

# History of pain research and management in Canada

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Scattered accounts of the treatment of pain by aboriginal Canadians are found in the journals of the early explorers and missionaries. French and English settlers brought with them the remedies of their home countries. The growth of medicine through the 18th and 19th centuries, particularly in Europe, was mirrored in the practice and treatment methods of Canadians and Americans. In the 19th century, while Americans learned about causalgia and the pain of wounds, Canadian insurrections were much less devastating than the United States Civil War. By the end of that century, a Canadian professor working in the United States, Sir William Osler, was responsible for a standard textbook of medicine with a variety of treatments for painful illnesses. Yet pain did not figure in the index of that book.

The modern period in pain research and management can probably be dated to the 20 years before the founding of the International Association for the Study of Pain. Pride of place belongs to *The Management of Pain* by John Bonica, published in Philadelphia in 1953 and based upon his work in Tacoma and Seattle. Ideas about pain were evolving in Canada in the 1950s with Donald Hebb, Professor of Psychology at McGill University in Montreal, corresponding with the leading American neurophysiologist, George H Bishop. Hebb's pupil Ronald Melzack engaged in studies of early experiences in relation to pain and, joining with Patrick Wall at Massachusetts Institute of Technology, published the 1965 paper in *Science* that revolutionized thinking.

Partly because of this early start with prominent figures and partly because of its social system in the organization of medicine, Canada became a centre for a number of aspects of pain research and management, ranging from pain clinics in Halifax, Kingston and Saskatoon – which were among the earliest to advance treatment of pain – to studying the effects of implanted electrodes for neurosurgery. Work in Toronto by Moldofsky and Smythe was probably responsible for turning ideas about fibromyalgia from the quaint concept of 'psychogenic rheumatism' into the more fruitful avenue of empirical exploration of brain function, muscle tender points

and clinical definition of disease. Tasker and others in Toronto made important advances in the neurophysiology of nociception by the thalamus and cingulate regions. Their work continues while a variety of basic and clinical studies are advancing knowledge of fundamental mechanisms, including work by Henry and by Sawynok on purines; by Salter and by Coderre on spinal cord mechanisms and plasticity; by Katz on postoperative pain; by several workers on children's pain; and by Bushnell and others in Montreal on cerebral imaging.

Such contributions reflect work done in a country that would not want to claim that its efforts are unique, but would hope to be seen as maintaining some of the best standards in the developed world.

**Key Words:** *Canadian Pain Society, Fibromyalgia, History, Pain clinics, Pain management, Pain research, Physiology, Psychiatry*

## Histoire de la recherche sur la douleur et de son traitement au Canada

**RÉSUMÉ :** On peut trouver des récits dispersés du traitement de la douleur par des Autochtones canadiens dans les journaux des premiers explorateurs et des missionnaires. Les pionniers français et anglais ont amené avec eux les remèdes de leur patrie d'origine. L'essor de la médecine pendant les 18<sup>e</sup> et 19<sup>e</sup> siècles, surtout en Europe, s'est reflété dans les méthodes de traitement des Canadiens et des Américains. Au 19<sup>e</sup> siècle, alors que les Américains ont acquis des connaissances sur la causalgie et la douleur des plaies, les insurrections canadiennes ont été moins dévastatrices que pendant la guerre de Sécession. À la fin du 19<sup>e</sup> siècle, Sir William Osler, un professeur canadien qui exerçait aux États-Unis, fut à l'origine d'un manuel standard de médecine contenant une panoplie de traitements pour les maladies douloureuses. Pourtant, la douleur ne figurait pas à l'index de ce livre.

La période moderne de la recherche sur la douleur et de son traitement a vraisemblablement débuté une vingtaine d'années avant la fondation de « L'association internationale pour l'étude de la douleur ». La place d'honneur revient à l'ouvrage *The Management of Pain* de John Bonica, publié à Philadelphie en 1953 et basé sur son travail à Tacoma et à

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Seattle. Au Canada, les théories sur la douleur se sont développées dans les années 50 avec Donald Hebb, professeur de psychologie à McGill, à Montréal, faisant miroir aux recherches menées par le plus important neurophysiologiste américain, George H Bishop. L'élève de Hebb, Ronald Melzack se lança dans des études des premières expériences en rapport avec la douleur, et se joignant à Patrick Wall du *Massachusetts Institute of Technology*, publia l'article de 1965 dans *Science* qui allait révolutionner la façon de penser.

En partie à cause de ce début précoce avec des personnalités importantes et en partie à cause de son système social dans l'organisation de la médecine, le Canada est devenu un centre de référence pour un certain nombre de facettes de la recherche sur la douleur et de son traitement, qui va des cliniques de la douleur à Halifax, Kingston et Saskatoon – parmi les premières à améliorer le traitement de la douleur – à l'étude des effets de l'implantation d'électrodes en neurochirurgie. Les travaux menés à Toronto par Moldofsky et Smythe sont probablement à

l'origine du revirement de la théorie sur la fibromyalgie, d'un concept bizarre de « rhumatisme d'origine psychogène » à la piste plus fructueuse de l'exploration empirique de la fonction cérébrale, des points musculaires douloureux et de la définition clinique de la maladie. À Toronto, Tasker et d'autres ont réalisé des progrès énormes dans la neurophysiologie de la nociception par les régions du cingulum et du thalamus. Leurs travaux se poursuivent tandis qu'une variété d'études fondamentales et cliniques font avancer les connaissances des mécanismes fondamentaux, incluant les travaux de Henry et de Sawynok sur les purines, ceux de Salter et de Coderre sur les mécanismes et la plasticité de la moelle épinière; de Katz sur la douleur postopératoire; de plusieurs chercheurs sur la douleur chez l'enfant et ceux de Bushnell et autres à Montréal sur l'imagerie cérébrale.

Ces contributions reflètent le travail mené au Canada, qui ne saurait affirmer que ses efforts sont uniques, mais qui espère être reconnu pour la qualité de sa recherche dans tous les pays développés.

### NATIVE SKILLS

In writing about the history of any broad subject it is often hard to determine a precise date from which to commence. One has to start somewhere, and nowhere is perfect. The history of pain research and management in Canada begins with various accounts of medical topics from the time of early contacts between Europeans and Native Canadians. In this case I plan to start with some Native Canadian material and continue the history of pain research in Canada to the present day. There will be a little about early origins and much more about recent events.

The information on early origins is noteworthy for its small quantity, but it has at least some original items. A fairly extensive survey of the available literature on Native medicine at the time of first contact with Europeans (1) furnishes scattered comments on the following occurrences: chest pains with inflammation held to result from the inhalation of freezing cold air (2); frequent rheumatism (3-7); headaches caused by constipation (8); and gentle treatment of a wound to avoid pain (9).

A number of Native groups knew ways of successfully treating simple fractures and sprains (1). The Micmac reset the bone and wrapped the limb in pads of moss soaked in turpentine. A cradle of birchbark was then wrapped around the limb, splints were applied and the whole dressing was held in place by long, thin strips of bark (10). In the 19th century, seaman John Jewitt described a very similar method that the Nootka used in British Columbia (6), and fur trader Ross Cox noted that the Flathead Indians near the Columbia River placed pieces of wood and tight bandages longitudinally around the affected limb, securing them with leather thonging (11).

The treatment of compound fractures was also known. John Gyles, who spent six years among the Maliseet at the end of the 17th century in what is now New Brunswick, described how the wound was cleansed, broken edges of skin sealed together and splints then applied and secured with cord (12).

The sweat bath and the rituals associated with it are the most widespread, most widely known and most characteris-

tic features of the Native medical system. Not surprisingly it was applied to the treatment of musculoskeletal pains (1,13,14). This treatment normally involved the injured person sitting in a tent heated with hot stones, and then jumping into nearby water.

Cox (15) described a treatment that did not involve heating up in the sweat bath, but rather plunging the injured person into cold water. This was provided for rheumatic pains occurring in tribe warriors. Cox and the Native treating him plunged into the frigid water after first breaking the ice. The Native massaged Cox's affected limbs under the water, after which Cox wrapped himself in a blanket and retreated to his bedroom where a good fire blazed and was soon warm and glowing. He repeated this treatment daily for 25 days after which his rheumatism disappeared and did not recur.

Scarification or cutting of the affected part of the body was also used by the Nootka for musculoskeletal pains (6), but I have no information as to whether this was more widely used, and counter-irritation does not seem to have been popular, if it was employed at all. On the other hand, some groups treated headache by bleeding (16-20). In further contrast, the Labrador Inuit Shaman treating headache bumped the patient's head rhythmically on the floor (21), either curing by inducing the second pain or stilling the complaint of the dissatisfied individual. Medicine men or Shamens were widely engaged in the treatment of both bodily complaints and psychological ones, and it can be expected that they must have treated pains in a variety of fashions, but details on the treatment of pain are lacking.

These reports reflect most of what appears in the diverse accounts of the life of the First Nations at the time of the first European contact or shortly thereafter in different areas of Canada.

### COLONIAL PRACTICES

The practices of the European settlers are probably better known and were typical of their countries of origin. The main usual 18th and 19th century remedies for pain were rest and opiates, as well as (in the second half of the 19th century) any

specific remedies that might be available, such as surgery under anesthesia for painful conditions such as appendicitis, strangulated hernia, fractures, etc. It is worth noting, however, that the American Civil War – with its enormous number of casualties – produced the recognition by Mitchell et al (22) of an outstandingly painful consequence of trauma to nerves: burning pain (or causalgia), now known as complex regional pain syndrome type II (23). Canadians saw less of this type of phenomenon because our battles and insurrections in 1812, 1837 and 1881 were, overall, much less extensive and, therefore, much less bloody than the internal conflict to the south.

At the turn of the 19th century the medicine of Europe and North America and its treatment of pain can be well appreciated from the writings of Sir William Osler, who taught at McGill University from 1874 to 1884, was Clinical Professor of Medicine at the University of Pennsylvania from 1884 to 1889, became Professor of Medicine at Johns Hopkins for the next five years and was translated to Oxford in 1904 as the Regius Professor of Medicine, remaining there until his death in 1919. Osler maintained his Canadian citizenship throughout, although in his lifetime that was the same as British citizenship. His ashes, like those of his wife, a great grand-daughter of a revolutionary American (Paul Revere), lie at McGill.

Osler's book, *The Principles and Practice of Medicine*, first appeared in 1892. The ninth and last edition was published posthumously in 1920. In the second edition in 1896 (24), the text comprised 1110 pages. The index of 33 pages makes no reference to pain but lists neuralgias, headache and migraine, and gastralgias but not causalgia. The list of contents have pain-related topics, including angina pectoris, gout, chronic rheumatism, rheumatic affections and muscular rheumatism, as well as nervous dyspepsia and numerous types of inflammation and sciatica.

Curiously, in the description of lesions of the brachial plexus there is no mention of pain, but in the description of sciatica, under diseases of the spinal nerves, the pain is thoroughly reviewed, and treatment is dealt with in some detail as follows:

*Rest in bed with fixation of the limb by means of a long splint is a most valuable method of treatment in many cases, one upon which Weir Mitchell has specially insisted. I have known it to relieve and in some instances to cure, obstinate and protracted cases which had resisted all other treatment. Hydrotherapy is sometimes satisfactory, particularly the warm baths or the mud baths. Many cases are relieved by a prolonged residence at one of the thermal springs.*

Osler goes on to recommend local applications and says:

*The hot iron or the thermo-cautery or blisters relieve the pain temporarily. Deep injections into the nerves give great relief.... It is best to use cocaine at first in doses of from one-eighth to a quarter of a grain.*

*If the pain is unbearable morphine may be used, but it is a dangerous remedy in sciatica and should be withheld as long as possible. The disease is so protracted, so liable to relapse and the patient's morale so undermined by the constant worry and the sleepless nights, that the danger of contracting the morphia habit is very great. On no consideration should the patient be permitted to use the hypodermic needle himself. It is remarkable how promptly, in some cases, the injection of distilled water into the nerve will relieve the pain. Acupuncture may also be tried; the needles should be thrust deeply into the most painful spot for a distance of about two inches and left for from fifteen to twenty minutes. The injection of chloroform into the nerve has also been recommended.... Electricity is an uncertain remedy.*

At about the same time on the other side of the Atlantic, deep inland in the Austro-Hungarian empire, Breuer and Freud were also reporting the treatment of a patient who had received quite high doses of morphine by injection for facial pain. They also assumed that many types of facial pain were 'hysterical', just as Osler reported in his book that psychological factors seem to be prominent in brunettes who develop other pains including 'gastralgia'. Freud had also experimented with cocaine – on himself (25).

This advice leaves me thinking how modern and up-to-date Osler was, in both the treatments he recommended and the mistakes that were being made. I will not attempt to say what the mistakes were, with one broad exception. There is a complete absence of attention to the idea of controlled evidence, never mind double-blind evidence. This is despite that Osler had advanced medical knowledge with microscopic studies that properly identified the blood platelets and was devoted to pathological examination for the improvement of diagnosis and in the understanding of disease.

Interestingly, as a final item in connection with standards of evidence, we have the following: "In very obstinate cases nerve stretching may be employed. It is sometimes successful; but in other instances the condition recurs and is as bad as ever" (24).

When it comes to what Osler calls "muscular rheumatism" (myalgia) the principal varieties recognized are lumbago; stiff neck or torticollis; pleurodynia; and other forms such as cephalodynia affecting the muscles of the head, scapulodynia, omodynia and dorsodynia affecting the muscles about the shoulder and upper part of the back. Similar treatments to those used for sciatica were recommended, but for acute cases of lumbago, acupuncture was said to be the most efficient treatment.

I have presented this material from Osler not to show that the greatest physician of his day may have got a lot of things wrong and neglected pain. He did not neglect pain and he got many more things right. Rather, I hope it will illustrate some of the basis and background for topics that are still problematic. Also – in order not to leave the suggestion that pain was neglected in all respects in the 19th and early 20th centuries –

I should indicate that many books and articles were written about neuralgia and other painful topics during the 18th and 19th centuries. However, rather like today, pain as such was not the favourite topic of writers of general medical textbooks.

### THE EARLY AND MIDDLE 20TH CENTURY

In the United States in the first two-thirds of this century, nerve action potential and the response to noxious stimuli by A-delta and C-fibres were identified.

The interpretation of these findings tended to be more mechanistic and much less sophisticated than the analyses of reflex action and motor phenomena by Sherrington and his students. Concomitantly, clinicians were finding much emotional material with respect to pain (26), as they always had done, and offered a mixture of organic and psychological explanations. Motives for complaints of pain abound in the literature; shell shock (27) and psychodynamic theories of pain became popular thereafter. I have identified a few reports by Canadian authors in favour of this theme (28-30), which is now declining. At that time it was claimed that the broader field of psychosomatic medicine could explain such conditions as migraine, dysmenorrhea, asthma and peptic ulcer, but this approach was increasingly abandoned even before the demonstration of the importance of *Helicobacter pylori* in peptic ulcer disease.

One of the most important studies in this period was by Allan Walters (31) in Toronto who presented data from a series of 430 cases referred to by him as having 'psychogenic' pain; his is the largest series in the literature. Walters distinguished three separate ways in which psychophysiological factors could evoke pain: psychogenic magnification of physical pain; psychogenic muscular pain (as a result of tension); and psychogenic regional pain. He proposed this last term in place of the older one of 'hysterical' pain because patients did not conform to what he regarded as the traditional picture of calm and contented hysteria. They were often depressed and anxious even though they may have had some form of conversion symptoms. Although I do not think that the term psychogenic regional pain was a good one, there is no doubt that Walters made a very positive contribution by emphasizing the mixed nature of the psychological phenomena that occurred with chronic pain – many of which I now see as being secondary to poorly understood muscular problems.

Walters was one of those who very early on very clearly understood the distinction between impulses travelling in nerve pathways and the experience of pain (32). I also remember him very fondly personally because of much kindness that he showed to me from 1972 onwards, both during and between visits to Canada before I settled here with my family in 1976.

Work that Spear and I did in the United Kingdom, and published jointly, followed soon after this (27). We provided some controlled evidence about differences between psychiatric patients with pain and without pain, and on those with more persistent pain compared with those with less persistent pain, distinctions that are now known as chronic and

acute pain. We also introduced a definition of pain that in 1979 (by which time I was working in London, Ontario) was adopted with some changes by the International Association for the Study of Pain (IASP) at the suggestion of the Subcommittee on Taxonomy (33). There is, of course, no point in my attempting to conceal the fact that I was the Chairman of the Committee.

My work in the 1960s was concerned primarily with psychiatric patients who had pain. At this time, Spear and I were looking for a general theory of pain that would take account of its occurrence both after physical events and in response to psychological factors. The definition followed from these efforts at understanding and has stayed fundamentally unchanged, although discussions, some of which have been raised from Canada by Kenneth Craig, should lead to some further improvement (34,35). Because my theme is what is past rather than what is ahead, I ought to leave that topic alone for the moment.

The growth and decline of the psychodynamic view of pain overlap with the emergence of pain clinics. John Bonica, who was not, of course, Canadian, was the principal protagonist of comprehensive pain clinics and without question was their main inspiration. His work was paralleled initially by that of another American, Alexander (36), but the trend towards comprehensive pain clinics, and indeed in the whole establishment, owes its origin and spread to Bonica. Bonica's first paper on this subject (37) appeared in 1950 in a relatively obscure American medical journal. His next paper on the topic (38) constituted a slight expansion of the material with somewhat more information about psychological aspects. This time it appeared in the *Canadian Medical Association Journal* and was based on a presentation he had given to the Annual Meeting of the Canadian Anaesthetists' Society (Western Division) in Calgary, February 21 to 23, 1951. This was obviously an important development in work on pain in Canada, and with Bonica's 1953 book *The Management of Pain* (39), encouraged the spread of work in nerve block clinics and pain clinics throughout this country.

About this time one curiosity in the field of pain received particular attention in Canada. Scattered cases of so-called 'congenital universal indifference to pain' had been reported in the literature, and the most detailed study was made in Montreal of a 22-year-old female patient who showed a remarkable absence of response to common pain-producing stimuli. The usual overt reactions or associated physiological changes such as a rise of blood pressure on noxious stimulation also did not occur in this patient (40). She was subsequently shown to have normal histological innervation of the skin, with fine free terminals and networks in the superficial layers, characteristic of the structures in normal subjects (41,42). In fact, no organic defect could be demonstrated, while psychological examination failed to show any evidence of a disorder that could plausibly result in this clinical picture. The assumption has generally been made that this case and others are most likely to be explained by defective integration of nociception at a higher level. A somewhat similar pattern of response to noxious stimulation was reported

as an acquired phenomenon in an individual who suffered from a small penetrating lesion in the region of the superior colliculi. This was an American patient who was also studied at the Montreal Neurological Institute (43).

Individual work on the treatment of pain through nerve blocks sprang up in different centres somewhat independently. My senior colleague in London, Earl S Russell, treated soldiers in the Korean War while serving with the Canadian Army Medical Corps. The anguish of soldiers with frostbitten hands stands out in his memory, and, because nothing seemed to control the intense vasospasm, he taught himself from a text how to do a stellate ganglion block to relieve their suffering. He continued to do stellate ganglion blocks in civilian life for Raynaud's disease, reflex sympathetic dystrophy and the like. Then, in the mid-1950s while working in Kingston, he responded to the request of an internist, Dr Saurey West, who was working on peripheral vascular disease and wanted a series of lumbar sympathetic blocks to be done for his patients. Because of problems with lumbar sympathetic blocks Russell undertook epidural injections by locating the epidural space, as had been described by Phil Bromage in Montreal, and inserting a ureteral catheter. Russell began to work increasingly on pain control, and on moving to London in 1967 continued with this service. By then Dr W Spoerel had established the use of epidural analgesia in London, Ontario where Dr Frank Walker was running a well-established pain clinic at St Joseph's Hospital. I cite these as examples of the growth of pain clinic work in one corner of Canada, although these pain clinics did not operate in the comprehensive mode. However, they did have consultative services readily available from colleagues in the hospitals where they were situated.

In Toronto, pain treatment by Dr Kenneth McKenzie was directed to the surgical management of tic douloureux. The Smythe Pain Clinic at the Toronto General Hospital was founded by Con Smythe, a prominent professional engineer and hockey figure, in honour of his wife Eleanor. It provided a city-wide service, at first for patients with cancer pain, and was run by Ray Evans. At first the clinic principally served patients with cancer pain, but over the years patients with a variety of problems not related to cancer came to the clinic. That clinic is now amalgamated with one at the Toronto Western Hospital. Dr Ronald Tasker worked with the Smythe Pain Clinic in treating the large cancer pain practice by cutaneous cordotomy. In conjunction with Leslie Organ he helped to perfect the physiological technique for corroborating the target site in cordotomy resulting in a number of publications over the years on this subject.

During the 1970s Tasker worked closely with J Allan Walters in seeing pain patients. Walters explored pentothal or amytal examinations in many of his patients, and these interested Tasker further in neuropathic pain, which led him into the rather extensive use of chronic dorsal column and deep brain stimulation for the relief of pain and to a search for realistic outcome statistics. Ron Tasker comments, "Either I'm not nearly as good a surgeon as some other people or else there is some difference in the way they calculate their results

in chronic pain. Naturally I wouldn't mention it unless I was convinced it was the latter" (personal communication). Tasker's deep brain stimulation was largely for neuropathic pain, whereas most published series dealt mainly with so-called failed back pain.

Tasker went on to do stereotactic surgery with brain mapping for physiological responses in the course of stereotactic operations (44). With the help of Fred Lenz (who was his PhD student) he switched to using microelectrodes as the only means of physiological localization and was able to explore the normal organization of the midbrain and thalamus, and later to study abnormal physiology as well, such as tremor cells in patients with Parkinson's disease and bursting cells. Tasker's collaboration continued with Jonathan Dostrovsky, Karen Davis and Bill Hutchison, studying stereotactic brain physiology connected both with pain and with Parkinson's disease, and occasional cingulotomies for psychiatric illness (45). The interest in pain is being perpetuated by Andres Lozano (neurosurgeon), Jonathan Dostrovsky and Karen Davis (46). The work is also reported in the *Textbook of Stereotactic and Functional Neurosurgery* (47), which contains a considerable section on chronic pain.

In Toronto, Peter Watson, working at the Smythe Pain Clinic, organized the first double-blind, placebo controlled trial of amitriptyline and demonstrated that it was analgesic both in patients with postherpetic neuralgia who were depressed and in those who were not depressed (48). As well, he contributed original findings on postherpetic neuralgia and the major current monograph on this topic (49).

## PHYSIOLOGY AND PSYCHOLOGY

As clinicians struggled to organize the extensive phenomena of pain in a unitary account, a longstanding controversy grumbled on in sensory physiology: whether pain was a specific modality like vision or hearing with a dedicated peripheral and central apparatus (specificity theory) or whether the nerve impulse pattern for pain was produced by intense stimulation of nonspecific receptors. This argument dated back particularly to Germany in the 19th century but continued in the English language literature well into the second half of the 20th century.

George H Bishop, an American physiologist, closely associated with the discovery of the differing action potentials of A, B and C fibres, might have been expected to line up with the specificity theorists. However, he engaged in an extended correspondence of 16 letters with Donald Hebb, in which they struggled with the dilemma of understanding the relationship between physical and emotional factors contributing to the apparent same experience known as pain. The bulk of the correspondence (nine letters) dates from December 28, 1950 to May 21, 1951 (50). The starting point was Hebb's discussion of pain in his seminal 1949 work *The Organization of Behaviour* (51). No new solutions were published from this correspondence, but Hebb influenced his student Ronald Melzack to work on pain.

One of Melzack's first publications dealt with the effects of early experience on the response to pain, showing how the

response altered in puppies that from birth were kept away from potential noxious stimulation (52). Melzack worked from 1954 to 1957 at the University of Oregon Medical School with WK Livingston, taught at University College, London, United Kingdom for a year, worked with Moruzzi in Pisa from 1958 to 1959 on descending control of sensory input, and then went to Massachusetts Institute of Technology in 1959 where he met Patrick D Wall. They had many chats on pain, and one day Melzack suggested that they put their ideas on paper. That gave rise to a paper in *Brain* (53) that was scarcely noticed. In 1965 Melzack and Wall published a paper in *Science* entitled "Pain mechanisms: a new theory" (54), offering a gate-theory of pain. This paper carefully discussed both specificity and pattern theories and argued strongly for the modulation of noxious input within the spinal cord. It also took into account the influence of descending pathways and provided the first unitary theory of pain that could reasonably accommodate all the existing knowledge of the complexity of the processes underlying the experience of pain. By 1996 the gate-theory had received over 1700 citations.

Details of the theory were challenged, but the paper gave rise to enormous interest and stimulated much work. Continuing physiological investigations, particularly by Wall and his many students and colleagues, established a commanding body of knowledge demonstrating the occurrence of plasticity in the nervous system in response to noxious stimulation. Among important work done in the field subsequently by Melzack that had a bearing on the basic physiology, was his paper with Ken Casey on parallel processing systems for pain (55).

Melzack returned to McGill in 1963. He studied phantom limb pain, developed the McGill Pain Questionnaire, and stimulated a wealth of work in clinical psychology and in physiology relating to pain. With his students John O'Keefe, David Dubuisson and Stephen Dennis, Melzack developed the rat hind-paw formalin test. His students have also included Mary Ellen Jeans, Terry Coderre and Joel Katz. The latter two have been winners of the Young Investigator Award of the Canadian Pain Society (CPS). Coderre has also received the Patrick D Wall Young Investigator Award of the IASP. Melzack encouraged his clinical colleague Phil Bromage to start a pain clinic, subsequently managed by Rick Catchlove at the Royal Victoria Infirmary. In addition he helped to initiate a pain clinic in 1974 at the Montreal General Hospital run by Dr Joseph Stratford with the assistance of Rick Monks, Mary Ellen Jeans and others. This is the first multidisciplinary pain clinic known to me in Canada. Melzack became the fourth President of the IASP and remains busy in the field.

#### CANADIAN PARTICIPATION IN THE IASP

The founding of the IASP was a unique achievement of one man: Dr John Bonica. Soon after its inception in 1973, plans were laid for Triennial Congresses of which the second in 1978 was held in Montreal and the eighth in Vancouver in 1996. Four meetings have been held in Europe (Florence,

Edinburgh, Hamburg and Paris). One was held in Adelaide and only one (since the founding meeting) in the United States. Approximately half the membership of the IASP resides in the United States, and this distribution of meetings reflected a deliberate 'family hold back' policy from America, essentially because John Bonica did not want the organization to be seen as American-dominated, or indeed to be so dominated (56). Canada has benefited in consequence.

Canadian work on the study of pain has always had a significant international aspect. This is true for Canadian medicine in a wider sense. We have already seen how Osler took his skills and his interests to other countries and how Hebb interacted with Bishop. As a country with a large flow of immigrants, Canada has received many physicians and scientists from elsewhere. Personally I am intrigued by the flow of people between Oxford and University College London, Montreal and London, Ontario. I first met Ron Melzack when I was working at the National Hospital for Nervous Diseases, Queen Square, London, United Kingdom and he was a few blocks away at University College as a Visiting Professor with Pat Wall. Over 70 years earlier Burton Sanderson was the Professor of Physiology at University College London with whom Osler studied and was Professor later at Oxford, while University College Hospital Medical School was the setting for my own clinical studies. Of course there have been interactions with many other centres on the part of different individual Canadians.

The most striking involvement in international affairs dealing with pain came with the foundation of the IASP. That organization has now grown to over 6000 members, including more than 300 Canadians. This is a fairly good representation internationally, but besides providing one President already in the person of Ronald Melzack, we also now have Barry Sessle (originally from Australia) as the President-Elect. Canadians have been represented on the Council of the IASP by Ronald Tasker and Mary Ellen Jeans, as well as by Melzack and Sessle. The two editions of the *Classification of Chronic Pain Syndromes* have been produced from a Canadian address and many Canadians working in Canada have served on the Editorial Board of *Pain*, including M Bruera, MC Bushnell, KD Craig, ME Jeans, PA McGrath, PJ McGrath, R Melzack, H Merskey, RA Ramsay and JA Walters.

The IASP is relatively unusual in that it was founded without the benefit of specific support from national societies. Most, but not all, international medical bodies of this scale appear to have been founded by coalitions of national societies, eg, the World Federation of Anesthesiologists and the World Psychiatric Association. National chapters of the IASP have followed in their wake. The Canadian chapter was founded in 1975 as described recently by Catchlove (57). Five subsequent members of the CPS attended the 1973 Issaquah meeting (where the IASP was founded), as well as myself, then in the United Kingdom. An Eastern Canadian Pain Society was set up in 1975, becoming a chapter of the IASP, and in 1979 the chapter title was changed to simply the Canadian Pain Society.

The first meeting was held in Montreal on September 18

and 19, 1976. The founding President was R Catchlove, succeeded in 1979 by R Evans, and in due course by I Purkis, J Henry, H Merskey, R Tasker, KD Craig and AJ Clark, the current President. The activities of the Society have grown gradually and steadily since foundation, and it now has over 400 members from many disciplines. During Jim Henry's presidency the bylaws were effectively revised by him and Barry Sessle on behalf of the Society (Barry Sessle at that time was Secretary of the CPS).

A very successful joint meeting – or at least one that was very well attended – was held in 1988 in Toronto with the American Pain Society and some 900 participants. One of the later meetings of the CPS led to a symposium on the prevention of postoperative pain, supported by the National Health Research and Development Program of the Department of Health for Canada, published by the Society (58). This production served as a model for the gift volume of the CPS and the American Pain Society, jointly offered to all those who attended the Vancouver IASP meeting (50).

### CONTINUING STUDIES

Having outlined some of the clinical work in central Canada it is time to look east and west. In Halifax, Ian Purkis founded a pain management unit in 1973, which he directed until 1988. Purkis was a founding member of the IASP and organized one of the first joint meetings of the CPS and another chapter of the IASP, which was held in Halifax in 1985 with the Intractable Pain Society of Great Britain and Ireland. He developed continuing medical education programs in the Maritimes, some of them related to pain management, visited China and introduced acupuncture into the management of pain. His publications on pain touched on pain relief in the elderly and cervical epidural steroids.

Pediatric pain programs have been developed in Halifax by Patrick McGrath (psychology) and Alan Finley (anesthesia), whose publications on children's pain are substantial. Work on children's pain has been fostered not only in Halifax but also in Montreal by Celeste Johnston and Bonnie Stevens, another winner of the CPS Young Investigator Award. Their work is based on both clinical care and research. Patricia McGrath in London, Ontario has likewise made significant contributions to the management of pain in children. Cancer pain has been the subject of particular attention in Edmonton (Eduardo Bruera) and palliative care in Montreal under the direction of Balfour Mount, the latter functioning as a significant authority for Canada and elsewhere.

In Saskatoon, Gordon Wyant ran a pain clinic and also was the Founding Editor of the journal *The Pain Clinic*. The idea of starting his clinic arose from interest created by Wyant's attendance at the First IASP Congress in Florence, Italy and from his completion of a three-month training course in Nanking, the Peoples' Republic of China. This course, sponsored by their government, aimed to popularize the use of acupuncture for purposes of pain control and as an alternative to chemical anesthesia (as well as a treatment modality for a variety of diseases). Despite initial difficulties, Wyant was able to establish a core staff of himself and Dr Carl Von

Baeyer as clinical psychologist, with support from nurses, two chiropractors, a dental physician and consultants in psychiatry, physical medicine, rheumatology, general and orthopedic surgery, general medicine and oncology. Acute teaching was provided, and a relatively small staff saw and treated over 3500 patients in the course of some nine years.

Despite a respectable publication record and the support of two successive Heads of the Department of Anesthesia, the clinic declined after the appointment of a new departmental head who withdrew support and locked the use of research funds accumulated over the years by the pain clinic. The dedicated space of the clinic was relinquished, and the effort drifted into oblivion after Dr Wyant's retirement from the Royal University Hospital. A part-time single discipline effort continues at St Paul's Hospital in Saskatoon. This is an important and sad illustration of the need to maintain awareness and support for work on pain (personal communication). Pain clinics are active in other cities, eg, Calgary and Vancouver.

Wyant was instrumental in setting up the Canadian Pain Foundation, meant to be a charitable organization that would foster research and education in the field of pain. This organization was established on the initiative of senior members of the CPS (Gordon Wyant, Barry Sessle and Jim Henry) and is supported by the CPS. It has not yet established sufficient funds to offer significant grants at large.

The physiological work of Jonathan Dostrovsky and Karen Davis in Toronto has been mentioned in conjunction with Tasker's contribution. Regarding craniofacial pain, Barry Sessle in Toronto is widely recognized for his contributions to physiology, and Jim Lund (Montreal) has significantly influenced theories of pain with studies of temporomandibular muscle function showing that the response by these muscles to pain is one of relaxation rather than increased contraction and clenching of the teeth (59). This obviously has a significant impact on theories of temporomandibular facial pain that attribute it to muscle clenching. Work in this field by Ralph Brooke in dentistry with the help of Peter Stenn (clinical psychology) showed that relaxation treatment was as good as biofeedback (60). A study by Michael Salter, Brooke and myself (61) showed that evidence for psychiatric problems was very limited in the majority of patients with the temporomandibular pain and dysfunction syndrome.

Studies of facial expression in pain began very much as a Canadian contribution. This perhaps starts with the work of Ken Craig in Vancouver, his student Ken Prkachin and Celeste Johnston. Many centres outside Canada are actively interested in the work being done by these colleagues.

Another field of development that began in Canada has been of particular importance. Hugh Smythe, defining tender points associated with generalized rheumatic pain – which was often regarded as psychogenic – recognized the important clinical patterns of what is now called fibromyalgia and what was then termed fibrositis. Smythe and Harvey Moldofsky, a psychiatrist with a sleep laboratory, were able to show, first, that fibromyalgia was often associated with an

unusual pattern of partial arousal during deep sleep in patients with diffuse pain and, second, the characteristic tender points identified by Smythe. Normal individuals developed the same electroencephalogram (EEG) pattern when woken repeatedly in the sleep laboratory (62). Extremely fit individuals did not. This work was the turning point for the development of modern ideas of fibromyalgia, taken up ultimately by the American College of Rheumatology (with many Canadian participants) and leading to the establishment of criteria for identifying patients who fit into the well-recognized syndrome.

It was later found that the EEG findings were neither always present in fibromyalgia nor specific, but the association between the disorder and the laboratory findings led to the appraisal of fibromyalgia as a disorder with a pathophysiological basis. Work in other parts of the world has also shown this, with the recognition of several types of chemical change (63). Substantial contributions to work in fibromyalgia have also been made in Canada by those who participated in the American College of Rheumatology trials, including such rheumatologists as Claire Bombardier of Toronto, Glen McCain (at the time in London, Ontario) and Simon Carrette of Quebec City. These trials defined the specific 18 tender points (64).

Contributions in epidemiology have been made particularly by Joan Crook, Eldon Tunks and others in Hamilton (65). Other studies, both in fibromyalgia and in epidemiology, by the Hamilton group have provided a number of important factual bases in the comparison of patients in pain clinics and outside in a study of the differences between fibromyalgia and myofascial pain.

In the 1980s, part of my own work was concerned with group studies of the frequency of psychological change or psychiatric disorder in different clinical populations of patients with pain. This work was undertaken with Drs Brooke, Russell, Nielsen, Tilsworth and others, and showed that much pain that might have been attributed to psychological causes lacked the evidence of such a pattern or etiology (66). I undertook further work with Guido Magni of Padua in analyzing figures from the United States National Health Statistics on the distribution of pain and depression in the United States population. This work reflects a multinational perspective. The data were collected in the United States as part of two national surveys. They were given to myself and Magni, then a Visiting Professor in London, Ontario, to analyze. Magni completed the analysis with the help of the Professor of Statistics in Padua, Silio Rigatti-Luchini, and his graduate students. We obtained information on the frequency of musculoskeletal pain throughout a general population, on its association with depression and on the interaction between the two variables (67).

In this catalogue, I want to return to activity in basic science. Jim Henry is working in research on purines. Michael Salter, a student of Henry and myself, is now a physiologist rather than a medical student as he was when he undertook the work with Brooke and myself. Salter initially undertook studies in cats that demonstrated that adenosine

inhibits nociceptive neurons in the dorsal horn of the spinal cord. His work was supported clinically by the demonstration by Marchand et al (68), also in Canada, that the analgesic effect of transcutaneous electrical nerve stimulation was blocked by the intravenous administration of the adenosine receptor antagonist caffeine. Work in his laboratory at the Hospital for Sick Children in Toronto has shown that NMDA receptors are upregulated by phosphorylation on the amino acid tyrosine (69).

Of the hundreds of tyrosine enzymes in the central nervous system, Salter's group has identified the one regulating NMDA receptors as an enzyme called Src (70). In their most recent work they have shown that Src causes long-lasting enhancement of synaptic transmission (71). Because enhanced synaptic transmission in nociceptive pathways is considered to be pivotal in some types of chronic pain, their results raise the possibility that Src may have a role in these types of pain.

Dr Jana Sawynok in Halifax is another distinguished purines expert, contributing, for example, to knowledge of the antinociceptive action of adenosine (72). Ron Melzack's former student Joel Katz, mentioned above, has made internationally recognized contributions to preoperative analgesia and its impact on postoperative pain (73), while he (74) and he and Melzack (75) have presented authoritative studies on the phenomenology and physiology of phantom pain. Terence Coderre, another of the impressive basic scientists coming from Montreal, is engaged in significant studies of molecular mechanisms. His prize-winning work noted earlier helped to provide a detailed and extended demonstration at the cellular level of the way in which central sensitization of the spinal cord may follow from peripheral injury (76,77).

Lastly, on a cerebral note, Bushnell, using positron emission tomography scanning in Montreal and working also with colleagues in Arizona (78) and in Richmond, Virginia (79), has elegantly demonstrated that the thermal grill illusion of noxious stimulation evokes activity in the anterior cingulate cortex (78) and that hypnotic suggestions of greater or less unpleasantness are associated with changes in anterior cingulate activity when noxious stimulation is actually present. I am not sure that these latter changes can be adequately characterized as related to affect, but they are famously intriguing.

## CONCLUSIONS

There is no conclusion to history. Telling some part of the story of the history of pain research and management in Canada has inevitably encroached upon current news. Work in the field is necessary and thriving, in basic research, clinical research and service. The story is not one of unremitting advances but rather of the gradual and intermittent accretion of information in various ways at different times and in many locations, and – although I have not dwelt on it much – some regression. If there is any consistent thread in the history of the subject, as seen through the eyes of the CPS and its members, that thread is the importance of integrating basic knowledge with clinical research and treatment. This is a very ordinary observation, yet it fits an extraordinary subject.



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## REFERENCES

- Merskey SJ. Canadian Native Health, Disease and Treatment 1534-1870. MA Thesis. University of Western Ontario, 1986.
- Williams G, ed. Andrew Graham's Observations on Hudson's Bay, 1767-1791. London: Hudson's Bay Research Society, 1969:230.
- Henry A. Travels and Adventures in Canada and the Indian Territories Between the Years 1760-1776. New York: Riley, 1809:118.
- Williams G, ed. Andrew Graham's Observations on Hudson's Bay, 1767-1791. London: Hudson's Bay Research Society, 1969:125.
- Lamb WK, ed. Simon Fraser: Letters and Journals 1806-1808. Toronto: MacMillan, 1960:153-4.
- Jewitt JR. Narrative of the Adventures and Suffering of John R Jewitt, Only Survivor of the Crew of the Ship "Boston", During a Captivity of Nearly Three Years Among the Savages of Nootka Sound. Reprinted. Fairfield: Galleon Press, 1967:142.
- Cox R. Adventures on the Columbia River. J&J Harper: New York, 1832:249-51.
- Hind HY. Narrative of the Canadian Red River Exploring Expedition of 1857; and of the Saskatchewan Exploring Expedition of 1858. London, 1860. Reprinted Edmonton: Hurtig, 1971:190.
- Thwaites RG. The Jesuit Relations and Allied Documents: 1663-64, vol 49. Cleveland: Burrows, 1896-1901:121.
- Dièreville Sieur de. Relation of the Voyage to Port Royal in Acadia or New France. Translated by C Webster. Toronto: Champlain Society Publications, 1933.
- Cox R. Adventures on the Columbia River. J&J Harper: New York, 1832:248.
- Trueman S. The Ordeal of John Gyles: Being an Account of his Odd Adventures, Strange Deliverances C [ie, etc.] as a Slave of the Malisets. Toronto: McLelland & Stewart, 1966. Reprinted 1973.
- Wallace WS, ed. John McLean's Notes of a Twenty-Five Years' Service in the Hudson Bay Territory (1821-1846). Toronto: Champlain Society Publications, 1932.
- Cox R. Adventures on the Columbia River. J&J Harper: New York, 1832:251.
- Cox R. Adventures on the Columbia River. J&J Harper: New York, 1832:249-57.
- Champlain S de. The Works of Samuel de Champlain, vols 1 to 7. Translated by HP Biggar. Toronto: Champlain Society, 1922;2:36,91-2.
- Dièreville Sieur de. Relation of the Voyage to Port Royal in Acadia or New France. Translated by C Webster. Toronto: Champlain Society Publications, 1933:143.
- Williams G, ed. Andrew Graham's Observations on Hudson's Bay, 1767-1791. London: Hudson's Bay Research Society, 1969:163.
- Parry WE. Journals of the First, Second, Third and Fourth Voyages for the Discovery of a North-West Passage from the Atlantic to the Pacific in 1819-20-21-22-23-24-25, in His Majesty's Ships, Hecla, Griper and Fury, vol 5. London: John Murray, 1828:315.
- Hind HY. Narrative of the Canadian Red River Exploring Expedition of 1857; and of the Saskatchewan Exploring Expedition of 1858. London, 1860. Reprinted Edmonton: Hurtig, 1971:59.
- Townsend CW, ed. Captain Cartwright and his Labrador Journal. Boston: Dona Estes & Co, 1911.
- Mitchell SW, Morehouse GR, Keen WW. Gunshot Wounds and Other Injuries of Nerves. Philadelphia: JB Lippincott, 1864.
- Merskey H, Bogduk N, eds. International Association for the Study of Pain: Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. Seattle: IASP Press, 1994.
- Osler W. The Principles and Practice of Medicine. New York: D Appleton & Co, 1896.
- Breuer J, Freud S. 1892-95 Studies on Hysteria. Complete Psychological Works of Freud. Standard edn, vol II. London: Hogarth Press, 1955.
- Thornton EM. The Freudian Fallacy: Freud and Cocaine. London: Palladin Books, 1986.
- Merskey H, Spear FG. Pain: Psychological and Psychiatric Aspects. London: Bailliere, Cassell & Tindall, 1967.
- Merskey H. The Analysis of Hysteria, 2nd edn. London: Gaskell Press, 1995.
- Scott WCM. Some embryological, neurological, psychiatric and psychoanalytic implications of the body scheme. *Int J Psychoanal* 1948;29:141-55.
- Ellman P, Savage OA, Wittkower E, Rodger TF. Fibrositis. A biographical study of 50 civilian and military cases. *Ann Rheum Dis* 1942;3:56-76.
- Walters AJ. Psychogenic regional pain alias hysterical pain. *Brain* 1961;84:1-18.
- Walters AJ. The psychological aspects of bodily pain. *Appl Ther* 1963;5:853-76.
- International Association for the Study of Pain. Pain Terms: A list with definitions and notes on usage. Recommended by an IASP Subcommittee on Taxonomy. *Pain* 1979;6:249-52.
- Craig KD. Implications of concepts of consciousness for understanding pain behaviour and the definition of pain. *Pain Res Manage* 1997;2:111-7.
- Merskey H. Pain consciousness and behaviour. *Pain Res Manage* 1997;2:118.
- Alexander FAD. Control of pain. In: Hale D, ed. *Anaesthesiology*. Philadelphia: Davis 1954:579-611.
- Bonica JJ. Organization and function of a pain clinic. *Northwest Med* 1950;49:593-6.
- Bonica JJ. The role of the anesthesiologist in the management of intractable pain. *Can Med Assoc J* 1951;65:103-7.
- Bonica JJ. The Management of Pain. Philadelphia: Lea & Febiger, 1953.
- McMurray BA. Experimental study of a case of insensitivity to pain. *Arch Neurol Psychiatr* 1950;64:650-64.
- Feindel W. Note on the nerve endings in a subject with arthropathy and congenital absence of pain. *J Bone Joint Surg* 1953;35:402-7.
- Baxter DW, Olszewski J. Congenital universal insensitivity to pain. *Brain* 1960;83:381-93.
- Teuber HL, Milner B, Vaughn HG. Persistent anterograde amnesia after stab wound of the basal brain. *Neuropsychol* 1968;6:267-82.
- Tasker RR, Organ LW, Hawrylyshyn PH. The Thalamus and Midbrain of Man. A Physiological Atlas Using Electrical Stimulation. Springfield: CC Thomas, 1982.
- Tasker RR, Filho-Vilela O. Deep brain stimulation for the control of intractable pain. In: Youmans JR, ed. *Neurological Surgery*. New York: Saunders, 1996:3512-27.
- Davis K, Kiss ZHT, Luo L, Tasker RR, Dostrovsky JO, Lozano AM. Phantom sensations generated by thalamic neurostimulation. *Nature* 1998;39:385-7.
- Gildenberg PL, Tasker RR. Textbook of Stereotactic and Functional Neurosurgery. New York: McGraw Hill, 1998.
- Watson CPN, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in post herpetic neuralgia. *Neurology* 1982;32:671-3.
- Watson CPN. Herpes Zoster and Post Herpetic Neuralgia. Amsterdam: Elsevier, 1993.
- Merskey H, ed. Thoughts and Findings on Pain: The Hebb-Bishop Correspondence and a Selection of Papers. Canadian and American Pain Societies. Toronto: Canadian Pain Society, 1996.

51. Hebb D. *The Organization of Behaviour*. New York: Wiley 1949.
52. Melzack R, Scott TH. The effects of early experience on the response to pain. *J Compar Physiol Psychol* 1957;50:155-61.
53. Melzack R, Wall PD. On the nature of cutaneous sensory mechanisms. *Brain* 1962;85:331-56.
54. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971-9.
55. Melzack R, Casey KL. Sensory motivational and central controlled determinants of pain: a new conceptual model. In: Shalod K, ed. *The Skin Senses*. Springfield: CC Thomas, 1968:423-43.
56. Bonica JJ, Albe-Fessard D, eds. *Advances in Pain Research and Therapy*, vol 1. New York: Raven Press, 1976:XXXII.
57. Catchlove R. A note on the history of the Canadian Pain Society: early development. *Pain Res Manage* 1997;2:229-30.
58. Merskey H, Prkachin K, eds. *The Prevention of Post Operative Pain*. Vancouver: Canadian Pain Society, 1993.
59. Lund JP, Stohler CS, Widmer CG. The relationship between pain and muscle activity fibromyalgia and similar conditions. In: Vaeroy H, Merskey H, eds. *Progress in Fibromyalgia and Myofascial Pain*. Amsterdam: Elsevier Science Publishers 1993:311-27.
60. Brooke R, Stenn P, Mothersill K. The diagnosis and conservative treatment of myofascial pain dysfunction syndrome. *Oral Surg* 1977;44:844-52.
61. Salter M, Brooke R, Merskey H, Fichter GF, Kapusianyk DH. Is the temporo-mandibular pain and dysfunction syndrome a disorder of the mind? *Pain* 1983;17:151-66.
62. Moldofsky H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med* 1975;4:341-51.
63. Vaeroy H. A contribution to the understanding of pain in fibromyalgia based on cerebral spinal fluid investigations. *Pain Res Manage* 1996;1:45-9.
64. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: Report of the Multi-Center Criteria Committee. *Arthritis Rheum* 1990;33:160-72.
65. Crook J, Tunks E, Rideout E, Brown G. Epidemiologic comparison of persistent pain sufferers in a specialty pain clinic and in the community. *Arch Phys Med Rehab* 1986;67:451-5.
66. Merskey H, Lau CL, Russell ES, et al. Screening for psychiatric morbidity. The pattern of psychological illness and premorbid characteristics in four chronic pain populations. *Pain* 1987;30:141-57.
67. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study of the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain* 1994;56:289-97.
68. Marchand S, Li J, Charest J. Efforts of caffeine on analgesia from transcutaneous electrical nerve stimulation. *N Engl J Med* 1995;333:325-6.
69. Wang YT, Salter MW. Regulation of NMDA receptors by protein-tyrosine kinases and phosphatases. *Nature* 1994;369:233-5.
70. Yu X-M, Askalan R, Keil GJ, Salter MW. NMDA channel regulation by channel-associated protein tyrosine kinase. *Science* 1997;275:674-8.
71. Lu YM, Roder JC, Davidow J, Salter MW. Src activation in the induction of long-term potentiation in CA1 hippocampal neurons. *Science* 1990;279:1363-8.
72. Poon A, Sawynok J. Antinociception by adenosine analogs and inhibitors of adenosine metabolism in an inflammatory thermal hyperalgesia model in the rat. *Pain* 1998;74:235-45.
73. Katz JP, Kavanaugh BP, Sandler AN, Nierenberg H. Pre-emptive analgesia: Clinical evidence of neuroplasticity contributing to post-operative pain. *Anesthesiology* 1992;77:439-46.
74. Katz J, Melzack R. Pain "memory" in phantom limbs: review and clinical observations. *Pain* 1990;43:319-36.
75. Katz J. Psychophysiological contributions to phantom limbs. *Can J Psychiatry* 1992;37:282-98.
76. Yashpal A, Pitcher GM, Parent A, et al. Noxious thermal and chemical stimulation induce increases in <sup>3</sup>H-Phorbol 12,13-dibutylate binding in spinal cord dorsal horn as well as persistent pain and hyperalgesia, which is reduced by inhibition of protein kinase. *Can J Neurosci* 1995;15:3263-72.
- 77.Coderre TJ, Fisher K, Fundytus ME. The Role of Ionotropic and Metabotropic Glutamate Receptors in Persistent Nociception. *Proceedings of the 8th World Congress on Pain, Progress in Pain Research and Management*, 8. Seattle: IASP Press 1997:259-75.
78. Craig AD, Reiman EM, Evans A, Bushnell MC. Functional imaging of an illusion of pain. *Nature* 1996;384:258-60.
79. Rainville P, Duncan GH, Price DD, Carrier M. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997;277:968-71.



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