phantom pain, as briefly outlined below. An understanding of the mechanisms underlying phantom pain is likely to lead to new and rational types of treatments.

Peripheral factors

1. Phantom pain is significantly more frequent in those amputees with long-term stump pain than in those without persistent pain.[9 37 38 46 59 67 80] It has been noted that phantom pain decreases with the resolution of stump-end pathology.[9]
2. Following a nerve cut, formation of neuromas are seen universally. Such neuromas show spontaneous and abnormal evoked activity following mechanical or chemical stimulation.[2 91] (for review[17]) The ectopic and increased spontaneous and evoked activity from the periphery is assumed to be the result of a novel expression or upregulation of sodium channels.[15 63]
3. Percussion of the stump or of identified stump neuromas induces stump and phantom pain. In a classical microneurographic study in two amputees, Nyström and Hagbarth showed that tapping of neuromas was associated with increased activity in afferent C fibres and increased pain sensation.[64] Consistent with these findings, a recent study shows that there is an inverse correlation between phantom pain intensity and pressure pain threshold of the stump early after amputation.[62]

4. Chabal and colleagues[10] showed that perineuromal injection of gallamine, which increases sodium conductance, produces phantom pain in amputees. However, lidocaine (an unspecific sodium channel blocker), when injected into the neuroma or surrounding tissue, blocks phantom pain.[10]
5. Also, in the dorsal root ganglion (DRG) cells, changes occur following a complete nerve cut. Cell bodies in DRG cells show similar abnormal spontaneous activity and increased sensitivity to mechanical and neurochemical stimulation.[39] DRG cells exhibit major changes with respect to the expression of sodium channels with a switch of one channel type to another.[95]
6. The sympathetic nervous system may also play an important role in generating and, in particular, in maintaining phantom pain. From animal studies, it is well known that application of norepinephrine or activation of the postganglionic sympathetic fibres excites and sensitizes damaged but not normal nerve fibres.[16] Sympatholytic blocks can abolish neuropathic pain and, in patients with pain relieved after a sympatholytic block, pain can be rekindled by injection of norepinephrine into the skin.[89] Long after limb amputation, injection of norepinephrine around a stump neuroma is reported to be intensely painful.[11] Catecholamine sensitivity may also manifest itself by the occurrence of a cooler extremity on the amputated side and it has been suggested that phantom pain intensity is inversely related to skin temperature of the stump.[44 82 83]

Spinal plasticity

- Sensitization of spinal pain transmission neurons is a normal physiological response of the undamaged nervous system. After nerve injury, there is an increase in this general excitability of spinal cord neurons, and C-fibres and Aδ-afferents gain access to secondary pain signalling neurons. Sensitization of dorsal horn neurons is mediated by release of glutamate and neurokinins. This sensitization may manifest itself as mechanical hyperalgesia and an expansion of peripheral receptive fields [for review[19]].
- While some amputees may show an abnormal superficial sensitivity to touching the stump, this is rarely sufficient to evoke phantom pain. On the other hand, pressure can often provoke phantom pain. The pharmacology of spinal sensitization involves increased activity in N-methyl D-aspartate (NMDA) receptor operated systems and many aspects of the central sensitization can be reduced by NMDA receptor antagonists.[19] In human amputees, for example, the stump or phantom pain evoked by repetitive stimulation of the stump ('wind-up' like pain) can be reduced by the NMDA antagonist ketamine.[58]
- Another type of anatomical reorganization, which also may produce dynamic mechanical allodynia, has been described recently. Neurons in lamina II normally receive A delta- and C-fibre input and respond best to noxious stimulation. Peripheral nerve damage may result in a substantial degeneration of C-fibre primary afferent terminals in laminae II. As a consequence of this loss of synaptic contacts normally made by C-fibre afferents onto pain signalling neurons in lamina II, central terminals of Aβ-mechanoreceptive afferents, which normally terminate in deeper laminae (III and IV), sprout into laminae I and II.[100] To what extent this spinal reorganization contributes to phantom pain is not known. But the fact that some patients do not show marked changes in stump sensitivity despite considerable phantom pain may be consistent with such spinal reorganization.

Cerebral reorganization

- The phantom limb percept, with its complex perceptual qualities and its modification by a variety of internal stimuli (e.g. attention, distraction or stress), shows that the phantom image may be a product of the brain.
- Electrophysiological studies have documented the existence of nociceptive specific neurons and wide dynamic range neurons in the cerebral cortex. Following limb amputation and deafferentation of adult monkeys, there is a reorganization of the primary somtosensory cortex, subcortex and thalamus.[24] After dorsal rhizotomy, a lowered threshold required to evoke activity in thalamus and cortex can be demonstrated. Also, adult monkeys display cortical reorganization in which the mouth and chin invade cortices corresponding to the representation of the arm and digits which have lost their normal afferent input.[18]
- In humans, similar reorganization has been observed using magnetoencephalographic techniques. Interestingly, this cerebral reorganization was seen mostly in patients with phantom pain and there was a linear relationship between pain and degree of reorganization.[25] Changes have also been observed at more subcortical levels. Using neuronal recording and stimulation techniques, Davis and colleagues found an unusually large thalamic stump representation.[13]

Summary of mechanisms

The above findings indicate that a series of mechanisms are involved in generating phantom pains and that these include elements in the periphery, spinal cord and brain. It is likely that the first events occur in the periphery, which subsequently generates a cascade of events that sweep more centrally and also recruit cortical brain structures. The latter may be reponsible for the complex and vivid sensation that characterizes certain phantom pain sensations. The unraveling of neuroplastic changes in periphery, spinal cord, and brain are also reflected in many of the features seen in phantom pain phenomena.

Table 3 Treatments for phantom pain

Medical	Non-medical	Surgical
TCA	TENS	Neurectomy
Anticonvulsants	Acupuncture	Stump revision
Lidocaine/mexiletine	Bio-feedback	Rhizotomy
Opioids/tramadol	Hypnosis	Cordotomy
NMDA receptor antagonists	Massage	Tractotomy
Beta-blockers	Ultrasound	DREZ lesion
Calcitonin	Electroconvulsive therapy	Tractotomy
Benzodiazepines		Lobectomy
Various nerve blocks		Sympathectomy
		Dorsal column stimulation
		Brain stimulation

Treatment

Treatment of phantom pain after amputation is difficult. Various treatment regimens have been, or are currently, in use. A survey of the literature in 1980 identified 68 different methods, of which 50 were still in use.[79] Clear evidence-based guidelines for the treatment of phantom pain can not be given, as most studies suffer from major methodological errors, such as small sample size, no or insufficient blinding and randomization, and short follow-up periods.[6] Until more reliable data become available, guidelines are probably the best approach. The situation is similar for other neuropathic pain states, for example, post-herpetic neuralgia and diabetic neuropathy. Treatment of phantom pain can be classified as medical, non-medical and surgical. Medical treatment is the most effective. In general, treatment should be based on non-invasive techniques as surgical procedures carry a risk of further deafferentiation resulting in even more pain. Table 3 lists treatments used for phantom pain.

Medical treatment

Numerous medical interventions have been proposed over the years but tricyclic antidepressants (TCA) and sodium channel blockers are currently considered to be the drug treatments of choice for neuropathic pain.[86]

A large number of randomized, controlled clinical trials have shown a beneficial effect of TCA in different neuropathic pain conditions and, recently, amitriptyline was shown to relieve nerve injury pain.[40] No controlled trials have been performed in phantom limb pain but TCAs are generally considered to be effective. Selective serotonin reuptake inhibitors (SSRI) are probably less effective in neuropathic pain. The TCA drug doxepin was reported to be effective in the treatment of phantom pain.[33] Others have reported a beneficial effect of the benzodiazepine clonazepam.[7] However, there is a general clinical impression that benzodiazepines do not produce substantial pain relief.

Carbamazepine, an anticonvulsant drug which is effective in neuropathic pain,[86] is a non-specific sodium channel blocker. Case reports have suggested that it is effective in phantom pain.[21 68] Novel anticonvulsants such as lamotrigine and gabapentin may also prove to effective in phantom pain.

Lidocaine and its oral congener mexiletine are used in different neuropathic pain conditions.[52] I.v. lidocaine was reported to be effective in neuropathic pain.[8] In an open-label study, mexiletine produced pain relief in 18 of 31 patients with phantom pain.[12]

Calcitonin may be effective in phantom pain. In a double-blind, crossover study, Jaeger and Maier demonstrated that i.v. calcitonin was effective in phantom pain when used in the early post-operative period.[35]

The effect of NMDA receptor antagonists have been examined in different neuropathic pain conditions, including phantom pain.[58 61 87] In a double-blind, placebo-controlled study, i.v. ketamine reduced pain, hyperalgesia and 'wind-up' like pain in 11 amputees with stump and phantom pain.[58] Memantine is another NMDA receptor antagonist available for oral use. In a recent double-blind, crossover trial, patients with pain following amputation (n=15) or nerve injury (n=4) were randomized to receive memantine or placebo in a 5-week treatment period. A washout period of 4 weeks was followed by another 5-week treatment period. Memantine, at a daily dose up to 20 mg, failed to have an effect on spontaneous pain, allodynia and hyperalgesia.[61]

Opioids were previously thought to be ineffective in neuropathic pain. Controlled studies are still lacking. However, presently, many feel that some patients can benefit from opioids with a limited risk of drug dependence.[6 14] The analgesic effect of oral and intrathecal opioids in phantom pain has been described by several authors.[34 65 90] Tramadol is an analgesic with both monoaminergic and opioid activity and it may prove to be an alternative to strong opioids as tolerance and dependence during long-term treatment with tramadol appears to be uncommon. NSAIDs and paracetamol are considered to be ineffective in phantom pain by most practitioners.

A large number of other treatments, for example, beta-blockers,[1] topical application of capsaicin,[74] various anaesthetic blocks[50 94] have been claimed to be effective in phantom pain but none of them have proven to be effective in well-controlled trials.

Non-medical treatment

Medical treatment can be combined with various non-invasive techniques such as transcutaneous electrical nerve stimulation (TENS), vibration therapy, acupuncture, hypnosis, biofeedback, and electroconvulsive therapy.[43 51 73 84] Despite the widespread use of some of these techniques clear evidence of effect is limited[22] (for review[28]). In a placebo-controlled, crossover design, Katz and Melzack found that TENS, applied to the outer ear, reduced phantom pain.[43] Lundeberg and colleagues found a similar effect of vibration therapy.[51]

Electrical stimulation of the spinal cord, deep brain structures, and motor cortex may relieve chronic neuropathic pain, including phantom pain. However, the effect of treatment often decreases with time.[47 55] (for review[85])

Surgical treatment

Surgical treatment for phantom pain has been attempted for decades but the results have generally been unfavourable. Stump revision or neurectomy may be effective if there is local specific pathology at the stump but, in properly healed stumps, there is almost never an indication for proximal extension of the amputation because of pain. Dorsal root entry zone (DREZ) lesions were primarily introduced for the treatment of painful brachial plexus avulsions but the treatment has also been used in phantom pain.[76] It is believed to have a limited effect. Other neurosurgical techniques, for example, cordotomy, thalamotomy, sympathectomy may provide short-term pain relief but pain often reappears. These treatments have been most abandoned today.

Prevention

The idea of a pre-emptive analgesic effect in phantom pain was initiated by observations that phantom pain in some cases seemed to be similar to pain experienced before the amputation[5 29 56] and that the presence of severe pain before amputation was associated with a higher risk of post-amputation phantom pain.[3 38 75] It was hypothesized that pre-amputation pain created an imprint in the memorizing structures of the central nervous system and that such an imprint could be responsible for persistent pain after amputation. Therefore, Bach and colleagues carried out a controlled study to examine if pre-operative epidurals could reduce the risk of phantom pain. They randomized 25 patients undergoing amputation of the lower limb by means of their year of birth to receive either epidural morphine, epidural bupivacaine or both in combination for 3 days before amputation (n=11) or conventional analgesia (n=14). All patients received epidural or spinal analgesia for amputation and 'post-operatively' their pain was treated with conventional analgesics. Patients were questionned about phantom pain after 1 week, and 6 and 12 months. Pain was categorized as either present or not present and, apparently, interviewers were not blinded to the treatment. Six patients died during the follow-up period. The incidence of phantom pain was reduced 6 months after amputation but not after 1 week or after 12 months in the epidural treatment group as compared with the control group.[4] Subsequent clinical trials have confirmed these results.

Jahangiri and colleagues prospectively followed 24 patients undergoing limb amputation. In a non-randomized design, patients received either an epidural infusion of bupivacaine, diamorphine and clonidine from 24 to 48 h pre-operatively and for at least 3 days after surgery (n=13) or on demand opioids (n=11). Amputation was carried out under general anaesthesia. The presence of phantom pain was graded on a scale of 1–10 and pain was considered significant when the score was $\geqslant$3. During follow-up, two patients died. The incidence of phantom pain was significantly lower in the epidural group after 1 week, and 6 and 12 months.[36]

In a letter, Schug and colleagues presented data from a non-randomized trial. Methods of blinding and pain assessment were not described. Twenty-three patients were divided into three groups. One group received an epidural infusion of bupivacaine and fentanyl for 24 h before amputation and continued for at least 48 h after surgery (n=8). Another group (n=7) had epidural anaesthesia for the amputation and 'post-operatively' pain was treated with epidural infusion of bupivacaine and fentanyl. The third group (n=8) received surgery under general anaesthesia and systemic analgesia for pain. After 1 yr, the incidence of phantom pain was significantly lower in the patients who had received pre-, intra- and post-operative epidural analgesia.[78]

Katsuly-Liapis and colleagues reported in abstract form 45 patients who were randomized into three groups to receive: (1) epidural analgesia with bupivacaine and morphine for 3 days before amputation and continued for 3 days after surgery (n=15), (2) epidural analgesia post-operatively (n=12) or (3) systemic analgesia with opioids and NSAID (n=18). After 6 months, the incidence of phantom pain was significantly lower in the patients who had epidural analgesia before, during, and after amputation compared with the other two groups. No details with respect to randomization, blinding, or pain assessment were presented.[41]

In a blinded and placebo-controlled trial, Nikolajsen and colleagues randomly assigned 60 patients into two groups. All patients had an epidural catheter on the day before the amputation. The epidural treatment group (n=29) received a pre-operative infusion of epidural bupivacaine and morphine for a median time of 18 h and the infusion was continued during the amputation. The control group (n=31) received equivalent amounts of epidural saline and systemic opioids. Both groups had general anaesthesia for the amputation and all received epidural bupivacaine and morphine for post-operative pain management. Phantom pain was assessed after one week, and 3, 6 and 12 months by a visual analogue scale (VAS). Blinding was ensured by the use of two independent investigators. One investigator was responsible for inclusion of patients and for post-operative pain assessment and the other for randomization and pre- and intra-operative pain treatment. The number of patients was reduced to 28 after 1 yr, mainly because of death. After 1 week, 52% of patients in the epidural treatment group and 56% of patients in the control group had phantom pain. Incidence and intensity of phantom pain were also similar in the two groups at the later post-operative interviews.[60] So,

according to this study, it is not possible to prevent phantom pain by a epidural block of short duration.

Others have examined the effect of a post-operative perineural analgesia on the prevention of phantom pain. Fisher and Meller (1991) introduced a catheter into the nerve sheath at the time of amputation and infused bupivacaine for 72 h post-operatively.[23] Similar methods were used by Elizaga and colleagues[20] and Pinzur and coworkers[70] but only the study by Fisher and Meller found an effect of treatment.[23]

Conclusion

It may not be possible to prevent phantom pain by pre-emptive approaches. A further understanding of the mechanisms underlying pain in amputees may lead to new and rational treatments. In future, perhaps we will see the development of new drugs with fewer side effects compare with drugs we use today.

References

1 Ahmed S. Phantom limb pain and propranolol. *BMJ* 1979; **1**: 415

2 Amir R, Devor M. Ongoing activity in neuroma afferents bearing retrograde sprouts. *Brain Res* 1993; **630**: 283–8

3 Appenzeller O, Bicknell JM. Effects of nervous system lesions on phantom experience in amputees. *Neurology* 1969; **19**: 141–6

4 Bach S, Noreng MF,Tjéllden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301

5 Bailey AA, Moersch FP. Phantom limb. *Can Med Assoc* 1941; **45**: 37–42

6 Baron R, Wasner G, Lindner V. Optimal treatment of phantom limb pain in the elderly. *Drugs Aging* 1998; **12**: 361–76

7 Bartusch SL, Sanders J, Dálessio JG, Jernigan JR. Clonazepam for the treatment of lancinating phantom limb pain. *Clin J Pain* 1996; **12**: 59–62

8 Boas RA, Covino BG, Shahnarian A. Analgesic responses to i.v. lidocaine. *Br J Anaesth* 1982; **54**: 501–5

9 Carlen PL, Wall PH, Nadvorna H, Steinbach T. Phantom limbs and related phenomena in recent traumatic amputations. *Neurology* 1978; **28**: 211–7

10 Chabal C, Jacobson L, Russell L, Burchiel KJ. Pain responses to perineuromal injection of normal saline gallamine, and lidocaine in humans. *Pain* 1989; **36**: 321–5

11 Chabal C, Jacobson L, Russell L, Burchiel KJ. Pain responses to perineuromal injection of normal saline, epinephrine, and lidocaine in humans. *Pain* 1992; **49**: 9–12

12 Davis RW. Successful treatment for phantom pain. *Orthopedics* 1993; **16**: 691–5

13 Davis KD, Kiss ZHT, Luo L, Tasker RR, Lozano AM, Dostrovsky JO. Phantom sensations generated by thalamic microstimulation. *Nature* 1998; **391**: 385–7

14 Dellemijn P. Are opioids effective in relieving neuropathic pain? *Pain* 1999; **80**: 453–62

15 Devor M, Govrin-Lippman R, Angelides K. Na^+ channels immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neurosci* 1993; **135**: 1976–92

16 Devor M, Janig W, Michaelis M. Modulation of activity in dorsal root ganglion neurones by sympathetic activation in nerve-injured rats. *J Neurophysiol* 1994; **71**: 38–47

17 Devor M, Seltzer Z. Pathophysiology of damaged nerves in relation to chronic pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 129–64

18 Dostrovsky JO. Immediate and long-term plasticity in human somatosensory thalamus and its involvement in phantom limbs. *Pain Suppl* 1999; **6**: 37–43

19 Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 165–81

20 Elizaga AM, Smith DG, Sharar SR, Edwards T, Hansen ST. Continuous regional analgesia by intraneural block: effect on postoperative opioid requirements and phantom limb pain following amputation. *J Rehab Res Dev* 1994; **31**: 179–87

21 Elliott F, Little A, Milbrandt W. Carbamazepine for phantom limb phenomena. *N Engl J Med* 1976; **295**: 678

22 Ezzo J, Berman B, Hadhazy VA, Jadad AR, Lao L, Singh BB. Is acupuncture effective for the treatment of chronic pain? *Pain* 2000; **86**: 217–25

23 Fisher A, Meller Y. Continuous postoperative regional analgesia by nerve sheath block for amputation surgery—a pilot study. *Anesth Analg* 1991; **72**: 300–3

24 Florence SL, Kaas JH. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *J Neurosci* 1995; **15**: 8083–95

25 Flor H, Elbert T, Muhlnickel, Pantev C, Wienbruch C, Taub E. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. *Exp Brain Res* 1998; **119**: 205–12

26 Furukawa T. Charles Bell's description of the phantom phenomenon in 1830. *Neurology* 1990; **40**: 1830

27 Hanowell ST, Kennedy SF. Phantom tongue pain and causalgia: case presentation and treatment. *Anesth Analg* 1979; **58**: 436–8

28 Hansson P, Lundeberg T. Transcutaneous electrical nerve stimulation, vibration and acupuncture as pain relieving measures. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 1341–51

29 Henderson WR, Smyth GE. Phantom limbs. *J Neurol Neurosurg Psych* 1948; **11**: 88–112

30 Herrmann LG, Gibbs EW. Phantom limb pain. Its relation to the treatment of large nerves at time of amputation. *Am J Surg* 1945; **67**: 168–80

31 Hill A, Niven CA, Knussen C: *Pain* memories in phantom limbs: a case study. *Pain* 1996, **66**: 381–4

32 Houghton AD, Nicholls G, Houghton AL, Saadah E, McColl L. Phantom Pain: natural history and association with rehabilitation. *Ann R Coll Surg Engl* 1994; **76**: 22–5

33 Iacono RP, Sandyk R, Baumford CR, Awerbuch G, Malone JM. Post-amputation phantom pain and autonomous stump movements responsive to doxepin. *Function Neurol* 1987; **2**: 343–8

34 Jacobsen L, Chabal C, Brody MC. A comparison of the effects of intrathecal fentanyl and lidocaine on established postamputation stump pain. *Pain* 1990; **40**: 137–41

35 Jaeger H, Maier C. Calcitonin in phantom limb pain: a double-blind study. *Pain* 1992; **48**: 21–27

36 Jahangiri M, Bradley JWP, Jayatunga AP, Dark CH. Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. *Ann R Coll Surg Engl* 1994; **76**: 324–6

37 Jensen TS, Krebs B, Nielsen J, Rasmussen P. Phantom limb,

phantom pain and stump pain in amputees during the first 6 months following limb amputation. *Pain* 1983; **17**: 243–56

38 Jensen TS, Krebs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation pain. *Pain* 1985; **21**: 267–78

39 Kajander KC, Wakisaka S, Bennett GJ. Spontaneous discharge originates in the dorsal root ganglion at the onset of a painful peripheral neuropathy in the rat. *Neurosci Lett* 1992; **138**: 225–8

40 Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain* 1995; **64**: 293–302

41 Katsuly-Liapis I, Georgakis P, Tierry C. Preemptive extradural analgesia reduces the incidence of phantom pain in lower limb amputees. Abstract. *Br J Anaesth* 1996; **76**: 125

42 Katz J, Melzack R. Pain 'memories' in phantom limbs: review and clinical observations. *Pain* 1990; **43**: 319–36

43 Katz J. Melzack R. Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain. *J Pain Symptom Manage* 1991; **6**: 73–83

44 Katz J. Psychophysical correlates of phantom limb experience. *J Neurol Neurosurg Psych* 1992; **50**: 811–21

45 Keil G. Sogenannte erstbeschreibung des phantomschmerzes von Ambroise Paré. *Fortschr Med* 1990; **108**: 62–6

46 Kooijman CM, Dijkstra PU, Geertzen JHB, Elzinga A, Schans CP. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain* 2000; **87**: 33–41

47 Krainick J-U, Thoden U, Riechert T. Pain reduction in amputees by long-term spinal cord stimulation. *J Neurosurg* 1980; **52**: 346–50

48 Krane EJ, Heller LB. The prevalence of phantom sensation and pain in pediatric amputees. *J Pain Sympt Manage* 1995; **10**: 21–9

49 Krøner K, Krebs B, Skov J, Jørgensen HS. Immediate and long-term phantom breast syndrome after mastectomy: incidence, clinical characteristics and relationship to pre-mastectomy breast pain. *Pain* 1989; **36**: 327–34

50 Lierz P, Schroegendorfer K, Choi S, Felleiter P, Kress HG. Continous blockade of both brachial plexus with ropivacaine in phantom pain: a case report. *Pain* 1998; **78**: 135–7

51 Lundeberg T. Relief of pain from nine phantom limbs by peripheral stimulation. *J Neurol* 1985; **232**: 79–82

52 Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain* 2000; **87**: 7–17

53 Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci USA* 1999: **96**: 7744–51

54 Montoya P, Larbig W, Grulke N, Flor H, Taub E, Birbaumer N. The relationship of phantom limb pain to other phantom limb phenomena in upper extremity amputees. *Pain* 1997; **72**: 87–93

55 Mundinger F, Salomáo JF. Deep brain stimulation in mesencephalic lemniscus medialis for chronic pain. *Acta Neurochir* 1980; **30**: 245–58

56 Nathan PW. Pain traces left in the central nervous system. In: Keele CA, Smith R, eds. *The Assessment of Pain in Man and Animals.* Edinburgh: E & S Livingstone, 1962; 129–34

57 Nathanson M. Phantom limbs as reported by S. Weir Mitchell. *Neurology* 1988; **38**: 504–5

58 Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 1996; **67**: 69–77

59 Nikolajsen L, Ilkjær S, Krøner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. *Pain* 1997; **72**: 393–405

60 Nikolajsen L, Ilkjær S, Krøner K, Christensen JH, Jensen TS. Randomized trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet* 1997; **350**: 1353–7

61 Nikolajsen L, Gottrup H, Kristensen AGD, Jensen TS. Memantine (a *N*-methyl D-aspartate receptor antagonist) in the treatment of neuropathic pain following amputation or surgery—a randomized, double-blind, cross-over study. *Anesth Analg* 2000; **91**: 960–6

62 Nikolajsen L, Ilkjær S, Jensen TS. Relationship between mechanical sensitivity and postamputation pain: a prospective study. *Eur J Pain* 2000; **4**: 1–8

63 Novakovic SD, Tzoumaka E, McGivern JG, Haraguchi M, Sangameswaran L, Gogas KR, Eglen RM, Hunter JC. Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic pain conditions. *J Neurosci* 1998; **18**: 2174–87

64 Nyström B, Hagbarth KE. Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neurosci Lett* 1981; **27**: 211–6

65 Omote K, Ohmori H, Kawamata M, Matsumoto M, Namiki A. Intrathecal buprenorphine in the treatment of phantom limb pain. *Anesth Analg* 1995; **80**: 1030–2

66 Ovesen P, Krøner K, Ørnsholdt J, Bach K. Phantom-related phenomena after rectal amputation: prevalence and clinical characteristics. *Pain* 1991; **44**: 289–91

67 Parkes CM. Factors determining the persistence of phantom pain in the amputee. *J Psychosom Res* 1973; **17**: 97–108

68 Patterson JF 1988 Carbamazepine in the treatment of phantom limb pain. *South Med J* 1988; **81**: 1101–2

69 Pezzin LE, Dillingham TR, Mackenzie EJ. Rehabilitation and the long-term outcomes of persons with trauma-related amputations. *Arch Phys Med Rehabil* 2000; **81**: 292–300

70 Pinzur MS, Garla PGN, Pluth T, Vrbos L. Continous postoperative infusion of a regional anaesthetic after an amputation of the lower extremity. *J Bone Joint Surg* 1996; **78**: 1501–5

71 Pohjolainen T. A clinical evaluation of stumps in lower limb amputees. *Prosthet Orthot Int* 1991; **15**: 178–84

72 Rajbhandari SM, Jarett JA, Griffiths PD, Ward JD. Diabetic neuropathic pain in a leg amputated 44 years previously. *Pain* 1999, **83**: 627–9

73 Rasmussen KG, Rummans. Electroconvulsive therapy for phantom limb pain. *Pain* 2000; **85**: 297–9

74 Rayner HC, Atkins RC, Westerman RA. Relief of local stump pain by capsaicin cream. *Lancet* 1989; **2**: 1276–7

75 Riddoch G. Phantom limbs and body shape. *Brain* 1941; **64**: 197–222

76 Saris SC, Iacono RP, Nashold BS Jr. Successful treatment of phantom pain with dorsal root entry zone coagulation. *Appl Neurophysiol* 1988; **51**: 188–97

77 Schott GD. Pain and its absence in an unfortunate family of amputees. *Pain* 1986; **25**: 229–31

78 Schug SA, Burrell R, Payne J, Tester P. Pre-emptive epidural analgesia may prevent phantom limb pain. *Region Anesth* 1995; **20**: 256

79 Sherman RA, Sherman CJ, Gall NG. A survey of current phantom limb treatment in the United States. *Pain* 1980; **8**: 85–99

80 Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb pain among American veterans. Results of a trial survey. *Am J Phys Med* 1983; **62**: 227–38

81 Sherman RA, Sherman CJ. A comparison of phantom sensations

among amputees whose amputations were of civilian and military origins. *Pain* 1985; **21**: 91–7

82 Sherman RA, Glenda GM. Concurrent variation of burning phantom limb and stump pain with near surface blood flow in the stump. *Orthopedics* 1987; **10**: 1395–402

83 Sherman RA, Vernice GD, Evans CB. Temporal relationship between changes in phantom limb pain intensity and chances in surface electromyogram of the residual limb. *J Int Psychophysiol* 1992; **13**: 71–7

84 Siegel EF. Control of phantom limb pain by hypnosis. *Am J Clin Hypnosis* 1979; **21**: 285–6

85 Simpson BA. Spinal cord and brain stimulation. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 1353–81

86 Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999; **83**: 389–400

87 Stannard C F, Porter G E. Ketamine hydrochloride in the treatment of phantom limb pain. *Pain* 1993; **54**: 227–230

88 Tessler MJ, Kleiman SJ. Spinal anaesthesia for patients with previous lower limb amputations. *Anaesthesia* 1994; **49**: 439–41

89 Torebjork E, Wahren L, Wallin G, Koltzenburg M. Noradrenaline-evoked pain in neuralgia. *Pain* 1995; **63**: 11–20

90 Urban BJ, France RD, Steinberger EK, Scoot DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb. *Pain* 1986; **24**: 191–6

91 Wall PD, Gutnick M. Ongoing activity in peripheral nerves: the physiology and pharmacology of impulses originating from a neuroma. *Exp Neurol* 1974; **43**: 580–93

92 Wall R, Novotny-Joseph P, Macnamara TE. Does preamputation pain influence phantom limb pain in cancer patients? *South Med J* 1985; **78**: 34–6

93 Wartan SW, Hamann W, Wedley JR, McColl I. Phantom pain and sensation among British veteran amputees. *Br J Anaesth* 1997; **78**: 652–9

94 Wassef MR. Phantom pain with probable reflex sympathetic dystrophy. Efficacy of fentanyl infiltration of the stellate ganglion. *Region Anesth* 1997; **22**: 287–90

95 Waxman SG. The molecular pathophysiology of pain: abnormal expession of sodium channel genes and its contributions to hyperexcitability of primary sensory neurons. *Pain Suppl* 1999; **6**: 133–40

96 Weiss SA, Lindell B. Phantom limb pain and etiology of amputation in unilateral lower extremity amputees. *J Pain Symptom Manage* 1996; **11**: 3–17

97 Weiss T, Miltner WH, Adler T, Bruckner L, Taub E. Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. *Neurosci Lett* 1999; **272**: 131–4

98 Whitaker HA. A historical note on phantom limb. *Neurology* 1979; **29**: 273

99 Wilkins KL, McGrath PJ, Finley GA, Katz J. Phantom limb sensations and phantom limb pain in child and adolescent amputees. *Pain* 1998; **78**: 7–12

100 Woolf CJ, Shortland P, Coggeshaal RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992; **355**: 75–8