The Biochemical Origin of Pain – Proposing a new law of Pain: The origin of all Pain is Inflammation and the Inflammatory Response PART 1 of 3 – A unifying law of pain

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The biochemical origin of pain — Proposing a new law of pain: The origin of all pain is inflammation and the inflammatory response. Part 1 of 3 — A unifying law of pain ☆

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Summary We are proposing a unifying theory or law of pain, which states: the origin of all pain is inflammation and the inflammatory response. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. Activation of pain receptors, transmission and modulation of pain signals, neuro plasticity and central sensitization are all one continuum of inflammation and the inflammatory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory response. We are proposing a re-classification and treatment of pain syndromes based upon their inflammatory profile. Treatment of pain syndromes should be based on these principles:

1. Determination of the inflammatory profile of the pain syndrome.
2. Inhibition or suppression of production of the appropriate inflammatory mediators, e.g. with inflammatory mediator blockers or surgical intervention where appropriate.
3. Inhibition or suppression of neuronal afferent and efferent (motor) transmission, e.g. with anti-seizure drugs or local anesthetic blocks.
4. Modulation of neuronal transmission, e.g. with opioid medication.

At the L.A. Pain Clinic, we have successfully treated a variety of pain syndromes by utilizing these principles. This theory of the biochemical origin of pain is compatible with, inclusive of, and unifies existing theories and knowledge of the mechanism of pain including the gate control theory, and theories of pre-emptive analgesia, windup and central sensitization.

☆ The paper is not under consideration elsewhere and none of the paper's contents have been previously published. All authors have read and approved the manuscript. Work was done at the L.A. Pain Clinic. The study was not supported by any grant. There is no conflict of interest.

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Description of the prior theories

Prior theories — The prior theories do not contain any unifying Law of Pain. Each disease entity, e.g. fibromyalgia, Complex Regional Pain Syndrome/Reflex Sympathetic Dystrophy (RSD/CRPS), carpal tunnel syndrome, rheumatoid arthritis and ankylosing spondylitis is considered distinct from the other entities and is classified in terms of symptomatology, structural pathology, genetic markers, presence of autoantibodies, etc. The prior theories assign a different mechanism to nociceptive and neuropathic pain, a different mechanism to acute and chronic pain, and a different mechanism to peripheral and central pain. The prior theories result in a treatment of pain syndromes that focuses mainly on structural pathology. Where present, treatment of inflammation in these disease entities has hitherto addressed one biochemical mediator of inflammation at a time (mostly focused on prostaglandin), instead of addressing the inflammatory soup of biochemical mediators that are present in all pain syndromes.

Four centuries ago Descartes described pain in terms of an alarm bell ringing in a bell tower. In 1898, in his landmark work, *The Integrative Action of the Nervous System* [1], the British physiologist, Sir Charles Scott Sherrington, proposed the key concept of nociception: pain as the evolved response to a potentially harmful, ''noxious'' stimulus. Livingston wrote in his *Pain Mechanisms* [2]: ''I believe that the concept of 'specificity' in the narrow sense in which it is sometimes used has led away from a true perspective. Pain is a sensory experience that is subjective and individual; it frequently exceeds its protective function and becomes destructive. The impulses, which subserve it, are not pain, but merely a part of its underlying and alterable physical mechanisms. The specificity of function of neuron units cannot be safely transposed into terms of sensory experience. A chronic irritation of sensory nerves may initiate clinical states that are characterized by pain and a spreading disturbance of function in both somatic and visceral structures. If such disturbances are permitted to continue, profound and perhaps unalterable organic changes may result in the affected part. A vicious circle is thus created [3].

In 1942 Paul Sudeck suggested that the signs and symptoms of RSD/CRPS including sympathetic hyperactivity might be provoked by an exaggerated inflammatory response to injury or operation of an extremity. His theory found no followers, as many doctors incorrectly believe that RSD/CRPS is solely initiated by a hyperactive sympathetic system.

In 1965, collaboration between Canadian psychologist Ronald Melzack and British physiologist Patrick Wall produced the gate control theory. Their paper, ''Pain Mechanisms: A New Theory [4], has previously been described as ''the most influential ever written in the field of pain''. Melzack and Wall suggested a gating mechanism within the spinal cord (substantia gelatinosa of the dorsal horns) that closed in response to normal stimulation of the fast conducting A-β ''touch'' nerve fibers; but opened when the slow conducting C ''pain'' fibers transmitted a high volume and intensity of sensory signals. The gate could be closed again if these signals were countered by renewed stimulation of the large fibers. By opening or closing in varying degrees, the neural gate modulates incoming pain signals before they reach the brain. The opening and closing of the gate is determined by the amount of activity in the pain fibers, the amount of activity in other peripheral fibers, activity of descending inhibitory pathways from neurons in the brainstem and cortex. In summary, the Gate Theory proposed that small (C) fibers activated excitatory systems that excited output cells — these latter cells had their activity controlled by the balance of large-fiber (A-β) mediated inhibitions and were under the control of descending systems. Wall went on to add to and refine the theory to include changes in afferents, prolonged central excitability, and changes in these systems after nerve damage. The concepts of convergence and modulation espoused by the gate control theory reduced the emphasis on destruction of pathways and led to the idea that pain could be controlled by modulation — reduce excitation or increase inhibition. The gate control theory explains why massage or applying heat reduces some pain and why people who are hypnotized or distracted may not notice pain. However, in a 1965 article, Melzack himself stated that the gate control theory is not able to explain several chronic pain problems [5]. The gate control theory does not provide an explanation of the biochemical and molecular mechanism of neuronal activation and transmission, does not explain the pathophysiology of pain syndromes and does not provide a road map for treatment of all pain syndromes.

More recently, Pain is currently defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. This definition was adapted in 1979, and published in the paper 'Pain terms; a list with definitions and notes on usage. Recommended by the IASP Sub-

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committee on Taxonomy', in the journal Pain in 1979 [6]. This definition was subsequently considered elusive, and the following statement was added in order to make the position more clear: 'Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. It is unquestionably a sensation in a part of the body but it is also unpleasant and therefore also an emotional experience. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is no way to distinguish their experience from that due to tissue damage, if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus...'

Pain is also currently classified as being peripheral or central in origin. Peripheral pain originates in muscles, tendons, etc., or in the peripheral nerves. Pain originating in the peripheral nerves, i.e. via trauma to the nerves, is classified as neurogenic pain. Central pain is currently thought to arise from central nervous system pathology: a ''primary'' CNS dysfunction. Some of this has been thought to arise due to maladaptive thought processes, true ''psychogenic'' pain [7]. But most of it has been thought to be due to structural changes in the CNS, e.g. spinal cord injury, multiple sclerosis, stroke and epilepsy [8,9].

Another current classification, that distinguishes between normally functioning nerves and nerves whose function has been altered by pathology is as follows: Nociceptive pain is pain in which normal nerves transmit information to the central nervous system about trauma to tissues. Neuropathic pain is pain in which there are structural and/or functional nervous system adaptations secondary to injury, that take place either centrally or peripherally [10]. The IASP defines central pain as ''pain initiated or caused by a *primary* lesion or dysfunction in the central nervous system'' [11].

Current theories of Pain state that physiological pain arises from damage to tissue (inflammatory pain), whereas neuropathic pain results from changes in damaged nerves [12]. When tissue is damaged, peripheral chemicals sensitize the sensory endings and after neuropathic pain, excitability changes occur within the nerve itself. These peripheral changes then alter activity in central systems [13]. The current theories further state that inflammation will produce peripheral sensitization [14] in that the system will be driven harder for a given stimulus. Ongoing ectopic activity in damaged peripheral nerves will continually produce transmitter release into the spinal cord, and this will cause subsequent neuronal activity [13,15,16]. After tissue and nerve injury, there are increases in the activity of calcium channels within the spinal cord responsible for both presynaptic transmitter release and postsynaptic neuronal excitability. Current theories on wind-up and central sensitization explain central pain on the basis of augmented transmitter release, an increased release of glutamate and enhanced activation of the glutamate receptors for glutamate, especially the *N*-methyl-D-aspartate (NMDA) receptor [13]. Central sensitization is said to occur when peripheral sensory neuron activity drives central spinal systems that amplify and prolong the incoming sensory messages.

The variations in the current treatment of pain syndromes reflect a lack of a unifying theory of pain. Depending on the physician, a patient with severe back pain and an magnetic resonance imaging (MRI) showing a 4 mm herniated disc may be given heat or cold therapy, trigger point injections, epidural steroid injections, radiofrequency (RF) neurotomy, cryotherapy of the lumbar facet medial branch nerve, heating of the intervertebral disk with intradiscal electro-thermal therapy (IDET), spinal cord stimulation, implantation of an intrathecal infusion pump, surgical laminectomy or surgical fusion. This demonstrates significant differences in understanding of the pathophysiology and treatment of pain syndromes. Current medical theories place an over reliance on structural abnormalities to explain pain syndromes. This is not surprising because our current imaging technologies are structure based. Physicians are comfortable treating what they see. Patients who have structural abnormalities such as an osteoarthritis or herniated disk on MRI scans get operated upon often times needlessly and end up with more joint, back or neck pain. Patients with severe pain who do not have structural abnormalities on MRI scans, e.g. patients with fibromyalgia are referred for psychiatric intervention. The fallacy of this approach has been confirmed in numerous published studies. In one of these studies [17], the authors performed magnetic resonance imaging on 67 individuals who had never had low-back pain, sciatica, or neurogenic claudication. The scans were interpreted independently by three neuro-radiologists who had no knowledge about the presence or absence of clinical symptoms in the subjects. About one-third of the subjects were found to have a substantial abnormality. Of those who were less than 60 years old, 20% had a herniated nucleus pulposus and one had spinal stenosis. In the group that was 60 years old or older, the findings were abnormal

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on about 57% of the scans: 36% of the subjects had a herniated nucleus pulposus and 21% had spinal stenosis. There was degeneration or bulging of a disc at least one lumbar level in 35% of the subjects between 20 and 39 years old and in all but one of the 60- to 80-year-old subjects. In view of these findings in asymptomatic subjects, the authors concluded that abnormalities on magnetic resonance images must be strictly correlated with age and any clinical signs and symptoms before operative treatment is contemplated. In another study [18], the authors examined the prevalence of abnormal findings on MRI scans of the lumbar spine in people without back pain. 52% of the asymptomatic subjects were found to have a bulge at least at one level, 27% had a protrusion, and 1% had an extrusion. Thirty-eight percent had an abnormality of more than one intervertebral disk. The prevalence of bulges, but not of protrusions, increased with age. The most common nonintervertebral disk abnormalities were Schmorl's nodes (herniation of the disk into the vertebral-body end plate), found in 19% of the subjects; annular defects (disruption of the outer fibrous ring of the disk), in 14%; and facet arthropathy (degenerative disease of the posterior articular processes of the vertebrae), in 8%. The findings were similar in men and women. The authors concluded that on MRI examination of the lumbar spine, many people without back pain have disk bulges or protrusions but not extrusions. The authors went further to state that given the high prevalence of these findings and of back pain, the discovery by MRI of bulges or protrusions in people with low back pain may frequently be coincidental. In another study [19], which tracked the natural history of individuals with asymptomatic disc abnormalities in magnetic resonance imaging the authors stated that the high rate of lumbar disc alterations recently detected in asymptomatic individuals by magnetic resonance imaging demands reconsideration of a pathomorphology-based explanation of low back pain and sciatica. In another controlled trial of arthroscopic surgery for osteoarthritis of the knee [20], 180 patients with osteoarthritis of the knee were randomly assigned to receive arthroscopic débridement, arthroscopic lavage, or placebo surgery. Patients in the placebo group received skin incisions and underwent a simulated débridement without insertion of the arthroscope. Patients and assessors of outcome were blinded to the treatment-group assignment. Outcomes were assessed at multiple points over a 24-month period with the use of five self-reported scores — three on scales for pain and two on scales for function — and one objective test of walking and stair climbing. A total of 165 patients completed the trial. The study results were astounding. At no point did either of the intervention groups report less pain or better function than the placebo group. For example, mean (±SD) scores on the Knee-Specific Pain Scale (range, 0 to 100, with higher scores indicating more severe pain) were similar in the placebo, lavage, and débridement groups: 48.9 ± 21.9, 54.8 ± 19.8, and 51.7 ± 22.4, respectively, at 1 year ($P = 0.14$ for the comparison between placebo and lavage; $P = 0.51$ for the comparison between placebo and débridement) and 51.6 ± 23.7, 53.7 ± 23.7, and 51.4 ± 23.2, respectively, at 2 years ($P = 0.64$ and $P = 0.96$, respectively). Furthermore, the 95% confidence intervals for the differences between the placebo group and the intervention groups exclude any clinically meaningful difference. The authors concluded that in this controlled trial involving patients with osteoarthritis of the knee, the outcomes after arthroscopic lavage or arthroscopic débridement were no better than those after a placebo procedure. This is further confirmation of the fallacy of a structure-based approach to the treatment of pain.

Medical treatment of pain syndromes has vastly improved with a greater recognition of the need to effectively control pain through the use of a variety of medications including NSAIDs, Corticosteroids, Opioids, Anti-seizure drugs, Antidepressants, etc. However, the vast majority of physicians have no experience in the utilization of inflammatory mediator blockers in the treatment of pain syndromes.

The biochemical origin of pain theory

We propose a Law of Pain which states that: The origin of all pain is inflammation and the inflammatory response [21]. This law unifies all pain syndromes as sharing a common origin of inflammation and the inflammatory response. It is our theory that nociceptive and neuropathic pain, acute and chronic pain, peripheral and central pain including windup, neuroplasticity and central sensitization are a continuum of inflammation and the inflammatory response.

In all organisms, the cellular response to injury, infection and the aging process is inflammation and the inflammatory response. Tissue injury may arise from a physical, chemical or biological trauma or irritation. Degeneration of tissue subsequent to aging or previous injury can also lead to inflammation. Injured tissues can be muscle, ligament, disks, joints or nerves. A variety of mediators (cytokines, neuropeptides, growth factors and neurotransmitters) are generated by tissue injury and

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inflammation. These include substances produced by damaged tissue, substances of vascular origin as well as substances released by nerve fibers themselves, sympathetic fibers and various immune cells [22]. The biochemical mediators produced by the immune cells include prostaglandin, nitric oxide, tumor necrosis factor α, interleukin 1-α, interleukin 1-β, interleukin-4, interleukin-6 and interleukin-8, histamine, serotonin. The biochemical mediators produced by the nerve cells include inflammatory protein Substance P, glutamate, calcitonin gene-related peptide (CGRP) neurokinin A and vasoactive intestinal peptide.

Cell enzymes that catalyze reaction pathways and generate these biochemical mediators of inflammation include cyclooxygenase (COX), lipoxygenase (LOX). A cell enzyme that is activated by inflammatory mediators such as TNF-α and interleukin-1 is Gelatinase B or Matrix Metallo-Proteinase 9 (MMP-9). Once activated MMP-9 helps immune cells migrate through the blood vessels to inflammatory sites or to metastatic sites. Activated, MMP-9 can also degrade collagen in the extra cellular matrix of articular bone and cartilage and is associated with joint inflammation and bony erosions [23].

There are three phases of an inflammatory response: initiation, maintenance and termination. Upon tissue injury or painful stimulation, specialized blood cells in the area such as basophils, mast cells and platelets release inflammatory mediators serotonin, histamine and nitric oxide. Subsequent to the binding of serotonin to its receptor, there is inflammation of the adjacent nerves and the nerve endings release short-lived inflammatory peptide proteins such as substance P, calcitonin gene-related peptide (CGRP). In addition, clotting factors in the blood produce and activate potent inflammatory mediator peptide proteins called neurokinin A, bradykinin, kallidin and T-kinin. All of these proteins increase blood flow to the area of injury, stimulate arachidonic acid metabolism to generate inflammatory mediators prostaglandins and attract specialized immune cells to the area. The first immune cells to the area are tissue macrophages, which provide the front line defense against bacterial infection. Macrophages release powerful enzymes to digest any bacteria that are present and produce potent inflammatory chemical mediators (called cytokines) to attract and activate other cells of the immune system. Shortly thereafter the area of bacterial invasion or tissue injury is invaded by the other immune cells, which include white blood cells such as T helper cells, lymphocytes, neutrophils, eosinophils, and other cells such as fibroblasts and endothelial cells. These immune cells respond to the chemical mediators, release destructive enzymes to kill any invading organism and release more chemical mediators to attract more immune cells. A consequence of this immune response is tissue damage, pain and spasm. In a sense the initial immune reaction ignites a cascade of immune reactions and generates an inflammatory soup of chemical mediators. These chemical mediators produced by the immune cells include prostaglandin, nitric oxide, tumor necrosis factor α, interleukin 1-α, interleukin 1-β, interleukin-4, interleukin-6 and interleukin-8, histamine, serotonin. In the area of injury and subsequently in the spinal cord, enzymes such as cyclooxygenase increase the production of these inflammatory mediators. These chemical mediators attract tissue macrophages and white blood cells to localize in an area to engulf (phagocytize) and destroy foreign substances. The chemical mediators released during the inflammatory response give rise to the typical findings associated with inflammation.

Effects of the inflammatory mediators

The inflammatory mediators activate local pain receptors and nerve terminals and produce hypersensitivity in the area of injury. Activity of the mediators results in excitation of pain receptors in the skin, ligaments, muscle, nerves and joints. Excitation of these pain receptors stimulate the specialized nerves, e.g. C fibers and A-δ fibers that carry pain impulses to the spinal cord and brain. Subsequent to tissue injury, the expression of sodium channels in nerve fibers is altered significantly thus leading to abnormal excitability in the sensory neurons. Nerve impulses arriving in the spinal cord stimulate the release of inflammatory protein Substance P. The presence of substance P and other inflammatory proteins such as calcitonin gene-related peptide (CGRP) neurokinin A and vasoactive intestinal peptide removes magnesium induced inhibition and enables excitatory inflammatory proteins such as glutamate and aspartate to activate specialized spinal cord NMDA receptors. These results in magnification of all nerve traffic and pain stimuli that arrive in the spinal cord from the periphery. Activation of motor nerves that travel from the spinal cord to the muscles results in excessive muscle tension. More inflammatory mediators are released which then excite additional pain receptors in muscles, tendons and joints generating more nerve traffic and increased muscle spasm. Persistent abnormal spinal reflex transmission due to local injury or even inappropriate postural habits may then result in a vicious circle

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between muscle hypertension and pain [24]. Separately, constant C-fiber nerve stimulation to transmission pathways in the spinal cord resulting in even more release of inflammatory mediators but this time within the spinal cord. The transcription factor, nuclear factor-κB (NF-κB), plays a pivotal role in regulating the production of inflammatory cytokines [25]. Inflammation causes increased production of the enzyme cyclooxygenase-2 (Cox-2), leading to the release of chemical mediators both in the area of injury and in the spinal cord. Widespread induction of Cox-2 expression in spinal cord neurons and in other regions of the central nervous system elevates inflammatory mediator prostaglandin E_2 (PGE_2) levels in the cerebrospinal fluid. The major inducer of central Cox-2 upregulation is inflammatory mediator interleukin-1 in the CNS [26]. Basal levels of the enzyme phospholipase A_2 activity in the CNS do not change with peripheral inflammation. The central nervous system response to pain can keep increasing even though the painful stimulus from the injured tissue remains steady. This ''wind-up'' phenomenon in deep dorsal neurons can dramatically increase the injured person's sensitivity to the pain.

Tissue injury with local release of inflammatory mediators produces an acute discharge in the sensory afferents innervating the injured or inflamed tissue. Activation of the polymodal nociceptive afferents (C fibers) depolarizes populations of dorsal horn wide dynamic range (WDR) neurons that project supraspinally. This output in turn evokes a supraspinally organized escape behavior. The hot plate test (thermal stimulus to the paw) or the local injection of an irritant such as formalin or capsaicin where the unconditioned stimulus evokes a somatotopically directed behavior (e.g. withdrawal or licking) are behavioral paradigms believed to reflect this underlying mechanism [27].

Electrophysiological studies have shown that the persistent activation of spinal WDR neurons by small, but not large, afferents, will lead to a progressive enhancement of the WDR response to each subsequent input, and an increase in the dimensions of the peripheral receptive field to which the spinal neuron will respond [28].

The neurotrophins are a family of growth promoting proteins that are essential for the generation and survival of nerve cells during development, neurotrophins promote growth of small sensory neurons and stimulate the regeneration of damaged nerve fibers They consist of four members, nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5).

Nerve growth factor and brain-derived neurotrophic factor modulate the activity of a sodium channel (NaN) that is preferentially expressed in pain signaling neurons that innervate the body (spinal cord dorsal root ganglion neurons) and face (trigeminal neurons). Transection of a nerve fiber (axotomy) results in an increased production of inflammatory cytokines and induces marked changes in the expression of sodium channels within the sensory neurons [29]. Following axotomy the density of slow (tetrodotoxin-resistant) sodium currents decrease and a rapidly repriming sodium current appears. The altered expression of sodium channels leads to abnormal excitability in the sensory neurons [30]. Studies have shown that these changes in sodium channel expression following axotomy may be attributed at least in part to the loss of retrogradely transported nerve growth factor [31].

In addition to effects on sodium channels, there is a large reduction in potassium current subtypes following nerve transection and neuroma formation. Studies have shown that direct application of nerve growth factor to the injured nerve can prevent these changes [32].

Abnormal development of sensory-sympathetic connections follow nerve injury, and contribute to the hyperalgesia (abnormally severe pain) and allodynia (pain due to normally innocuous stimuli). These abnormal connections between sympathetic and sensory neurons arise in part due to sprouting of sympathetic axons. Studies have shown that sympathetic axons invade spinal cord dorsal root ganglia (DRG) following nerve injury, and activity in the resulting pericellular axonal 'baskets' may underlie painful sympathetic-sensory coupling [33]. Sympathetic sprouting into the DRG may be stimulated by neurotrophins such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5). Local tissue inflammation can also result in pain hypersensitivity in neighboring uninjured tissue (secondary hyperalgesia) by spread and diffusion of the excess inflammatory mediators that have been produced as well as by an increase in nerve excitability in the spinal cord (central sensitization). This can result in a syndrome comprising diffuse muscle pain and spasm, joint pain, fever, lethargy and anorexia.

The complex interaction of inflammatory mediators

The inflammatory mediators interact in a complex way to induce, enhance and propagate persistent pain. There are also natural anti-inflammatory

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mediators produced by the body to simmer down inflammation and the inflammatory response.

Interleukin-1β

This is a potent pain-generating mediator. Interleukin-1 β stimulates inflammatory mediators prostaglandin E_2 (PGE_2), cyclooxygenase-2 (COX-2) and matrix metalloproteases (MMPs) production [34,35] interleukin-1 β is a significant catalyst in cartilage damage. It induces the loss of proteoglycans, prevents the formation of the cartilage matrix [36] and prevents the proper maintenance of cartilage. Interleukin-1 β is a significant catalyst in bone resorption. It stimulates osteoclasts cells involved in the resorption and removal of bone [34,37,36].

Interleukin-6

This is another potent pain-generating inflammatory mediator. IL-6 is one of a family of cytokines collectively termed ''the interleukin-6-type cytokines''. The cytokines which make up this family are IL-6, leukemia inhibitory factor (LIF), oncostatin-M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), and interleukin-11 [38,39]. IL-6 is involved in a myriad of biologic processes, perhaps explaining its long list of synonyms (B-cell stimulatory factor-2, B cell differentiation factor, T cell-replacing factor, interferon-β_2, 26-kDa protein, hybridoma growth factor, interleukin hybridoma plasmacytoma factor 1, plasmacytoma growth factor, hepatocyte-stimulating factor, macrophage granulocyte-inducing factor 2, cytotoxic T cell differentiation factor, thrombopoietin) [40]. Among its many functions, IL-6 plays an active role in inflammation, immunology, bone metabolism, reproduction, arthritis, neoplasia, and aging. IL-6 expression is regulated by a variety of factors, including steroidal hormones, at both the transcriptional and post-transcriptional levels. IL-6 appears to play an important role in bone metabolism through induction of osteoclastogenesis and osteoclast activity [41,42]. In rodents, inhibition of IL-6 gene expression is in part responsible for estrogen's ability to inhibit osteoclast activation [43–46]. These findings are further supported by the observation that IL-6 gene knockout mice are protected from cancellous bone loss associated with ovariectomy. IL-6 neutralizing antibody also blocks bone resorption induced by a variety of agents including TNF [47]. In addition to increasing osteoclast numbers, IL-6 has been shown to stimulate bone resorption in rat long bones [48] and fetal mouse metacarpi [49], calvaria [50], and bone resorption pit assays [51,52]. Although it is not clear that IL-6 alone is sufficient to mediate these activities [53], these data demonstrate the importance of IL-6 in enhancing osteoclastic activity thus providing a mechanism for IL-6 promoting osteoporosis. IL-1 β may induce IL-6 production in human osteoblasts (MG-63 cells) by the following sequence of steps: IL-1 β-induced COX-2 activation, prostaglandin E(2) production, and PGE receptor-1 (EP-1 receptor) signaling prior to IL-6 production [54]. IL-6 functions in a wide variety of other systems including the reproductive system by participating in the menstrual cycle [55] and spermatogenesis, skin proliferation, megakaryocytopoiesis, macrophage differentiation, and neural cell differentiation and proliferation [56]. A significant amount of interleukin-6 is produced in the rat spinal cord following peripheral nerve injury that results in pain behaviors suggestive of neuropathic pain. These spinal IL-6 levels correlated directly with the mechanical allodynia intensity following nerve injury [57]. During times of stress or inflammation IL-6 levels are increased. Inflammatory joint disease, particularly rheumatoid arthritis [58], is associated with increased synovial fluid levels of IL-6 [59].

Interleukin-6 is the primary chemical mediator involved in bone inflammation and bone pain. Interleukin-6 increases the activity of the osteoclasts and leads to excessive breakdown of bone, leakage of calcium into the blood, loss of bone density and bone inflammation, which is associated with bone pain. Interleukin-6 production is increased by interleukin-1β and tumor necrosis factor α. Patients with rheumatoid arthritis (RA) develop both generalized and periarticular osteoporosis. Both of them are believed to be associated with increased production of inflammatory cytokines (TNF-α, IL-1 β, IL-6) and increased formation and activation of osteoclasts [60].

Interleukin-8

This is a pain-generating inflammatory mediator. In one study of patients with post-herpetic neuralgia, the patients who received methylprednisolone, had interleukin-8 concentrations decrease by 50%, and this decrease correlated with the duration of neuralgia and with the extent of global pain relief [61] ($P < 0.001$ for both comparisons).

Interleukin-10

This is one of the natural anti-inflammatory cytokines, which also include Interleukin-1 receptor antagonist (IL-1ra), interleukin-4, interleukin-13

and transforming growth factor-β1 (TGF-β1). interleukin-10 (IL-10) is made by immune cells called macrophages during the shut-off stage of the immune response. Interleukin-10 is a potent anti-inflammatory agent, which acts partly by decreasing the production of inflammatory cytokines interleukin-1 β (interleukin-1 β), tumor necrosis factor-α (TNF-α) and inducible nitric oxide synthetase (iNOS), by injured nerves and activated white blood cells, thus decreasing the amount of spinal cord and peripheral nerve damage [62,63]. In rats with spinal cord injury (SCI), a single injection of IL-10 within half an hour resulted in 49% less spinal cord tissue loss than in untreated rats. The researchers observed nerve fibers traveling straight through the spared tissue regions, across the zone of injury. They also reported a decrease in the inflammatory mediator TNF-α, which rises significantly after SCI.

Prostaglandins

These are inflammatory mediators that are released during allergic and inflammatory processes. Phospholipase A2 enzyme, which is present in cell membranes, is stimulated or activated by tissue injury or microbial products. Activation of phospholipase A2 causes the release of arachidonic acid from the cell membrane phospholipid. From here there are two reaction pathways that are catalyzed by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX). These two enzyme pathways compete with one another. The cyclooxygenase enzyme pathway results in the formation of inflammatory mediator prostaglandins and thromboxane. The lipoxygenase enzyme pathway results in the formation of inflammatory mediator leukotriene. Because they are lipid soluble these mediators can easily pass out through cell membranes.

In the cyclooxygenase pathway, the prostaglandins D, E and F plus thromboxane and prostacyclin are made. Thromboxanes are made in platelets and cause constriction of vascular smooth muscle and platelet aggregation. Prostacyclins, produced by blood vessel walls, are antagonistic to thromboxanes as they inhibit platelet aggregation.

Prostaglandins have diverse actions dependent on cell type but are known to generally cause smooth muscle contraction. Prostaglandins sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity. Peripheral inflammation also generates pain hypersensitivity in neighboring uninjured tissue (secondary hyperalgesia), because of increased neuronal excitability in the spinal cord (central sensitization) [64]. Prostaglandins are very potent but are inactivated rapidly in the systemic circulation. Leukotrienes are made in leukocytes and macrophages via the lipoxygenase pathway. They are potent constrictors of the bronchial airways. They are also important in inflammation and hypersensitivity reactions as they increase vascular permeability and attract leukocytes.

Tumor necrosis factor α

Subsequent to tissue injury, this inflammatory mediator is released by macrophages as well as nerve cells. During an inflammatory response, nerve cells communicate with each other by releasing neuro-transmitter glutamate. This process follows activation of a nerve cell receptor called CXCR4 by the inflammatory mediator stromal cell-derived factor 1 (SDF-1). An extraordinary feature of the nerve cell communication is the rapid release of inflammatory mediator tumor necrosis factor-α (TNF-α). Subsequent to release of TNF-α, there is an increase in the formation of inflammatory mediator prostaglandin. Excessive prostaglandin release results in an increased production of neurotransmitter glutamate and an increase in nerve cell communication resulting in a vicious cycle of inflammation. There is excitation of pain receptors and stimulation of the specialized nerves, e.g. C fibers and A-δ fibers that carry pain impulses to the spinal cord and brain.

Studies have established that herniated disk tissue (nucleus pulposus) produces a profound inflammatory reaction with release of inflammatory chemical mediators. Disk tissue applied to nerves may induce a characteristic nerve sheath injury [65—67] increased blood vessel permeability, and blood coagulation. The primary inflammatory mediator implicated in this nerve injury is Tumor necrosis factor-α but other mediators including interleukin 1-β, matrix metalloproteinase, nitric oxide, prostaglandin E2, and interleukin-6 may also participate in the inflammatory reaction. Recent studies have also shown that local application of nucleus pulposus may induce pain-related behavior in rats, particularly hypersensitivity to heat and other features of a neuropathic pain syndrome.

Nitric oxide

This inflammatory mediator is released by macrophages. Other mediators of inflammation such as reactive oxygen products and cytokines, considerably contribute to inflammation and inflammatory pain by causing an increased local production of cyclooxygenase enzyme. The cyclooxygenase enzyme pathway results in the formation of inflamma-

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tory mediator prostaglandins and thromboxane. Concurrently to the increased production of the cyclooxygenase-2 (COX-2) gene, there is increased production of the gene for the enzyme inducible nitric oxide synthetase (iNOS), leading to increased levels of nitric oxide (NO) in inflamed tissues. In these tissues, NO has been shown to contribute to swelling, hyperalgesia (heightened reaction to pain) and pain. NO localized in high amounts in inflamed tissues has been shown to induce pain locally and enhances central as well as peripheral stimuli. Inflammatory NO is thought to be synthesized by the inducible isoform of nitric oxide synthetase (iNOS).

Substance P (sP)

An important early event in the induction of neuropathic pain states is the release of Substance P from injured nerves which then increases local Tumor Necrosis Factor α (TNF-α) production. Substance P and TNF-α then attract and activate immune monocytes and macrophages, and can activate macrophages directly. Substance P effects are selective and Substance P does not stimulate production of interleukin-1, interleukin-3, or interleukin-6. Substance P and the associated increased production of TNF-α has been shown to be critically involved in the pathogenesis of neuropathic pain states. TNF protein and message are then further increased by activated immune macrophages recruited to the injury site several days after the primary injury. TNF-α can evoke spontaneous electrical activity in sensory C and A-δ nerve fibers that results in low-grade pain signal input contributing to central sensitization. Inhibition of macrophage recruitment to the nerve injury site, or pharmacologic interference with TNF-α production has been shown to reduce both the neuropathologic and behavioral manifestations of neuropathic pain states [68].

Gelatinase B or matrix metallo-proteinase 9 (MMP-9)

This enzyme is one of a group of metalloproteinases (which includes collagenase and stromelysin) that are involved in connective tissue breakdown. Normal cells produce MMP-9 in an inactive, or latent form. The enzyme is activated by inflammatory mediators such as TNF-α and interleukin-1 that are released by cells of the immune system (mainly neutrophils but also macrophages and lymphocytes) and transformed cells [69,70]. MMP-9 helps these cells migrate through the blood vessels to inflammatory sites or to metastatic sites. Activated, MMP-9 can also degrade collagen in the extra cellular matrix of articular bone and cartilage and is associated with joint inflammation and bony erosions [71]. Consequently, MMP-9 plays a major role in acute and chronic inflammation, in cardiovascular and skin pathologies as well as in cancer metastasis.

Natural suppression of the inflammatory response and gate control

How does the inflammatory response end?

Immune cells produce anti-inflammatory cytokine mediators that help to suppress the inflammatory response and suppress the production of pro-inflammatory cytokines. The natural anti-inflammatory cytokines are Interleukin-1 receptor antagonist (IL-1ra), interleukin-10, interleukin-4, interleukin-13 and transforming growth factor-β1 (TGF-β1). Research has shown that administration of these anti-inflammatory cytokines prevents the development of painful nerve pain that is produced by a naturally occurring irritant protein called Dynorphin A [72].

Under normal circumstances, the inflammatory response should only last for as long as the infection or the tissue injury exists. Once the threat of infection has passed or the injury has healed, the area should return to normal existence.

One of the ways that the inflammatory response ends is by a phenomenon known as ''Apoptosis''.

Most of the time, cells of the body die by being irreparably damaged or by being deprived of nutrients. This is known as Necrotic death. However, cells can also be killed in another way, i.e. by ''committing suicide''. On receipt of a certain chemical signal, most cells of the body can destroy themselves. This is known as Apoptotic death. There are two main ways in which cells can commit Apoptosis. (1) By receiving an Apoptosis signal. When a chemical signal is received that indicates that the cell should kill itself, it does so. (2) By not receiving a ''stay-alive'' signal. Certain cells, once they reach an activated state, are primed to kill themselves automatically within a certain period of time, i.e. to commit Apoptosis, unless instructed otherwise. However, there may be other cells that supply them with a ''stay-alive'' signal, which delays the Apoptosis of the cell. It is only when the primed cell stops receiving this ''stay-alive'' signal that it kills itself.

The immune system employs method two above. The immune cells involved in the inflammatory response, once they become activated, are primed to commit Apoptosis. Helper T cells emit the stay-alive signal, and keep emitting the signal for as long as they recognize foreign antigens or a state

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of injury in the body, thus prolonging the inflammatory response. It is only when the infection or injury has been eradicated, and there is no more foreign antigen that the helper T cells stop emitting the stay-alive signal, thus allowing the cells involved in the inflammatory response to die off.

If foreign antigen is not eradicated from the body or the injury has not healed, or the helper T cells do not recognize that fact, or if the immune cells receive the stay-alive signal from another source, then chronic inflammation may develop.

The final pathway for the natural suppression of the inflammatory response is in the spinal cord where there is a complex network of inhibitory neurons ('gate control') that is driven by descending projections from brain stem sites. These inhibitory neurons act to dampen and counteract the spinal cord hyper excitability produced by tissue or nerve injury. Thus, peripherally evoked pain impulses pass through a filtering process involving inhibitory transmitters γ-aminobutyric acid (GABA), glycine and enkephalins. The activity of these substances in the spinal cord usually attenuates and limits the duration of pain. In the case of persistent pain, there is evidence of pathological reduction of the supraspinal inhibitory actions in combination with ectopic afferent input in damaged nerves [73].

Discussion

The various biochemical mediators of inflammation (cytokines, neuropeptides, growth factors and neurotransmitters) are present in differing amounts in all pain syndromes and are responsible for the pain experience. Every pain syndrome has a unique inflammatory profile with a predominance of certain inflammatory mediators (see Table 1 which lists the biochemical mediators for which drugs are currently available). This inflammatory profile is not static but dynamic and variable in the same patient and from one patient to another. The inflammatory profile is derived from the original injury or trauma and modified by ongoing injuries and aggravations including iatrogenic interventions. It is important to understand that:

1. Inflammation can exist without structural damage that is visible with our current imaging technology.
2. Structural damage will result in inflammation and the inflammatory response.
3. Inflammation and the inflammatory response will produce structural damage. Classification and treatment of pain syndromes should depend on the complex inflammatory profile and should not be based alone on symptomatology, structural pathology, genetic markers or presence of autoantibodies.

We believe the Sudeck started on the right path when in 1942, he suggested that the signs and symptoms of RSD/CRPS including sympathetic hyperactivity might be provoked by an exaggerated inflammatory response. However, inflammation and the inflammatory response do not just provoke the signs and symptoms of sympathetic hyperactivity. It is our unifying theory that inflammation and the inflammatory response are the biochemical origin of pain.

Our Unifying Theory of Pain encompasses the Gate Theory, provides an explanation for the biochemical origin of Pain and a road map for the treatment of all pain syndromes.

We believe that the definition of Pain by the IASP Subcommittee on Taxonomy is incorrect and wrongly places a focus on the presence of visible tissue damage or a structural pathophysiological cause. The biochemical mediators of inflammation are not visible on MRI or X-rays but can now be measured in the serum and CSF and in the future, we will be able to image the mediators by MRI spectroscopy.

Our theory of Pain explains the biochemical origin of pain that hitherto was unfortunately classified as 'psychogenic' or due to 'maladaptive thought processes'.

The classification of Pain as being peripheral or central in origin is incorrect. Central pain may arise from peripheral injury. This is well documented in patients with neuropathic pain or RSD/CRPS.

The current theories that we are replacing have failed to realize that the mechanisms for wind-up, central sensitization and neuroplasticity are but an integral part of inflammation and the inflammatory process.

Our theory explains that peripheral and central pain including windup and central sensitization are a continuum of inflammation and the inflammatory response. The current theories mention inflammation as a component of the peripheral pain mechanism. None expand on the role of the biochemical mediators in the inflammatory response and none of these theories provide any role for inflammatory mediator blockers or immune modulators in the treatment of pain syndromes. The cellular response to injury is inflammation and the inflammatory response. In our theory, inflammation and the inflammatory response are the biochemical origin and a therapeutic target of both peripheral and central pain.

Every drug that is currently used in the treatment of pain has a mechanism of action that is

Table 1 Inflammatory mediator profile of pain syndromes

Pain syndrome	Inflammatory profile
Arthritis	IL-1 β, IL-6, TNF-α
Back/neck pain (herniated disk)	Prostaglandin, TNF-α, IL-1 β
Bursitis/tendonitis	Prostaglandin, IL-1 β
Fibromyalgia	Substance P, IL-1 β, IL-6
Neuropathic pain	Substance P, Prostaglandin, IL-1 β, IL-6, TNF-α, glutamate
Migraine	Serotonin, substance P
Osteoporosis	IL-6, TNF-α
RSD/CRPS	Substance P, IL-1 β, IL-6, TNF-α, glutamate

Note that these mediators as well as other mediators may be present in varying quantities at varying times in any pain syndrome.

compatible with the principles we hereby outline in our unifying theory of pain.

Principles for treatment of pain syndromes

1. Determination of the inflammatory profile of the pain syndrome.
2. Inhibition or suppression of production of the appropriate inflammatory mediators, e.g. with inflammatory mediator blockers or surgical intervention where appropriate.
3. Inhibition or suppression of neuronal afferent and efferent (motor) transmission, e.g. with anti-seizure drugs or local anesthetic blocks.
4. Modulation of neuronal transmission, e.g. with opioid medication.

Pain syndromes may be treated medically or surgically. The goal is inhibition or suppression of production of the inflammatory mediators. A successful outcome is one that results in less inflammation and thus less pain.

Conclusion

In accordance with our Law of Pain, the origin of all pain is inflammation and the inflammatory response. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. Activation of pain receptors, transmission and modulation of pain signals, neuro plasticity and central sensitization are all one continuum of inflammation and the inflammatory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory response. We are proposing a re-classification and treatment of pain syndromes based upon their inflammatory profile. Treatment of pain syndromes should be based on these principles:

1. Determination of the inflammatory profile of the pain syndrome.
2. Inhibition or suppression of production of the appropriate inflammatory mediators, e.g. with inflammatory mediator blockers or surgical intervention where appropriate.
3. Inhibition or suppression of neuronal afferent and efferent (motor) transmission, e.g. with anti-seizure drugs or local anesthetic blocks.
4. Modulation of neuronal transmission, e.g. with opioid medication.

At the L.A. Pain Clinic, we have successfully treated a variety of pain syndromes by utilizing these principles. This unifying theory of the biochemical origin of pain is compatible with, inclusive of, and unifies existing theories and knowledge of the mechanism of pain including the gate control theory, and theories of pre-emptive analgesia, windup and central sensitization. Our current knowledge is rudimentary and but a beachhead in the vast frontier of inflammation and the inflammatory response. We have medications for only a few of these mediators. More research is needed to understand and develop new drugs and interventions to treat inflammation and the inflammatory response and thus to conquer pain.

References

[1] Sherrington CS. The integrative action of the nervous system. New Haven (CT): Yale University Press; 1906.
[2] Livingstone WK. Pain mechanisms. New York: Macmillan; 1943.
[3] Online Exhibit. Pain and suffering in history — narratives of science, medicine and culture. John C. Liebeskind History of Pain Collection at the Louise M. Darling Biomedical Library, UCLA.

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[4] Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150(699):971–9.
[5] Melzack R. Pain: past present and future. Can J Exp Psychol 1993;47(4):615–29.
[6] Pain terms: a list with definitions and notes on usage. Recommended by the IASP subcommittee on taxonomy pain 1979;6(3):249.
[7] Don Ranney. Anatomy of pain: paper presented at the Ontario inter-urban pain conference, Waterloo; 1996.
[8] Boivie J. Central pain syndromes. In: Campell JN, editor. Pain 1996 – an updated review. Seattle: IASP Press; 1996. p. 23–9.
[9] Dubner R, Basbaum A. Spinal dorsal horn plasticity following tissue or nerve injury. In: Walls PD, Melzack R, editors. Textbook of pain. Edinburgh: Churchill Livingstone; 1994. p. 225–41 [chapter 11].
[10] Jensen TS. Mechanisms of neuropathic pain. In: Campbell JN, editor. Pain – an updated review. Seattle: IASP Press; 1996. p. 7–86.
[11] Merskey HM, Bogduk N. Classification of chronic pain. 2nd ed. Seattle: IASP Press; 1994. p. 211.
[12] Dickenson AH. Editorial I – Gate Control Theory of pain stands the test of time. Brit J Anaesth 2002;88(6):755–7.
[13] McMahon SB, Lewin GR, Wall PD. Central hyperexcitability triggered by noxious inputs. Curr Opin Neurobiol 1993;3(4): 602–10.
[14] Millan MJ. The induction of pain: an integrative review. Prog Neurobiol 1999;57:1–164.
[15] Dickenson AH. Spinal cord pharmacology of pain. Br J Anaesth 1995;75:193–200.
[16] Suzuki R, Dickenson AH. Neuropathic pain: nerves bursting with excitement. Neuroreport 2000;11:R17–21.
[17] Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72(3):403–8.
[18] Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331(2):69–73.
[19] Boos N, Semmer N, Elfering A, Schade V, Gal I, Zanetti M, et al. Natural history of individuals with asymptomatic disc abnormalities in magnetic resonance imaging: predictors of low back pain-related medical consultation and work incapacity. Spine 2000;25(12):1484–92.
[20] Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81–8.
[21] Omoigui S. The biochemical origin of pain: how a new law and new drugs have led to a medical breakthrough in the treatment of persistent pain? Hawthorne (CA): State-of-the-Art Technologies Publishers; 2002.
[22] Dray A. Inflammatory mediators of pain. Br J Anaesth 1995;75(2):125–31.
[23] Goldbach-Mansky Raphaela, Lee Jennifer M, Hoxworth Joseph M, Smith II David, Duray Paul, Schumacher Jr Ralph H, et al. El-Gabalawy active synovial matrix metalloproteinase-2 is associated with radiographic erosions in patients with early synovitis. Arthritis Res 2000;2:145–53.
[24] Zimmermann M. Pathophysiological mechanisms of fibromyalgia. Clin J Pain 1991;7(Suppl. 1):S8–S15.
[25] Sakaue G, Shimaoka M, Fukuoka T, Hiroi T, Inoue T, Hashimoto N, et al. NF-kappa B decoy suppresses cytokine expression and thermal hyperalgesia in a rat neuropathic pain model. Neuroreport 2001;12(10):2079–84.
[26] Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410(6827): 471–5.
[27] Yaksh TL, Lynch III C, Zapol WM, Maze M, Biebuyck JF, Saidman LJ, editors. Anesthesia: biologic foundations. Philadelphia (PA): Lippincott; 1997. p. 685–718.
[28] Dickenson AH, Stanfa LC, Chapman V, Yaksh TL. Anesthesia: biologic foundations. In: Yaksh TL, Lynch III C, Zapol WM, Maze M, Biebuyck JF, Saidman LJ, editors. Philadelphia: Lippincott; 1997. p. 611–24.
[29] Oyelese AA, Rizzo MA, Waxman SG, Kocsis JD. Differential effects of NGF and BDNF on axotomy-induced changes in GABAA receptor-mediated conductance and sodium currents in cutaneous afferent neurons. J Neurophysiol 1997;78:31–42.
[30] Waxman SG. The molecular pathophysiology of pain: abnormal expression of sodium channel genes and its contributions to hyperexcitability in primary sensory neurons. Pain 1999;6:S133–40.
[31] Black JA, Langworthy K, Hinson AW, Dibb-Hajj SD, Waxman SG. NGF has opposing effects on Na+ channel III and SNS gene expression in spinal sensory neurons. NeuroReport 1997;8:2331–5.
[32] Everill B, Kocsis JD. Reduction of potassium currents in identified cutaneous afferent DRG neurons after axotomy. J Neurophysiol 1999;82:700–8.
[33] Ramer MS, Bisby MA. Adrenergic innervation of rat sensory ganglia following proximal or distal painful sciatic neuropathy: distinct mechanisms revealed by anti-NGF treatment. Eur J Neurosci 1999;11(3):837–46.
[34] Horai R, Saijo S, Tanioka H, et al. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. J Exp Med 2000;191:313–20.
[35] Arend WP. Interleukin-1 receptor antagonist. Adv Immunol 1993;54:167–227.
[36] van Lent PLEM, van de Loo FAJ, Holthuysen AEM, van den Bersselaar LAM, Vermeer H, van den Berg WB. Major role for interleukin 1 but not for tumor necrosis factor in early cartilage damage in immune complex arthritis in mice. J Rheumatol 1995;22:2250–8.
[37] Gravallese EM, Goldring SR. Cellular mechanisms and the role of cytokines in bone erosions in rheumatoid arthritis. Arthritis Rheum 2000;43:2143–51.
[38] Sehgal PB, Wang L, Rayanade R, Pan H, Margulies L. In: Mackiewicz A, Koji A, Sehgal PB, editors. Interleukin-6-type cytokines, vol. 762. New York: New York Academy of Sciences; 1995. p. 1–14.
[39] Jon Wanagat Evan T Keller', Ershler WB. Molecular and cellular biology of interleukin-6 and its receptor. Front Biosci 1996;1:d340–57.
[40] Akira S, Taga T, Kishimoto T. Interleukin-6 in biology and medicine. Adv Immunol 1993;54:1–78.
[41] Kurihara N, Bertolini D, Suda T, Akiyama Y, Roodman GD. IL-6 stimulates osteoclast-like multinucleated cell formation in long term human marrow cultures by inducing IL-1 release. J Immunol 1990;144:4226–30.
[42] Tamura T, Udagawa N, Takahashi N, Miyaura C, Tanaka S, Koishihara Y, et al. Soluble interleukin-6 receptor triggers osteoclast formation by interleukin-6. Proc Natl Acad Sci USA 1993;90:11924–8.
[43] Passeri G, Girasole G, Markus T, Abrams JS, Manolagas SC, Jilka RL. 17b-estradiol regulates IL-6 production and osteoclast development in murine calvaria cell cultures. J Bone Miner Res 1991;6:S263.

Please cite this article in press as: Omoigui S, The biochemical origin of pain – Proposing a new law of pain..., Med Hypotheses (2007), doi:10.1016/j.mehy.2006.11.028

[44] Girasole G, Jilka RL, Passeri F, Boswell S, Boder G, Williams DC, et al. 17b-Estradiol inhibits interleukin-6 production by bone marrow-derived stromal cells and osteoblasts in vitro: a potential mechanism for the antiosteoporotic effect of estrogens. J Clin Invest 1992;89:883–91.
[45] Jilka RL, Hangoc C, Girasole G, Passeri G, Williams DC, Abrams JS, et al. Increased osteoclast development after estrogen loss: mediation by interleukin-6. Science 1992;257:88–91.
[46] Miyaura C, Kusano K, Masuzawa T, Chaki O, Onoe Y, Aoyagi M, et al. Endogenous bone resorbing factors in estrogen deficiency: Cooperative effects of IL-1 and IL-6. J Bone Miner Res 1995;10:1365–73.
[47] Black KS, Mundy GR, Garrett IR. Interleukin-6 causes hypercalcemia in vivo, and enhances the bone resorbing potency of interleukin-1 and tumor necrosis factor by two orders of magnitude in vitro. J Bone Miner Res 1991;6:S271.
[48] Greenfield EM, Shaw SM, Gornik SA, Banks MA. Adenyl cyclase and interleukin 6 are downstream effectors of parathyroid hormone resulting in stimulation of bone resorption. J Clin Invest 1995;96:1238–44.
[49] Löwik CWGM, van der Pluijm G, Bloys H, Hoekman K, Bijvoet OL M, Asrden LA, et al. Parathyroid hormone (PTH) and PTH-like protein (PLP) stimulate interleukin-6 production by osteogenic cells: a possible role of interleukin-6 in osteoclastogenesis. Biochem Biophys Res Commun 1989;162:1546–52.
[50] Ishimi Y, Miyaura C, Jin CH, Akatsu T, Abe E, Nakamura Y, et al. IL-6 is produced by osteoblasts and induces bone resorption. J Immunol 1990;145:3297–303.
[51] Roodman GD, Kurihara N, Ohsaki Y, Kukita T, Hosking D, Demulder A, et al. Interleukin-6: a potential autocrine/paracrine factor in Paget's disease of Bone. J Clin Invest 1992;89:46–52.
[52] Ohsaki Y, Takahashi S, Scarcez T, Demulder A, Nishihara T, Williams R, et al. Evidence for an autocrine/paracrine role for interleukin-6 in bone resorption by giant cells from giant cell tumors of bone. Endocrinology 1992;131:2229–34.
[53] De La Mata J, Uy HL, Guise TA, Story B, Boyce BF, Mundy GR, et al. Interleukin-6 enhances hypercalcemia and bone resorption mediated by parathyroid hormone-related protein in vivo. J Clin Invest 1995;95:2846–52.
[54] Takaoka Y, Niwa S, Nagai H. Interleukin-1beta induces interleukin-6 production through the production of prostaglandin E(2) in human osteoblasts, MG-63 cells. J Biochem (Tokyo) 1999;126(3):553–8.
[55] Tabibzadeh S, Kong QF, Babaknia A, May LT. Progressive rise in the expression of interleukin-6 in human endometrium during menstrual cycle is initiated during the implantation window. Mol Hum Reprod 1995;1:2793–9.
[56] Hama T, Miyamoto M, Tsukui H, Nishio C, Hatanaka M. Interleukin-6 as a neurotrophic factor for promoting the survival of cultured basal forebrain cholinergic neurons from postnatal rats. Neurosci Lett 1989;104:340–4.
[57] Arruda JL, Sweitzer S, Rutkowski MD, DeLeo JA. Intrathecal anti-IL-6 antibody and IgG attenuates peripheral nerve injury-induced mechanical allodynia in the rat: possible immune modulation in neuropathic pain. Brain Res 2000;879(1–2):216–25.
[58] Kotake S, Sato K, Kim KJ, Takahashi N, Udagawa N, Nakamura I, et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids form rheumatoid arthritis patients are responsible for osteoclast-like cell formation. J Bone Miner Res 1996;11:88–95.
[59] Houssiau F, Devoglaer JP, Van Damme J, Nagant de Deuxchaisnes C, Van Snick J. Interleukin 6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides. Arthritis Rheum 1988;31:784–8.
[60] Kameda H, Takeuchi T. Osteoporosis associated with rheumatoid arthritis. Nippon Rinsho 2003;61(2):292–8.
[61] Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M, et al. Intrathecal methylprednisolone for intractable postherapetic neuralgia. N Engl J Med 2000;343(21):1514–9.
[62] Bethea JR, Nagashima H, Acosta MC, Briceno C, Gomez F, Marcillo AE, et al. Systemically administered interleukin-10 reduces tumor necrosis factor-alpha production and significantly improves functional recovery following traumatic spinal cord injury in rats. J Neurotrauma 1999;16(10):851–63.
[63] Plunkett JA, Yu CG, Easton JM, Bethea JR, Yezierski RP. Effects of interleukin-10 (IL-10) on pain behavior and gene expression following excitotoxic spinal cord injury in the rat. Exp Neurol 2001;168(1):144–54.
[64] Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410(6827):471–5 [Comment in: Nature 2001;410(6827):425, 427].
[65] Kayama S, Konno S, Olmarker K, Yabuki S, Kikuchi S. Incision of the anulus fibrosis induces nerve root morphologic, vascular, and functional changes. An experimental study. Spine 1996;21:2539–43.
[66] Olmarker K, Rydevik B, Nordborg C. Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. Spine 1993;18:1425–32.
[67] Olmarker K, Myers RR. Pathogenesis of sciatic pain: role of herniated nucleus pulposus and deformation of spinal nerve root and DRG. Pain 1998;78:9–105.
[68] Myers RR, Wagner R, Sorkin LS. Hyperalgesic actions of cytokines on peripheral nerves. In: Watkins LR, Maier SF, editors. Cyokines and pain: progress in inflammation research. Basal: Birkhauser Verlag; 1999. p. 133–58.
[69] Borden P, Heller RA. Transcriptional control of matrix metalloproteinases and the tissue inhibitors of matrix metalloproteinases. Crit Rev Eukaryot Gene Exp 1997;7:159–78.
[70] He C. Molecular mechanism of transcriptional activation of human gelatinase B by proximal promoter. Cancer Lett 1996;106:185–91.
[71] Goldbach-Mansky R, Lee JM, Hoxworth JM, Smith 2nd D, Duray P, Schumacher Jr RH, et al. Active synovial matrix metalloproteinase-2 is associated with radiographic erosions in patients with early synovitis. Arthritis Res 2000;2:145–53.
[72] Laughlin TM, Bethea JR, Yezierski RP, Wilcox GL. Cytokine involvement in dynorphin-induced allodynia. Pain 2000;84(2–3):159–67.
[73] Olgart L. A breakthrough in the research on pain. Survey of the synaptic network may result in new analgesics. Lakartidningen 1997;94(48):4461–6.

Please cite this article in press as: Omoigui S, The biochemical origin of pain – Proposing a new law of pain..., Med Hypotheses (2007), doi:10.1016/j.mehy.2006.11.028