

Chronic post-surgical pain: 10 years on

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In the past ten years there has been recognition that chronic post-surgical pain is a significant problem. This is a complex area of research and although the quality of studies has improved many difficulties remain. Several recent publications have examined risk factors. Severe acute postoperative pain emerges as a factor that we may be able to influence. There is a need for education of the medical profession and the general public, so that effective measures are introduced and unnecessary and inappropriate operations minimized.

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The first paper on chronic post-surgical pain (CPSP) was published by Crombie and colleagues¹⁷ 10 vr ago, Since then there have been several reviews. 49 58 59 76 When the first review was written, it was noteworthy that the standard of research on outcomes after individual operations was often poor. For example, in one study looking at outcomes after hernia surgery, the methods section detailed how to perform the hernia repair but not how many patients were studied, for how long, or what outcome measures were used. Pain was often completely ignored. In the past 10 yr, there have been many excellent papers and it is heartening that in a recent review of inguinal hernia in the British Medical Journal, the authors state 'chronic pain is the most common and serious long term problem after repair of an inguinal hernia'. 37 This reflects an acceptance of chronic pain as an important outcome of surgery.

Recent research has shown a shift of emphasis away from mere number counting to the examination of risk factors and the possibility of prevention. There have been publications on this topic in general and on particular surgical procedures. The procedures are also shown us? This paper will not attempt to cover the same ground as the initial reviews, but will draw on recent publications to highlight areas of interest and controversy. There will be an emphasis on risk factors and aspects of the problem that could lead to a reduction in the number of patients suffering chronic pain after surgery. It will ask more questions than it answers, in the hope of stimulating debate and further research.

How much of a problem is chronic post-surgical pain?

The incidence of CPSP varies from operation to operation and between studies, but what is clear is that it is common. Table 1 shows the approximate incidence of chronic pain after some common operations, together with data on the numbers of operations performed in the UK and the USA. It is difficult to obtain accurate figures for numbers of operations performed, as the classification of operations for statistical purposes is different from the classifications used in studies of CPSP. The figures for numbers of operations in the UK are estimates based on Hospital Episode Statistics.³³ In the UK, the total number of operations in 2005-6 was around 7 million, but this includes many procedures that are not true surgical operations, such as endoscopies and normal deliveries of babies, or operations that are unlikely to be associated with CPSP, such as cataract operations. The figures for individual operations in the USA in 1994 are taken from Rutkow. 93 In the USA, the total number of operations performed in 1994 was approximately 22 629 000. 113 Rutkow's paper reported that the 10 most frequently performed operations in the USA increased from 5.7 million in 1983 to almost 8 million in 1994, an increase of 38%. The pattern and type of surgery will have changed since then, but the trend is likely to be similar. There is a wide variation in the figures for incidence of CPSP for several reasons, including differences in surgical techniques, study design, patient populations, and definitions. It is interesting that the first paper on the most common operation, Caesarean section, was not published until 2004.⁷²

These figures are estimates, but they give some insight into the magnitude of the problem and clearly there is a large population at risk. Taking just the seven operations listed above for each country and assuming the best case scenario, using the lowest figures for incidence for each operation there could be more than 41 000 cases in the UK and 394 000 in the USA each year. If we assume the worst case figures above, it could be as many as 103 000 in the

Table 1 Approximate numbers of operations carried out in England and the USA and incidence of CPSP

Type of operation	Incidence of chronic pain	No. of ops in UK in 2005-6	No. of ops in USA in 1994
Total operations		7 125 000	22 629 000
Mastectomy	20-50%	18 000	131 000
Caesarean	6%	139 000	858 000
section			
Amputation	50-85%	15 000	132 000
Cardiac surgery	30-55%	29 000	501 000
Hernia repair	5-35%	75 000	689 000
Cholecystectomy	5-50%	51 000	667 000
Hip replacement	12%	61 000	
Thoracotomy	5-65%		660 000

UK and 1.5 million in the USA. This is a major public health issue: it affects large numbers of patients, has important economic consequences,⁶ ⁹⁷ and has a significant effect on quality of life. ²⁹ ⁵⁴ ⁹⁸ Chronic pain after surgery is usually, in part at least, neuropathic, and this makes it hard to treat; prevention is therefore of great importance.

What are the problems in the research?

There are several problems that arise when investigating CPSP. The first is definition; the original review of the subject⁵⁹ discussed this and proposed a working definition.

- (i) The pain should have developed after a surgical procedure.
- (ii) The pain should be of at least 2 months duration.
- (iii) Other causes for the pain should be excluded, for example, continuing malignancy (after surgery for cancer) or chronic infection.
- (iv) In particular, the possibility that the pain is continuing from a pre-existing problem should be explored and exclusion attempted. (There is an obvious grey area here in that surgery may simply exacerbate a pre-existing condition but attributing escalating pain to the surgery is clearly not possible as natural deterioration cannot be ruled out.)

Unfortunately, few studies use a definition and where one is used, it differs from study to study. ⁸⁴ Another problem related to definition is the diversity of the syndromes. Using breast surgery as an example, patients complain of a range of unpleasant symptoms after operations, tingling, numbness, sensitivity, and swelling and pain. ⁸² ¹⁰⁶ The type of pain also varies: phantom pain, ²³ ⁵² neuropathic pain caused by damage to the intercostobrachial nerve, ¹¹⁴ or scar pain. ⁴¹ Patients often find it difficult to differentiate between the symptoms, for example, after amputation some patients cannot easily separate phantom pain, stump pain, and other unpleasant sensations. ³⁴

Research in this area is usually carried out on large populations, using questionnaires. We rely on the patients' reports of their symptoms and feelings, and there are several studies that show how unreliable patients' memories are for pain after surgery. Clinical data are difficult to obtain in this type of study, mainly because of the expense of conducting individual interviews and examinations. This means that in some cases the quality and reliability of the data is open to question.

One puzzling feature of CPSP relates to the incidence found in studies compared with the number of patients seen in Pain Clinics. Clinics known to have a special interest in this problem see large numbers of patients, but some doctors working in Pain Clinics report that they do not see many patients with CPSP. If the figures described above are correct, then Pain Clinics should be seeing large numbers of these patients. It is interesting to note that studies on outcomes after surgery, in which chronic pain is the main measure studied, find a higher incidence than those in which it is not. Is it that patients do not mention it unless they are asked? Do the studies overestimate the incidence? If the incidence is as high as the studies suggest, what is happening to these patients? Are they being treated appropriately in primary care or are they simply suffering in silence and being ignored?

Mechanisms

The mechanisms of CPSP are complex and ill understood. Different mechanisms will be responsible for different pain syndromes even after the same operation, for example, phantom pain, stump pain, and back pain after lower limb amputation.⁹⁹ Clearly, many of the syndromes are neuropathic and result from changes in the nervous system after injury. Surgery should be seen as an injury, obviously in most cases necessary and performed for good reason, but nonetheless an injury. Castillo and colleagues¹² have shown that the incidence of chronic pain after lower limb trauma is similar to that which occurs after many operations. An understanding of the types of changes that occur in the nervous system after disease and injury is important, but the subject is immensely complicated. 115 However, a basic appreciation of the mechanisms is useful for several reasons. First, if injury is responsible for initiating the changes in the nervous system, then it is likely that subsequent surgery may make it worse, by further winding up the nervous system. 117 Given the complexity of the changes, it is unlikely that simple treatments such as nerve blocks will produce long-term benefit. A multidimensional approach, involving the psychological dimension and physical and pharmacological treatments, will probably be required. An appreciation of the complexity of the mechanisms will also help to guide future research.

Many patients who suffer pain after surgery assume that something went wrong or the surgeon made a mistake. This is clearly not the case, and education of patients and doctors about the problem of CPSP would help patients come to terms with their problem. Patients who attribute blame for their chronic pain report more behavioural disturbance and distress, a poor response to treatments, and have lower expectations of the success of future treatments. Turk and Okifuji found that patients' beliefs that they were injured led to lower pain thresholds and tolerance, general deconditioning, and reduced activity. Removing the climate of blame would help patients and doctors. It seems that chronic pain after surgery is an inevitable consequence of surgery in a proportion of cases, like wound infection. If this was accepted and CPSP discussed openly and included in the information given to patients before operations much subsequent grief could be avoided.

Nerve injury and chronic pain

One area that deserves special mention is nerve injury. It is usually assumed that nerve injury is the cause of most neuropathic post-surgical pain syndromes, but what do we mean by nerve injury? Clearly, peripheral nerve injury is an important factor in the aetiology of neuropathic pain, but is there a simple relationship between damage to peripheral nerves and CPSP? Damage to the intercostal nerve is assumed to be an important cause of chronic pain after thoracotomy. Richardson and colleagues⁹⁰ found a point prevalence of post-thoracotomy neuralgia of 22% at 2 months and 14% at 12 months. An interesting series of papers from Nottingham investigated this topic; the first showed that all patients who have rib retraction during thoracotomy sustain intercostal nerve damage. 91 The damage occurs at several levels and can be caused by spreading the ribs, as a result of direct pressure, ischaemia, and stretching. The second study confirmed that neuropathic pain was common and caused significant morbidity. 61 Neuropathic pain was associated with more severe chronic pain, was more persistent, and caused greater impact on patients' lives. Surgical technique influenced the incidence. In the third study, the authors carried out neurophysiological tests on the nerves before the operation and before closing the chest and then examined the patients at 6 weeks and 3 months after operation. The authors did not find an association between nerve injury measured at the time of thoracotomy and chronic pain or altered sensation at 3 months follow-up. 60 This suggests a more complicated aetiology for neuropathic postthoracotomy pain than injury to the intercostal nerve alone.

In the case of pain after mastectomy, Carpenter¹¹ has stated 'the generally accepted risk factor of damage to the intercostobrachial nerve is mostly anecdotal'. In Carpenter's study, two patients who had only a lumpectomy, with no axillary dissection, developed post-mastectomy pain syndrome¹⁰² as well as four women in whom the intercostobrachial nerve was spared. Several studies on breast surgery have studied the effect of

preserving the intercostobrachial nerve. In a prospective randomized, controlled trial, Abdullah and colleagues² studied the effect of preserving or sacrificing the intercostobrachial nerve during axillary clearance. They found that, for a variety of reasons, it was not always possible to preserve the nerve. Although there was a significant difference in pain, numbness, and altered sensations at discharge, at 3 months, there was no significant difference between the groups, although as expected the incidence of sensory deficit was less in the preservation group. At 3 months, symptoms had worsened in both groups, particularly in the group whose nerves were preserved. Two patients with objective sensory loss had no symptoms whereas eight patients with sensory symptoms had no objective sensory deficit. Other studies have shown similar results. 94 108 In a study of 38 patients with ipsilateral arm pain after mastectomy, Vecht and colleagues¹¹⁴ found that only eight of the patients could be diagnosed as having post-surgical pain. All had axillary node dissection. The authors identified eight other causes in the remaining 30 patients. It is interesting that studies of symptoms after breast and axillary surgery show a higher incidence of numbness than pain. In a study of patients who had undergone axillary dissection, but no radiotherapy, chemotherapy, and had no evidence of recurrence, 70% of patients reported numbness and only 30% reported pain.³⁶ Polinsky⁸² reported that 81% of patients who underwent axillary surgery complained of numbness, but only 22-32% reported pain, depending on the type of surgery. In a study comparing psychophysical examination of patients with post-mastectomy pain with patients who had similar surgery but no pain, Gottrup and colleagues³⁰ found that patients in both groups showed decreased sensitivity to thermal and pinprick stimuli on the affected side. Pressure pain threshold on the affected side was decreased in the pain group, but not in the pain-free group. The main finding was that repetitive pinprick stimulation around the scar in the pain group produced increased evoked pain intensity, sometimes called wind-up hyperalgesia. The magnitude of the evoked pain correlated with spontaneous pain intensity. The authors concluded that this indicated central sensitization.

Damage to nerves during surgery is obviously an important cause of chronic pain after surgery, but from the discussion above it is clear that this is a complex issue. Merely avoiding the sectioning of major nerve trunks is not sufficient to prevent CPSP and sectioning nerves clearly does not always result in chronic pain. It is not possible to perform operations without injuring elements of the nervous system at some level.

Three questions emerge: first, what level of nerve injury is required to induce the changes that result in neuropathic pain? Secondly, can damage to tissues other than nerves cause neuropathic pain? Lastly, what is the relative contribution of central and peripheral changes in the nervous system?

Risk factors and prevention

Ideally, if you want to prevent an event, you would wish to understand the causes and reasons for its occurrence. It is not necessary to have a complete understanding of causation however. John Snow was not only a pioneer in the field of Anaesthetics, but also in Epidemiology. In 1854. there was a cholera outbreak in London. Snow traced the source of the outbreak to a water pump in Broad Street and when the handle was removed the epidemic declined. He knew nothing of the cholera bacterium, but suspected that the disease was water-borne. We may not understand the causes of CPSP in detail, but we can still try to develop strategies to reduce its incidence. Why some people develop chronic pain after surgery whereas others, who have had an identical operation and anaesthetic do not, is mysterious. The causation is complex and is obviously related to injury and change of function but psychosocial factors are also important. The incidence and severity of chronic pain after an operation is not directly related to the size of the operation. As stated by Brandsborg and colleagues⁷ 'Several studies, however, have shown that surgery per se carries a significant risk for chronic or long-lasting pain. This is not only after major surgery such as amputation and thoracotomy, but also after minor procedures...'.

The risk factors can be broadly grouped into patient factors and medical factors. Each patient will bring their own genotype, medical history, past experiences, beliefs, and psychosocial circumstances to the problem. The environmental factors which then act on that patient will include type of surgery and anaesthesia, perioperative analgesia, and other treatments given.

Demographic factors

In both breast surgery and hernia repair, increasing age seems to reduce the risk of chronic pain. In breast surgery, younger patients tend to have larger tumours, with more postoperative and long-term pain. 109 Smith and colleagues¹⁰¹ showed an incidence of chronic pain after mastectomy of 26% in those aged >70 yr, 40% in those between 50 and 69 yr of age, and 65% in those between 30 and 49 yr of age. Younger patients tend to have more severe pathology, poorer prognosis, and more recurrence⁵¹ ¹²¹ and also a poor response to radiotherapy and chemotherapy. 112 These may be contributory factors. Using adjusted models of risk, Poleshuck and colleagues⁸¹ found the probability for developing chronic pain after breast cancer surgery decreased by 5% with each year of increasing age. Poobalan and colleagues⁸³ reported similar findings for pain after hernia surgery. Whether other demographic factors, such as employment, housing, and marital status, are important is controversial. 83 101 Age and employment may affect the levels of activity which could confound the issue.

Psychosocial factors

There are many publications on the influence of psychosocial factors on acute postoperative pain. Munafo and Stevenson⁶⁶ found a consistent relationship between preoperative anxiety and acute postoperative pain across 12 studies. Taenzer and colleagues¹⁰⁵ showed that after elective gall bladder surgery about half the variability in outcome measures could be predicted by measures such as anxiety, extroversion, depression, educational level, previous chronic pain history, and attitudes to medication. Katz and colleagues⁴⁶ have shown that preoperative anxiety is a risk factor for pain up to 30 days after breast surgery. Several studies have shown that acute postoperative pain is influenced by catastrophizing (exaggerated negative beliefs and responses).³² 75

There have been fewer studies on the influence of psychosocial factors on chronic pain after surgery and the results are contradictory. Katz and colleagues⁴⁵ found that measures of depression and anxiety were comparable in those who did and did not have pain after thoracotomy. The number of patients in this study was small and the preoperative measures of anxiety and depression were administered the day before surgery, which might have influenced the results. In the study by Taenzer and colleagues, ¹⁰⁵ the authors point out that 'a health professional wishing to identify a patient at risk for experiencing high levels of postoperative pain is best advised to consider the patient's typical emotional reactions rather than his preoperative emotional status'. In a study of women who had surgery for breast cancer, Tasmuth and colleagues 107 found increased levels of anxiety and depression before surgery, compared with healthy women. At 1 yr after surgery, anxiety levels had returned to normal in all patients, but in those with chronic pain, depression remained at a higher level. Jess and colleagues³⁹ studied patients having laparoscopic cholecystectomy and found higher levels of neuroticism at 1 vr in those who had chronic pain, compared with those who did not. The preoperative neuroticism scores were not significantly different. The authors question whether the higher scores at 1 yr could be the result of the chronic pain rather than an aetiological factor.

Peters and colleagues⁷⁸ studied the somatic and psychological predictors of long-term unfavourable outcomes after surgery. The most important somatic predictors of unfavourable outcome were duration of the operation (longer than 3 h) and severe postoperative pain. Fear of surgery was associated with more pain, poor global recovery, and quality of life at 6 months. Optimism was associated with better recovery and higher quality of life, but did not affect chronic pain nor physical functioning. Catastrophizing was neither a risk factor for chronic pain nor functional limitation in this study.

It is interesting that severe acute postoperative pain is consistently found to be a risk factor for chronic pain across many studies, but the psychological factors that seem to be risk factors for acute pain do not show the same association in CPSP. In the field of chronic pain in general, quality of life is more affected by cognitive factors, particularly pain catastrophizing, than by pain intensity.⁵³ It seems likely therefore that psychosocial factors will be important in CPSP. We need further studies on the influence of psychosocial factors in CPSP, but this is a difficult area of study. The instruments used to measure the variables may need to be modified to suit the specific circumstances. For example, the implications of a total hip replacement for osteoarthritis are totally different from having a thoracotomy for lung cancer. Normative data for various types of surgery would be useful. The influence of psychosocial factors on outcome after surgery is important because it is possible that interventions may be able to help.⁴⁰

Genetic factors

A paper on pain after cardiac surgery showed that patients often develop pains at two separate sites: in the leg, where the vein is harvested for grafting, and the chest. Devor 19 wrote an interesting comment on this paper, pointing out that the incidence of pain in both sites concurrently was much higher than would be expected if the chances of developing pain at each site were independent. He suggested that this was evidence that certain people are predisposed to develop pain after nerve injury. This supposition is supported by animal work showing that genetic factors influence whether mice develop neuropathic pain after nerve injury. 20 95 Further evidence for a genetic predisposition to chronic pain syndromes comes from Diatchenko and colleagues²¹ who showed an association between a genetic polymorphism and temporo-mandibular ioint disorder.

Many clinicians working in this field suspect that there are certain conditions which may be markers for developing chronic pain after an injury. These conditions include fibromyalgia syndrome, migraine, irritable bowel syndrome (IBS), irritable bladder, and Raynaud's syndrome, especially in those patients who also have burning hot feet at night. Two studies on chronic pain after hernia repair found many patients with a history of backache, IBS, or headache. In a study of women with pain after hysterectomy those with pain problems elsewhere than in the pelvis before the operation had an increased risk of CPSP. The most common sites were head, neck, shoulders, and low back, which is similar to the areas usually associated with pain in fibromyalgia.

Preoperative pain

Several studies on hernia repair have suggested that preoperative pain is a risk factor for CPSP. 56 83 120 In a well-designed study specifically on this topic, Page and colleagues 74 found that about a quarter of patients did not have pain at rest before their hernia repair, half had mild pain with the remainder having mild to moderate pain at rest. As expected more patients suffered pain on movement. A year after the operation, 25% had no pain at rest and only 22% no pain on moving. Some patients who were pain free before the repair suffered pain afterwards and 5% said that their day-to-day life was worse 1 yr after the surgery.

In a study of pain after amputation, Nikolajsen and colleagues⁷¹ found that preamputation pain was associated with an increased risk of stump and phantom pain, in the immediate postoperative period and at 3 months. Keller and colleagues⁵⁰ showed that 48% of those taking narcotic analgesics before thoracotomy had chronic post-thoracotomy pain, compared with only 5% of those not taking narcotics.

Kroner and colleagues⁵² reported a correlation between breast pain before operation and phantom breast pain. Intensity of pain before total hip arthroplasty does not seem to correlate with chronic pain afterwards.⁶⁸

Acute postoperative pain

Many studies have shown a correlation between severity of acute postoperative pain and CPSP. Kalso and colleagues⁴³ were probably the first to show a link between acute postoperative pain and long-term pain after thoracotomy. Richardson and colleagues⁹⁰ showed that severe postoperative pain was associated with chronic post thoracotomy pain and that regional anaesthetic techniques reduced the incidence. Katz and colleagues⁴⁵ in a paper specifically studying risk factors showed that early postoperative pain was the only factor that significantly predicted long-term pain. More recent studies have confirmed the importance of the nociceptive input at the time of thoracotomy and the postoperative period.⁸⁰

Postoperative pain is also a risk factor for pain after hernia surgery, surgery for breast cancer, total hip arthroplasty, and Caesarean section.

Surgical factors

Although the size of the operation does not show a simple correlation with CPSP, the type of operation and how it is performed influences the incidence of CPSP. Peters and colleagues⁷⁸ found more chronic pain and poorer outcomes in general, in operations lasting more than 3 h. This is not surprising as these patients will probably have had more serious pathology, complications, or other health issues affecting both the complexity of the operation and the outcome. Wallace and colleagues¹¹⁶ studied the incidence of pain after different types of breast surgery. The incidence varied from 53% for mastectomy with reconstruction by implant, to 31% for mastectomy only, to 22% for breast reduction. For hernia surgery, there appears to be no correlation between CPSP and different types of open repair, but less pain after laparoscopic repair.¹⁰ The

reduction in chronic pain after laparoscopic repair is confirmed by two systematic reviews.¹ ⁸⁴ Open cholecystectomy has a higher incidence of CPSP than laparoscopic cholecystectomy.¹⁰³

The experience of the surgeon can affect morbidity and mortality. Tasmuth and colleagues to studied chronic pain after breast surgery for cancer and found that patients who had their surgery in low volume, less experienced units suffered more CPSP than patients from high volume, specialist units. On the other hand, Courtney and colleagues showed no correlation between the grade of the surgeon and severe pain after hernia repair. Whether inpatient surgery is preferable to day-case surgery is controversial. Showed no correlation between the grade of the surgeon and severe pain after hernia repair.

Whether the condition for which the operation was performed influences the incidence of chronic pain is controversial. For lower limb amputation, the cause of the amputation does not affect the incidence of chronic pain afterwards. ^{35 38} In the case of thoracotomy, Richardson and colleagues ⁹⁰ found a higher incidence of chronic pain after surgery for benign oesophageal disease than for lung cancer, but other studies have shown no difference. ^{43 77} In hernia surgery, the type of hernia does not seem to influence the prevalence of chronic pain, ¹⁶ but whether surgery for recurrent hernias carries a higher risk is controversial. ^{10 16 83}

Several studies have suggested that concomitant treatments, such as radiotherapy and chemotherapy, can increase the risk of chronic pain. 100 106 109 Although other studies have not supported this, 52 90 a rigorous recent study by Poleshuck and colleagues 1 found that radiotherapy, independent of other variables, increased the risk of chronic pain after surgery for breast cancer.

Anaesthesia and analgesia

Most people working in this field believe that pain around the time of the operation sensitizes the nervous system¹¹⁹ and this hypersensitized state contributes to the development of chronic pain. It seems sensible then to try to reduce the nociceptive input to the spinal cord during and after the operation. Anaesthetic techniques that achieve this should show a reduction in both postoperative pain and chronic pain. Animal work has shown encouraging results, but Aida³ has pointed out that this is not easily translated into the clinical situation. In animal research, the subjects are healthy and have no pre-existing pain. The stimulus is usually to an extremity, with segmental somatic innervation only, for a short and circumscribed period. In our patients, the operation may be prolonged, over a large region of the body with complex innervation, and the pain may persist for days afterwards. If the pain breaks through the analgesic regimen at any time, even for a brief period, that may be enough to sensitize the nervous system, causing long-term problems and persistent pain. It is not surprising then that the evidence for the effect of different anaesthetic and analgesic regimens on chronic pain after surgery is confused. There are several papers that show benefit from regional anaesthesia, for example, after hysterectomy, ⁷ Caesarean section, ⁷² iliac crest bone harvesting, ⁸⁹ and thoracotomy. ⁷³ ⁹⁰ ⁹⁶ ¹¹⁰ However, there are also studies that have not shown benefit.^{42 44 63} Several studies have looked at multimodal analgesic techniques and the use of drugs such as gabapentin, 24 25 venlafaxine, 88 and ketamine, 47 118 but once again the results are not consistent. At one time, it was thought that delivering pre-emptive analgesia would reduce postoperative problems such as phantom pain, but subsequent studies have not confirmed this. 47 69 70 Despite the conflicting evidence at present, it remains a reasonable hope that a multimodal approach, reliably delivered and tailored to the needs of individual patients for particular operations, will eventually reduce the incidence of CPSP.

Prevention

Because post-surgical pain syndromes are usually hard to treat, prevention is important. At present, there is limited evidence for effective strategies and clearly there is a need for further research. Two strategies are obvious however.

Effective management of postoperative pain

The evidence that severe postoperative pain is associated with a high incidence of CPSP is overwhelming. There is no proof of a causative link, however, and it is possible that some patients are more susceptible to both acute postoperative pain and CPSP. However, good perioperative analgesia should be part of a comprehensive programme of perioperative care⁴⁸ for many reasons, ethical, humanitarian, and medical. As discussed above, the choice of anaesthetic and analgesic regimen that will best provide a safe and pain-free recovery from surgery is still evolving. Unfortunately, in many cases we are still failing to deliver the current best practice to many patients, 31 64 often because of failure to implement changes into routine care. 67 86 87 The reasons for this are complex, and clinicians, research workers, administrators, and policy makers will have to address a variety of issues, including lack of resources, technical problems, conflicting interests, and organizational and cultural barriers.85

Surgery as a risk factor

For CPSP, one risk factor is obvious, surgery. At present, the only certain way to reduce the number of cases of CPSP is to reduce the number of operations. Is this feasible? If we look at phantom pain, the best way to reduce the incidence would be to prevent amputations. Lower limb amputations are normally a result of vascular disease, often related to diabetes and smoking. Measures to reduce smoking and obesity are the best way therefore to prevent phantom limb pain. Obesity is a risk factor for many

problems that can result in surgery such as osteoarthritis, certain types of cancer, gall bladder disease, and heart disease. Screening programmes to diagnose diseases early, for example, breast cancer, may result in less invasive surgery, with less postoperative morbidity. It is clear then that public health measures have an important role to play.

Are all operations necessary or appropriate? Chronic pain is common after hernia surgery. Page and colleagues tecorded pain before and after inguinal hernia repair. They showed that patients with pain before the operation benefit from surgery, but some patients with no pain before hernia repair had significant pain afterwards. Watchful waiting has been shown to be safe and cost-effective in patients with asymptomatic inguinal hernias. It is a matter of debate whether surgery is appropriate in asymptomatic hernias and possibly some other operations as well.

Many patients with abdominal pain have visceral hyperalgesic syndromes. On investigation, no cause is seen on scans and endoscopies. Patients and their relatives often put surgeons under great pressure to do something, and eventually a laparoscopy or laparotomy may be performed. 15 In some cases, this will be the start of a treadmill of operations, when the patient's pain becomes worse, and then further surgery is demanded to rectify the problem, which of course only makes matters worse. 117 The author has one patient with fibromyalgia, who reported that she had undergone 54 operations, mostly performed abroad. These included multiple laparotomies for abdominal pain and bilateral mastectomies for breast pain (no malignancy), followed by several operations because of continuing pain in the breast area. When asked why she persisted, she said she always believed the next operation would cure her!

Awareness of the risk of chronic pain is particularly relevant when patients wish to have surgery for reasons other than illness or disability, for example, male and female sterilization and some cosmetic surgery operations, which may be performed for aesthetic rather than medical reasons. Chronic pain after vasectomy has been the subject of several studies. 55 62 65 These show an incidence of around 15%. A review article in 2003¹⁴ examined the possible mechanisms in relation to changes that occur after vasectomy. It is disappointing then to find in a recent publication on sterilization the statement: 'Whether a postvasectomy pain syndrome exists remains controversial'. 79 The incidence of pain after breast augmentation operations has been reported to be 13% in a Norwegian study⁹² and varying from 21% to 50% depending on the type of operation according to Wallace and colleagues116 from California. This study also found an incidence of 22% after breast reduction surgery. 116 Cosmetic surgery is widely advertised and easily available, but most of the websites of organizations offering breast augmentation and reduction operations do not mention chronic pain as a complication.

Conclusions

Chronic pain after surgery is common. The standard of research has improved markedly in recent years, but much work remains to be done, particularly in the fields of mechanisms and risk factors. Improving the management of acute postoperative pain is one strategy which may prevent CPSP, but there are many technical, organizational, and cultural barriers to be overcome in order to achieve that improvement.

There is clearly a need for education of the medical profession and the general public about the problem. If patients and their doctors were aware of the risks, it might deter some patients from undergoing inappropriate and unnecessary operations.

References

- I Aasvang E, Kehlet H. Chronic postoperative pain: the case of inguinal herniorrhaphy. *Br | Anaesth* 2005; **95**: 69–76
- 2 Abdullah TI, Iddon J, Barr L, Baildam AD, Bundred NJ. Prospective randomized controlled trial of preservation of the intercostobrachial nerve during axillary node clearance for breast cancer. Br | Surg 1998; 85: 1443-5
- 3 Aida S. The challenge of preemptive analgesia. Pain Clinical Updates 2005; XIII: 1-4
- 4 Bach S, Noreng MF, Tjellden 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 Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002; 346: 1138–44
- 6 Blyth FM, March LM, Cousins MJ. Chronic pain-related disability and use of analgesia and health services in a Sydney community. Med J Aust 2003; 179: 84–7
- 7 Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS. Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. Anesthesiology 2007; 106: 1003–12
- 8 Bray GA. Risks of obesity. Endocrinol Metab Clin North Am 2003; 32: 787–804, viii
- 9 Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WC, Chambers WA. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. *Pain* 2003; 104: 265-73
- 10 Callesen T, Kehlet H. Postherniorraphy pain. Anesthesiology 1997; 87: 1219–30
- 11 Carpenter JS, Sloan P, Andrykowski MA, et al. Risk factors for pain after mastectomy/lumpectomy. Cancer Pract 1999; 7: 66-70
- 12 Castillo RC, MacKenzie EJ, Wegener ST, Bosse MJ. Prevalence of chronic pain seven years following limb threatening lower extremity trauma. *Pain* 2006; 124: 321–9
- 13 Chaturvedi N, Abbott CA, Whalley A, Widdows P, Leggetter SY, Boulton AJM. Risk of diabetes related amputation in South Asians vs Europeans in the UK. Diabet Med 2002; 19: 99–104
- 14 Christiansen CG, Sandlow JI. Testicular pain following vasectomy: a review of postvasectomy pain syndrome. J Androl 2003; 24: 293–8
- 15 Cole JA, Yeaw JM, Cutone JA, et al. The incidence of abdominal and pelvic surgery among patients with irritable bowel syndrome. Dig Dis Sci 2005; 50: 2268-75

- 16 Courtney CA, Duffy K, Serpell MG, O'Dwyer PJ. Outcome of patients with severe chronic pain following repair of groin hernia. Br J Surg 2002; 89: 1310-4
- 17 Crombie IK, Davies HTO, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 1998; 76: 167–71
- 18 DeGood DE, Kiernan B. Perception of fault in patients with chronic pain. *Pain* 1996; **64**: 153-9
- 19 Devor M. Evidence for heritability of pain in patients with traumatic neuropathy. *Pain* 2004; 108: 200–1; author reply 202
- 20 Devor M, Raber P. Heritability of symptoms in an experimental model of neuropathic pain. *Pain* 1990; 42: 51-67
- 21 Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005; 14: 135–43
- 22 Dijkstra PU, Geertzen JH, Stewart R, van der Schans CP. Phantom pain and risk factors: a multivariate analysis. J Pain Symptom Manage 2002; 24: 578-85
- 23 Dijkstra PU, Rietman JS, Geertzen JH. Phantom breast sensations and phantom breast pain: a 2-year prospective study and a methodological analysis of literature. Eur J Pain 2007; 11: 99–108
- 24 Fassoulaki A, Melemeni A, Stamatakis E, Petropoulos G, Sarantopoulos C. A combination of gabapentin and local anaesthetics attenuates acute and late pain after abdominal hysterectomy. Eur J Anaesthesiol 2007: 24: 521–8
- 25 Fassoulaki A, Triga A, Melemeni A, Sarantopoulos C. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. Anesth Analg 2005; 101: 1427–32
- 26 Fitzgibbons RJ Jr, Giobbie-Hurder A, Gibbs JO, et al. Watchful waiting vs repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. JAMA 2006; 295: 285–92
- 27 Flum DR, Salem L, Elrod JA, Dellinger EP, Cheadle A, Chan L. Early mortality among medicare beneficiaries undergoing bariatric surgical procedures. JAMA 2005; 294: 1903–8
- 28 Franneby U, Sandblom G, Nordin P, Nyren O, Gunnarsson U. Risk factors for long-term pain after hernia surgery. *Ann Surg* 2006; 244: 212–9
- 29 Galvez R, Marsal C, Vidal J, Ruiz M, Rejas J. Cross-sectional evaluation of patients functioning and health-related quality of life in patients with neuropathic pain under standard care conditions. Eur | Pain 2007; 11: 244-55
- 30 Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS. Psychophysical examination in patients with post-mastectomy pain. Pain 2000; 87: 275–84
- 31 Gramke HF, de Rijke JM, van Kleef M, et al. The prevalence of postoperative pain in a cross-sectional group of patients after day-case surgery in a university hospital. Clin J Pain 2007; 23: 543-8
- 32 Granot M, Ferber SG. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. Clin J Pain 2005; 21: 439–45
- 33 Health Episode Statistics. 2007; Available from www.hesonline. nhs.uk
- 34 Hill A. Phantom limb pain: a review of the literature on attributes and potential mechanisms. J Pain Symptom Manage 1999; 17: 125–42
- 35 Houghton AD, Saadah E, Nicholls G, McColl L, Houghton AL. Phantom pain: natural history and association with rehabilitation. Ann R Coll Surg Engl 1994; 76: 22-5
- 36 Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. Br J Cancer 1992; 66: 136–8

- 37 Jenkins JT, O'Dwyer PJ. Inguinal hernias. Br Med J 2008; 336: 269–72
- 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 limb pain. *Pain* 1985; 21: 267–8
- 39 Jess P, Jess T, Beck H, Bech P. Neuroticism in relation to recovery and persisting pain after laparoscopic cholecystectomy. Scand | Gastroenterol 1998; 33: 550-3
- **40** Johnston M, Vogele C. The benefits of psychological preparation for surgery: a meta-analysis. *Ann Behav Med* 1993; **15**: 245–56
- 41 Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain* 2003: 104: 1-13
- 42 Kalliomaki ML, Meyerson J, Gunnarsson U, Gordh T, Sandblom G. Long-term pain after inguinal hernia repair in a population-based cohort; risk factors and interference with daily activities. Eur J Pain 2008; 12: 214–25
- 43 Kalso E, Perttunen K, Kaasinen S. Pain after thoracic surgery. Acta Anaesthesiol Scand 1992; 36: 96–100
- 44 Katz J, Cohen L. Preventive analgesia is associated with reduced pain disability 3 weeks but not 6 months after major gynecologic surgery by laparotomy. Anesthesiology 2004; 101: 169–74
- 45 Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin 1 Pain 1996: 12: 50-5
- 46 Katz J, Poleshuck EL, Andrus CH, et al. Risk factors for acute pain and its persistence following breast cancer surgery. Pain 2005; 119: 16–25
- 47 Katz J, Schmid R, Snijdelaar DG, Coderre TJ, McCartney CJ, Wowk A. Pre-emptive analgesia using intravenous fentanyl plus low-dose ketamine for radical prostatectomy under general anesthesia does not produce short-term or long-term reductions in pain or analgesic use. Pain 2004; 110: 707–18
- **48** Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br | Anaesth* 1997; **78**: 606–17
- 49 Kehlet H, Jensen TS, Woolf C. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367: 1618–25
- 50 Keller SM, Carp NZ, Levy MN, Rosen SM. Chronic post thoracotomy pain. J Cardiovasc Surg 1994; 35: 161–4
- 51 Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. Br Med J 2000; 320: 474–8
- 52 Kroner K, Knudsen UB, Lundby L, Hvid H. Long term phantom breast syndrome after mastectomy. Clin J Pain 1992; 8: 346–50
- **53** Lame IE, Peters ML, Vlaeyen JW, Kleef M, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. *Eur J Pain* 2005; **9**: 15–24
- 54 Lame IE, Peters ML, Vlaeyen JWS, van Kleef M, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. Eur J Pain 2005; 9: 15–24
- 55 Leslie TA, Illing RO, Cranston DW, Guillebaud J. The incidence of chronic scrotal pain after vasectomy: a prospective audit. BJU Int 2007; 100: 1330–3
- 56 Liem MS, van Duyn EB, van der Graaf Y, van Vroonhoven TJ. Recurrences after conventional anterior and laparoscopic inguinal hernia repair: a randomized comparison. *Ann Surg* 2003; 237: 136–41
- 57 Macrae WA. Can we prevent chronic pain after surgery? In: Shorten G, Carr DB, Harmon D, Puig MM, Browne J, eds. Postoperative Pain Management. Philadelphia: Saunders Elsevier, 2006; 259–64

- 58 Macrae WA. Chronic pain after surgery. Br J Anaesth 2001; 87: 88-98
- 59 Macrae WA, Davies HTO. Chronic postsurgical pain. In: Crombie IK, Linton S, Croft P, Von Korff M, LeResche L, eds. Epidemiology of Pain. Seattle: International Association for the Study of Pain, 1999; 125–42
- 60 Maguire MF, Latter JA, Mahajan R, Beggs FD, Duffy JP. A study exploring the role of intercostal nerve damage in chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006; 29: 873–9
- 61 Maguire MF, Ravenscroft A, Beggs D, Duffy JP. A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006; 29: 800-5
- **62** Manikandan R, Srirangam SJ, Pearson E, Collins GN. Early and late morbidity after vasectomy: a comparison of chronic scrotal pain at 1 and 10 years. *BJU Int* 2004; **93**: 571–4
- 63 McCartney CJL, Brull R, Chan VWS, et al. Early but not long-term benefit of regional compared with general anesthesia for ambulatory hand surgery. Anesthesiology 2004; 101: 461-7
- 64 McLeod G, Davies H, Munnoch N, Bannister J, MacRae W. Postoperative pain relief using thoracic epidural analgesia: outstanding success and disappointing failures. *Anaesthesia* 2001; 56: 75–81
- 65 McMahon AJ, Buckley J, Taylor A, Lloyd SN, Deane RF, Kirk D. Chronic testicular pain following vasectomy. Br J Urol 1992; 69: 188–91
- 66 Munafo MR, Stevenson J. Anxiety and surgical recovery. Reinterpreting the literature. J Psychosom Res 2001; 51: 589–96
- 67 Nagi H. Acute pain services in the United Kingdom. Acute Pain 2004; 5: 89–107
- 68 Nikolajsen L, Brandsborg B, Lucht U, Jensen TS, Kehlet H. Chronic pain following total hip arthroplasty: a nationwide questionnaire study. Acta Anaesthesiol Scand 2006; 50: 495–500
- 69 Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower limb amputation. Lancet 1997; 350: 1353-7
- 70 Nikolajsen L, Ilkjaer S, Jensen TS. Effect of preoperative extradural bupivacaine and morphine on stump sensation in lower limb amputees. Br J Anaesth 1998; 81: 348–54
- 71 Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. *Pain* 1997; 72: 393–405
- 72 Nikolajsen L, Sorensen HC, Jensen TS, Kehlet H. Chronic pain after Caesarean section. Acta Anaesthesiol Scand 2004; 48: 111–6
- 73 Obata H, Saito S, Fujita N, Fuse Y, Ishizaki K, Goto F. Epidural block with mepivacaine before surgery reduces long-term postthoracotomy pain. Can | Anaesth 1999; 46: 1127–32
- 74 Page B, Paterson C, Young D, O'Dwyer PJ. Pain from primary inguinal hernia and the effect of repair on pain. Br J Surg 2002; 89: 1315–8
- 75 Pavlin DJ, Sullivan MJ, Freund PR, Roesen K. Catastrophizing: a risk factor for postsurgical pain. Clin J Pain 2005; 21: 83–90
- 76 Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. Anesthesiology 2000; 93: 1123–33
- 77 Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. Acta Anaesthesiol Scand 1999; 43: 563-7
- 78 Peters ML, Sommer M, de Rijke JM, et al. Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Ann Surg 2007; 245: 487–94
- 79 Peterson HB. Sterilization. Obstet Gynecol 2008; 111: 189-203

- 80 Pluijms WA, Steegers MA, Verhagen AF, Scheffer GJ, Wilder-Smith OH. Chronic post-thoracotomy pain: a retrospective study. Acta Anaesthesiol Scand 2006; 50: 804–8
- 81 Poleshuck EL, Katz J, Andrus CH, et al. Risk factors for chronic pain following breast cancer surgery: a prospective study. J Pain 2006; 7: 626–34
- 82 Polinsky ML. Functional status of long-term breast cancer survivors: demonstrating chronicity. Health Soc Work 1994; 19: 165–73
- 83 Poobalan AS, Bruce J, King PM, Chambers WA, Krukowski ZH, Smith WC. Chronic pain and quality of life following open inguinal hernia repair. Br J Surg 2001; 88: 1122-6
- 84 Poobalan AS, Bruce J, Smith WC, King PM, Krukowski ZH, Chambers WA. A review of chronic pain after inguinal herniorrhaphy. Clin J Pain 2003; 19: 48–54
- 85 Powell AE, Davies HTO, Bannister J, Macrae WA. Chapter 169, Acute pain services and organizational change. In: Nicholas MK, ed. Clinical Pain Management: Practice and Procedures in Pain Management, 2nd Edn. London: Hodder Arnold, 2008
- 86 Powell AE, Davies HTO, Bannister J, Macrae WA. Rhetoric and reality on acute pain services in the NHS: a national postal questionnaire survey. Br I Anaesth 2004: 92: 689–93
- 87 Rawal N. 10 years of acute pain services—achievements and challenges. Reg Anesth Pain Med 1999; 24: 68-73
- 88 Reuben SS, Makari-Judson G, Lurie SD. Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of postmastectomy pain syndrome. *J Pain Symptom Manage* 2004; 27: 133–9
- 89 Reuben SS, Vieira P, Faruqi S, Verghis A, Kilaru PA, Maciolek H. Local administration of morphine for analgesia after iliac bone graft harvest. *Anesthesiology* 2001; 95: 390–4
- 90 Richardson J, Sabanathan S, Mearns AJ, Sides C, Goulden CP. Post-thoracotomy neuralgia. Pain Clin 1994; 7: 87–97
- 91 Rogers ML, Henderson L, Mahajan RP, Duffy JP. Preliminary findings in the neurophysiological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg 2002; 21: 298–301
- 92 Romundstad L, Breivik H, Roald H, Skolleborg K, Romundstad PR, Stubhaug A. Chronic pain and sensory changes after augmentation mammoplasty: long term effects of preincisional administration of methylprednisolone. *Pain* 2006; 124: 92–9
- 93 Rutkow IM. Surgical operations in the United States. Then (1983) and now (1994). Arch Surg 1997; 132: 983–90
- 94 Salmon RJ, Ansquer Y, Asselain B. Preservation versus section of intercostal-brachial nerve (IBN) in axillary dissection for breast cancer—a prospective randomized trial. Eur J Surg Oncol 1998; 24: 158-61
- 95 Seltzer Z, Wu T, Max MB, Diehl SR. Mapping a gene for neuropathic pain-related behaviour following peripheral neurectomy in the mouse. *Pain* 2001; 93: 101–6
- 96 Senturk M, Ozcan PE, Talu GK, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 2002; 94: 11-5; table of contents
- 97 Smith BH, Hopton L, Chambers WA. Chronic pain in primary care. Fam Pract 1999; 16: 475-82
- 98 Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. Clin J Pain 2007; 23: 143–9
- 99 Smith DG, Ehde DM, Legro MW, Reiber GE, del Aguila M, Boone DA. Phantom pain, residual limb, and back pain after lower extremity amputations. Clin Orthoped Relat Res 1999; 361: 29–38

- 100 Smith J, Thompson JM. Phantom limb pain and chemotherapy in pediatric amputees. Mayo Clin Proc 1995; 70: 357–64
- 101 Smith WCS, Bourne D, Squair J, Phillips DO, Chambers WA. A retrospective cohort study of post mastectomy pain syndrome. Pain 1999: 83: 91-5
- 102 Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics, and impact of postmastectomy pain syndrome: an investigation of women's experiences. *Pain* 1995; 61: 61–8
- 103 Stiff G, Rhodes M, Kelly A, Telford K, Armstrong CP, Rees BI. Long-term pain: less common after laparoscopic than open cholecystectomy. Br J Surg 1994; 81: 1368–70
- 104 Stroupe KT, Manheim LM, Luo P, et al. Tension-free repair versus watchful waiting for men with asymptomatic or minimally symptomatic inguinal hernias: a cost-effectiveness analysis. J Am Coll Surg 2006; 203: 458–68
- 105 Taenzer P, Melzack R, Jeans ME. Influence of psychological factors on postoperative pain, mood and analgesic requirements. Pain 1986; 24: 331–42
- 106 Tasmuth T, Blomqvist C, Kalso E. Chronic post-treatment symptoms in patients with breast cancer operated in different surgical units. Eur J Surg Oncol 1999; 25: 38–43
- 107 Tasmuth T, Estlanderb AM, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. Pain 1996; 68: 343-7
- 108 Tasmuth T, Kataja M, Blomqvist C, von Smitten K, Kalso E. Treatment-related factors predisposing to chronic pain in patients with breast cancer—a multivariate approach. Acta Oncol 1997: 36: 625–30
- 109 Tasmuth T, von Smitten K, Hietanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. Ann Oncol 1995; 6: 453–9
- 110 Tiippana E, Nilsson E, Kalso E. Post-thoracotomy pain after thoracic epidural analgesia: a prospective follow-up study. Acta Anaesthesiol Scand 2003; 47: 433–8

- 111 Turk DC, Okifuji A. Perception of traumatic onset, compensation status, and physical findings: impact on pain severity, emotional distress, and disability in chronic pain patients. | Behav Med 1996; 19: 435–53
- 112 Tutt A, Ross G. Commentary: much still to learn about relations between tumour biology, prognosis, and treatment outcome in early breast cancer. Br Med J 2000; 320: 478–9
- 113 US Dept of Health and Human Resources. Health United States. 1996–7. Available from www.cdc.gov/nchs/hus.htm
- 114 Vecht CJ, Van der Brand HJ, Wajer OJM. Post-axillary dissection pain in breast cancer due to a lesion of the intercostobrachial nerve. Pain 1989: 38: 171-6
- 115 Villanueva L, Dickenson AH, Ollat H. The Pain System in Normal and Pathological States. Seattle: IASP Press, 2004
- 116 Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. Pain 1996; 66: 195-205
- 117 Wilder-Smith OH, Tassonyi E, Senly C, Otten P, Arendt-Nielsen L. Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception. Br J Anaesth 1996; 76: 816-21
- 118 Wilson JA, Nimmo AF, Fleetwood-Walker SM, Colvin LA. A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. Pain 2008; 135: 108–18
- 119 Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000: 288: 1765-9
- 120 Wright D, Paterson C, Scott N, Hair A, O'Dwyer PJ. Five-year follow-up of patients undergoing laparoscopic or open groin hernia repair: a randomized controlled trial. *Ann Surg* 2002; 235: 333-7
- 121 Yildirim E, Dalgic T, Berberoglu U. Prognostic significance of young age in breast cancer. J Surg Oncol 2000; 74: 267-72