Chronic post-surgical pain: 10 years on

W. A. Macrae

Ninewells Hospital and Medical School, Dundee DD1 9SY and The Bute Medical School, University of St Andrews, St Andrews, KY16 9TS, Scotland

E-mail: w.a.macrae@dundee.ac.uk

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 colleagues 10 yr ago. Since then there have been several reviews. 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’. 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. What issues have emerged and what has recent research 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. 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. In the USA, the total number of operations performed in 1994 was approximately 22 629 000. 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.

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
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, and has a significant effect on quality of life. 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 subject 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. 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.

The type of pain also varies: phantom pain, neuropathic pain caused by damage to the intercostobrachial nerve, or scar pain. 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.

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. 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 colleagues 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. 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. 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 colleagues 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. 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. 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. This suggests a more complicated aetiology for neuropathic post-thoracotomy pain than injury to the intercostal nerve alone.

In the case of pain after mastectomy, Carpenter 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 syndrome 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 colleagues 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. In a study of 38 patients with ipsilateral arm pain after mastectomy, Vecht and colleagues 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. Polinsky 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 colleagues 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 colleagues, 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. Smith and colleagues 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 recurrence and also a poor response to radiotherapy and chemotherapy. These may be contributory factors. Using adjusted models of risk, Poleshuck and colleagues found the probability for developing chronic pain after breast cancer surgery decreased by 5% with each year of increasing age. Poobalan and colleagues reported similar findings for pain after hernia surgery. Whether other demographic factors, such as employment, housing, and marital status, are important is controversial.

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 chronic pain after surgery and the results are contradictory. Katz and colleagues 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, 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 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 colleagues studied patients having laparoscopic cholecystectomy and found higher levels of neuroticism at 1 yr 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 colleagues 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
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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9} Devor\textsuperscript{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.\textsuperscript{20, 95} Further evidence for a genetic predisposition to chronic pain syndromes comes from Diatchenko and colleagues\textsuperscript{21} who showed an association between a genetic polymorphism and temporo-mandibular joint 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.\textsuperscript{16, 120} 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.\textsuperscript{7} 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.\textsuperscript{56, 83, 120} In a well-designed study specifically on this topic, Page and colleagues\textsuperscript{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 colleagues\textsuperscript{71} 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 colleagues\textsuperscript{50} 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 colleagues\textsuperscript{52} 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.\textsuperscript{68}

**Acute postoperative pain**

Many studies have shown a correlation between severity of acute postoperative pain and CPSP. Kalso and colleagues\textsuperscript{43} were probably the first to show a link between acute postoperative pain and long-term pain after thoracotomy. Richardson and colleagues\textsuperscript{90} showed that severe postoperative pain was associated with chronic post thoracotomy pain and that regional anaesthetic techniques reduced the incidence. Katz and colleagues\textsuperscript{45} 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.\textsuperscript{80}

Postoperative pain is also a risk factor for pain after hernia surgery.\textsuperscript{7} Surgery for breast cancer,\textsuperscript{81} total hip arthroplasty,\textsuperscript{66} and Caesarean section.\textsuperscript{72}

**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 colleagues\textsuperscript{78} 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 colleagues\textsuperscript{116} 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.\textsuperscript{10} The
studies have not supported this, a rigorous recent 90
leagues showed no correlation between the grade of
specialist units. On the other hand, Courtney and col-
units suffered more CPSP than patients from high volume,
who had their surgery in low volume, less experienced
pain after breast surgery for cancer and found that patients
chronic pain, but whether surgery for recurrent hernias
type of hernia does not seem to influence the prevalence of
ancient and analgesic regimens on chronic pain after surgery for breast cancer.

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 recorded 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. 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. 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. These show an incidence of around 15%. A review article in 2003 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 syndrome exists remains controversial’. The incidence of pain after breast augmentation operations has been reported to be 13% in a Norwegian study and varying from 21% to 50% depending on the type of operation according to Wallace and colleagues from California. This study also found an incidence of 22% after breast reduction surgery. 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.

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