New trends

Chronic non-malignant pelvic-perineal pain: Management by anesthetic blocks. From theory to practice I: Philosophic and pathophysiologic approach

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Abstract: The principles of treatment of chronic painful diseases have to be understood in the context of the sophisticated warning mechanisms that exist between the brain and peripheral tissue. Current pharmacological approach to pain control is essentially based on acute, nociceptive pain, whereas chronic non malignant pain is different, involving a restructuring of both peripheral and central neural networks, leading to wider cerebral integration and interpretation. New plans of treatment must be developed according to recent pathophysiological data on neuropathic pain, neuroinflammation, and neuroplasticity. Interpretation of physical phenomena occurring in human body derived from the mechanical philosophy of Descartes and linked with materialism and reductionism is today an anachronistic point of view. Data derived from fMRI (functional magnetic resonance imaging) suggest that mind and brain are indistinguishable from each other: behavioural influences, experience, motivation, exercise and drugs may modify neuronal circuits and determine a different response to similar inputs. On the other hand, repeated harmful afferent inputs may induce a chronic pathologic condition difficult to resolve by standard medical therapy: systemic opiates may only represent a way to relieve symptoms, but they are unable to offer a definitive resolution of the chronic painful state. Increased intraepithelial innervation by mast cells hyperactivation and microglia activation in nervous system lead to modifications of central circuits; these structural and functional variations may explain allodynia and hyperalgesia, and burning sensations as well. In vivo studies demonstrate morphological changes in the brain, as a consequence of pain perception, and that these may be reversible in nature if a correct treatment, based on these observations, is provided.

Key words: Neuroinflammation; Chronic pelvic pain; Neuroplasticity.

INTRODUCTION

One of the key principles in the treatment of non-malignant chronic pain may be linked to a philosophic view based on a pyramidal mental construction. When considering the wider dimension of pain, one element of significance is time, in particular time elapsed since the onset of pain.

Nociceptive pain reflects an experience in actual time, and its usefulness can be seen as an alarm or warning to a potentially dangerous situation. The classical physiological understanding has been constructed along the lines of an immediate cause-effect relationship: where nociceptive afferent inputs from peripheral structures are centrally processed and indentified as painful stimulation, under normal circumstances. This is known as acute nociceptive pain which can be managed successfully with many available drugs. When the harmful nociceptive sensation ends, the consequence is a cessation of pain. On the contrary, chronic pain may not only be associated with a simple experience of temporal duration, or continuous nociceptive stimulation, but may linked to a restructuring of both peripheral and central networks, involving cerebral representation. Chronic pain may be expressed as a form of neuropathic pain, in particular when burning sensations are present. Current pharmacological therapy is often unsatisfactory and only a token analgesic effect is obtained at a high price in terms of side effects and quality of life. Standard and consolidated scientific pathophysiological opinions are largely ineffective in explicating clinical suffering due to chronic neuropathic pain or producing a satisfactory solution of the difficult problem. On this account a new perspective is required, especially if we want to meet the patients expectations. As is often the case, a more convincing theory can be proposed by reviewing past assumptions in the context of new insights.

Historical synopsis

At the beginning of civilization, medicine was completely linked to the science of nature and to philosophy, as Empedocles or Pythagoras showed in their vision of life. Likewise, Hippocratic medicine was closely related to nature and its philosophic interpretation.

However, in successive centuries medicine evolved independently of the common *natural* origins to become a practical science devoted to the diagnosis and treatment of diseases. Principles of modern medicine came to be based mainly on the mechanical philosophy of Descartes who believed that man kind (as other living things) is nothing more than complicated machines or artifacts, composed of parts lacking any intrinsic relationship to each other. The universe itself was seen as completely reducible to mechanical principles and this view was closely linked with materialism and reductionism: all phenomenon could eventually be explained in terms of "*mechanical laws*", including the correct interpretation of physiology and, consequently, pathophysiology.

Rapid development of technology and biologic discovery of microscopic living structure together with extraordinary advancement of chemistry and biochemistry led medical scientists to the belief that pure knowledge of biological data was sufficient for interpretation of most phenomena involved in diseases. At the same time, mind was considered to be quite different from the brain, and believed to be a fixed and unchangeable network, with the former being similar to software, and the latter to hardware, speaking in terms of a common day analogy.

Yet, to the contrary, demonstration of neuroplasticity in recent data derived from fMRI (functional magnetic resonance imaging)[1,2] suggest that the mind and the brain are indistinguishable from each other: behavioural influences, experience, motivation, exercise, meditation, drugs, to mention a few factors, may modify neuronal circuits and determine a different response to similar inputs. On the other hand, repeated and potentially harmful inputs may induce a chronic pathologic condition which is often intractable by current medical therapy. As a matter of fact, systemic analgesic drugs, including opiates, may relieve symptoms of chronic pain but are unable to structurally modify the peripheral and central network generating and maintaining persistent pain.

1. Peripheral concerns

Several experimental studies on biochemical and histological characteristics of peripheral tissues, such as vaginal mucosa, removed for examination from patients affected by intractable vaginal/perineal pain, have demonstrated the presence of higher density of nerve fiber endings, many of which are very close to skin surface, when compared with specimens obtained from normal cases (Figure 1).

This reduced distance of nerve fiber endings and skin and the significant increase of total number of nerve fibers, may be clinically related to allodynia and hyperalgesia in chronic neuropathic pain syndromes, such as vulvodynia[3]. It is not difficult to speculate that such an increased peripheral nervous system network might be seen as a protective mechanism warning of potentially harmful and dangerous inputs from skin, even if no injury is really occurring.

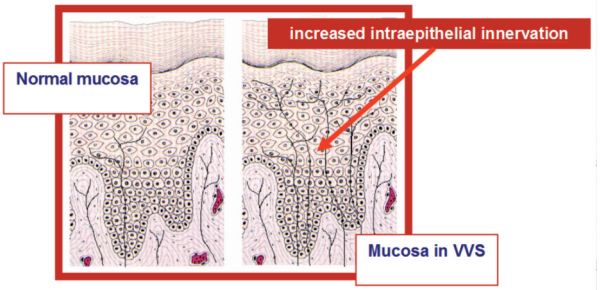

Figure 1. - Schematic representation of histological microscopic view of vulvar mucosa affected by chronic vulvodynia (VVS)(on the right) in comparison with a normal mucosa (on the left). Increased intraepitelial innervation is clearly exemplified.[3]

Recent data[4-7] shows that aggressive factors, such as continuous mechanical peripheral irritants or infections, can induce hyperactivation of mast cells and microglia (Figure 2): where both types of cells are predominantly involved as active immune system, the responses to hostile biological incursions and the weapons of defense consist of mediators that include histamine, tryptase, serotonin, proteoglycans, prostanoids, and newly formed lipid mediators (eicosanoids) as thromboxane, prostaglandins D2, leukotriene C4, platelet-activating factor; and in addition, cytokines such as eosinophil chemotactic factor and TNFalpha, as well as nerve growth factor (NGF).

When irritants such as chemical substances, repetitive mechanical trauma or infective factors become chronic, mast cells becomes up-regulated. Their production of NGF promotes nerve pain fibers proliferation, which correlates with hyperalgesia, and superficial sensitivity causing "allodynia", in which the perception shifts from tactile to burning pain.[8,9] This explains why pain becomes persistent in spite of every current non-invasive treatment. When nerves begin to function in an abnormal fashion, and signal pain is present without any apparent peripheral damage, the term "neuropathic pain" may be applicable. This pain also describes the process by which the neurons involved in pain transmission are converted from a state of normal sensitivity to one in which they are hypersensitive.

Mast cells are heterogeneous and exhibit site-specific adaptations induced by micro-environmental triggers that lead to selective expression of potential mast cell characteristics. This flexibility of phenotype has important functional implications and allows these cells to adapt to organ or tissue specific roles, which range from providing innate defense against bacteria and protection from venom of bees and snakes to participating in multiple aspects of adaptive

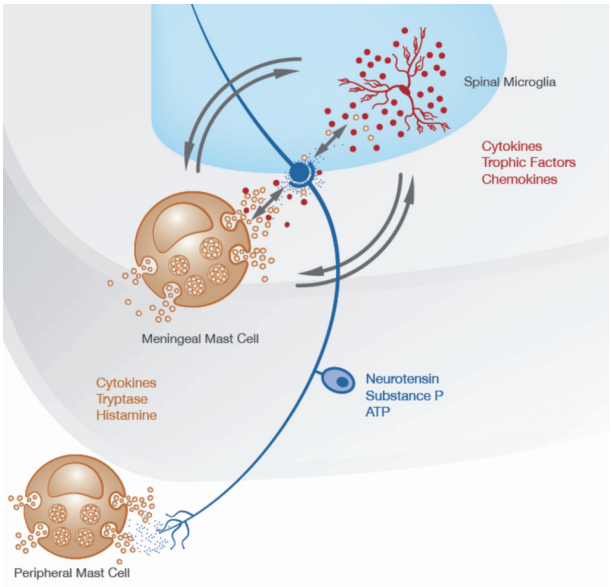

Figure 2. - Interactions between mast cells and microglia in persistent pain. Mast cells may interact with microglia indirectly via primary somatosensory neurons, or directly by interaction of mediators-receptors expressed by both cellular types. Mast cells and microglia directly interact with pain neurons and significantly influence functioning of somatosensory system promoting develop of chronic pain.

immune response such as antigen presentation and lymphocyte recruitment to draining lymph nodes, as well as down-regulation of immune response.

Mast cells and sensory neurons are important sites for the sustained action of NGF in producing increased sensitivity during inflammatory state.[10]

A key characteristic of mast cells is their ability to span across the division between nervous and immune system. Indeed, much of our understanding of the bi-directional relationship between the nervous and immune system has come from the study of mast cell-nerve interaction. In fact, morphologic as well as functional associations between mast cell and nerves are found in most tissues and these interactions are involved in the regulation of physiologic homeostatic processes as well in disease mechanisms.[11]

Mast cells are immunocytes with secretive functions that act locally to maintain tissue integrity, local haemodynamics and tissue homeostatic mechanism; their pathogenic roles have been extended to include not only allergic diseases and helminthiasis, but also autoimmune diseases, such as rheumatoid arthritis, allograft tolerance, angiogenesis in tissue repair and carcinogenesis.

Mast cells can be activated by a range of neurotransmitters and, reciprocally, a variety of molecules synthesized and released by mast cells can influence neuronal activity, while mast cell-derived cytokines, including TNF and NGF, lower the threshold for activation of local neurons and promote nerve fiber growth.

There is anatomical evidence for mast cell association with peripheral myelinated and unmyelinated nerves. In addition, while mast cells are distributed widely in connective tissue and at mucosal surfaces they are concentrated at interfaces with the external environment, near blood vessels, lymphatic vessels, and nerve fibers. Positioned at these strategic locations, mast cells act as sentinels of immune system, protecting against invading microbes and signaling environmental changes.

Close proximity of mast cells and neurons containing Substance P (SP), Calcitonin Gene-Related Peptide (CGRP) or both has been described in a variety of anatomical sites

such as gastrointestinal tract, trachea, peripheral lung, urinary bladder and several other tissues. These interactions underlie the classic inflammatory axon reflex where antigen or noxious stimuli causes the activation of sensory c-fibers that in turn, through collateral axons, provide an efferent route for the lateral spread of inflammatory signals. Mast cells may be implicated in inflammatory processes in which degranulation is generally not observed: in fact, ultrastructural alterations of their electron-dense granular core, frequently seen, are indicative of secretion but without degranulation, a process termed piece-meal degranulation, in which even molecules stored within the same granule can be separately secreted. For example, serotonin can be released independently from histamine as well as differential synthesis and release of prostaglandins and leukotrienes have also been reported.

Also, mast cell granules carry a variety of bioactive chemicals which may be transferred to adjacent cells of the immune system and neurons in a process of transgranulation via mast cell pseudopodia.[12]

Mast cells posses a remarkable degree of plasticity and apparently even fully differentiated CTMC (Connective-Tissue type Mast Cells) will transform their phenotype to that of MMC (Mucosal Mast Cells) if transplanted into a mucosal environment. Alternatively, mast cell may be classified based on the protease content of secretive granules that differ between tissues. Tryptase is present in all cell sybtypes and can activate cells through cleavage of protease-activated receptors (PAR). Protease regulate neurons and glia in the central nervous system by cleaving PAR.

Furthermore, tryptase has been shown to cleave PAR2 on primary spinal afferent neurons, which causes the release of SP and CGRP and sensitization of co-expressed TRP (Transient Receptor Potential) channels that together cause plasma extravasation, amplification of inflammation and consequent hyperalgesia. Mast cell proteases have also been demonstrated to degrade nerve products by enzymatic cleavage and thus may act to limit the effects of neurogenic signals.

NGF receptors found on mast cells act as autoreceptors regulating NGF synthesis and release. NGF has also been shown to induce degranulation and histamine release from mast cells. The NGF produced by mast cells can act on neurons by inducing the expression of neuropeptideds and lowering the threshold of firing. Indeed, mast cell proliferation in response to NGF is partially mediated by mast cell degranulation.

Interestingly, NGF can exhibit anti-inflammatory as well as proinflammatory effects depending on the situation and the concentration of the growth factor.

As far as sensory neuropeptides are concerned, peripheral sensory nerves involved in pain, touch and temperature perception regulate inflammation locally through the release of a number of neuropeptides including SP, CGRP and vasoactive intestinal peptide (VIP). The stimulation of peripheral nerves results in local inflammation (vasodilation, vascular leakiness, edema and pain). In particular, SP, an 11 aminoacid peptide that acts principally at the neurokin-1 (NK-1) G-protein coupled receptor, and is generally regarded as pro-inflammatory, stimulates secretion of TNF, IL-1, Il-2 and IL-6 from macrophages and T lymphocytes. SP is perhaps the best-known and most studied neurotransmitter in relation to mast cell activation. In addition to degranulation, SP also promotes production of lipid mediators such as prostaglandins D2 and leukotriene C4 and proinflammatory cytokines including TNF and Il-6. Low concentration of SP incapable of inducing mediator release can increase cellular responsiveness to subsequent stimulus and so "prime" the cell to degranulate with reapplication of a subthreshold dose. It is important to note that not all mast cells are activated by SP and expression of functional NK-1 receptors appears to be dependent on microenvironmental factors. Neuron-derived SP induces degranulation in associated mast cells and association of mast cells to neurons for several days can change phenotypic and functional characteristics of the mast cell. This functional relationship between mast cells and SP containing sensory nerves is thought to play role in the stress induced exacerbation of a number of inflammatory conditions.

CGRP is a 37 aminoacid neuropeptide that mediates its effects through G-protein coupled receptors and is expressed predominantly in sensor nerve fibers. CGRP can directly activate mast cells and this suggests that this neuropeptide has a role in the functional relationship between mast cells and neuronal network. On the other hand, NGF induces sympathetic postganglionic neural sprouting to encase primary sensory neurons within the dorsal root ganglion (DRG), as well as trkA (tropomyosin receptor kinase A) expressing nociceptor sprouting causing hyperinnervation of the epidermis. Therefore, there is convincing evidence of an NGF-mediated nerve-fiber sprouting.[13] Now, NGF, which is produced from a variety of tissues, in the skin can be released by basal keratinocytes and in hollow viscera by epithelial cells as well as by mast cells, macrophages, and Schwan cells. NGF levels are increased in inflamed tissues and the release of IL-1beta, PDGF (Platelet derived growth factor), TNFalpha, IL-4 and TGF-beta, in turn stimulates a further production of NGF. NGF and its high- and low-affinity receptors, tropomyosin-related kinase receptor (trk)A and trkB, respectively, are up-regulated in the skin of allergic patients. NGF may thereby modulate itch perception in inflamed skin as well as neurogenic inflammation by supporting nerve-sprouting. An experimental study has identified a clear and understandable mechanism by which the blockade of NGF or TrkA could produce a preventive analgesic effect in a chronic pain state.[14] In fact, peripherally produced NGF is involved in the development and maintenance of nociceptive sensory neuron sensitivity and an up-regulation of NGF is responsible for alterations in pain-related behaviour. Therefore, blockade of NGF production and/or its action may be a new strategy to avoid nerve hypersensitivity due to inflammation, and possibly a novel non-canonical anti-inflammatory analgesic treatment.[15]

There are many independent lines of evidence that indicate bidirectional cross-talk between mast cells and sensory nerves, suggesting that in certain instances they can be functionally and anatomically assembled within certain tissues with mast cells being co-localized with nerve fibers expressing SP and CGRP and/or other peptidergic mediators, releasing histamine, serotonin, and tryptase, thus leading to sensory nerves activation and contributing to neurogenic inflammatory reactions. Above all, mast cells by releasing NGF and TNFalpha, are thought to regulate sensory nerves development, degeneration, and regeneration. Therefore, both mast cells and sensory nerves have been suggested to co-orchestrate a variety of physiological and pathological processes, such as wounds healing and stress responses and to contribute to the pathogenesis of inflammatory and autoimmune diseases.

The anatomical and pathophysiological role of mast and neuronal cells in inflamed tissues are important to remember as potential mechanisms involved in neuroinflammation associated with chronic pain syndromes.

2. Central concerns

When a patient is suffering from a form of chronic pain such as the Chronic Pelvic Pain Syndrome (CPPS),[16] not on-

ly are peripheral tissues involved, but also the central nervous system is strongly implicated.

If the pivotal role of mast cells in response to harmful peripheral stimulation is well established, as per the discussion above, the significance of microglia has also been highlighted as a parallel reaction within the central nervous system (CNS) in response to potential threats to the body.

The preservation of the species is one of the most important innate mechanism which the brain continuously tries to maintain pursuing it as a vital goal.

Several clinical studies and investigations have shown the benefits that hypnosis may produce in surgical patients demonstrating positive effects on emotional distress, pain, medication consumption and improved physiological parameters in recovery.[17] Hypnosis decreases the probability of new analgesic requests by distraction mechanisms which cause mainly reduction in frontal lobes activity. Anticipation of pain may in itself induce changes in brain nociceptive networks and hypnotic suggestions may modulate pain-related cortical activity by focusing or diverting away attention.[18] On the other hand, anticipation of a virtual pain can induce a real painful feeling of about 40% of the pain felt under direct nociceptive application.

Of course, every real or potential situation in which the fight or flight response is activated, the sympathetic system is alerted in order to quickly and adequately respond by finding a satisfactory solution to the actual problem. Acute pain is one the fundamental factor activating a rapid sympathetic response, both conscious and unconscious (i.e. automatically produced). In these conditions, pain acts as an alarm bell, and is useful in minimizing tissue damage. But, if the harmful situation is continuously re-occurring or renewed, the unremitting alarm status leads to a permanent physical disorder and chronic pain itself becomes a chronic self-maintaining disease.

Initially, pain is simply a reaction peripheral mechanism, but in time central mechanisms are progressively engaged. The pathophysiology of peripheral neuropathic pain is therefore based both on abnormal peripheral inputs and abnormal central processing.[19] Peripheral mechanisms include (a) nociceptors sensitization, (b) spontaneous activation of primary afferent fibres ectopically firing from the site of lesion and, (c) "neurogenic inflammation", as discussed earlier. The latter is characterized by algogenic substances released which may move backwards along the sensory nerves by the up-regulation and release of mast cells through neurogenic activation and de-granulation. A close interaction between mast cells and pain nerve fibers, with reciprocal potentiation, seems to be a key feature of peripheral neuropathic pain. As far as the central mechanisms are concerned, *wind up* phenomenon occurs due to the progressive increase of cellular firing following repeated identical stimuli.[20] Furthermore, spinal and supraspinal propagation of abnormal local changes caused by peripheral nerve lesions leads to aberrant central elaboration. In the biochemical field, excitatory aminoacids and NMDA (n-methyl-d-aspartate) receptors play a crucial role in the genesis of chronic neuropathic pain.

The dorsal horn of the spinal cord appears to play an important role at the beginning and in the maintenance of neuropathic pain. Tsuda et al[21] have demonstrated that activation of p38 mitogen-activated protein kinase (p38MAPK) in hyperactive microglia of the dorsal horn contributes to pain hypersensitivity in response to innocuous stimuli (tactile allodynia) following peripheral nerve injury. In fact, intrathecal administration of a specific p38MAPK inhibitor (SB203580) suppresses the development of nerve injury-induced tactile allodynia. Other investigations[22] show that galectin-1 (one of the endogenous galactoside-binding lectins, involved in a variety of functions, such as neurite outgrowth, synaptic connectivity, cell proliferation and apoptosis) increases in the dorsal horn at 1 to 2 weeks after axotomy and that intrathecal administration of anti-recombinant human galectin-1 antibody partially but significantly attenuates the upregulation of substance P receptor (SPR) in the spinal dorsal horn and the mechanical hypersensitivity induced by the peripheral nerve injury. These data suggest that endogenous galectin-1 may support neuropathic pain after the peripheral nerve injury at least partly by increasing SPR in the dorsal horn.

Tissue injury of almost any kind, but especially peripheral or central neural tissue injury, can lead to long-lasting spinal and supraspinal re-organization that includes the forebrain.[23] These forebrain changes may be adaptive and facilitate functional recovery, or they may be maladaptive, preventing or prolonging the painful condition.[24] In an experimental model of heat allodynia, functional brain imaging showed that: (a) the forebrain activity during heat allodynia is different from that during normal heat pain, and (b) during heat allodynia, specific cortical areas, in the dorsolateral prefrontal cortex, can attenuate specific components of the pain experience, by reducing the functional connectivity of subcortical pathways. The forebrain of patients with chronic neuropathic pain may undergo pathologically induced changes that can impair the clinical response to all forms of treatment. Therefore, chronic pain can be understood not only as an altered functional state, but also as a consequence of altered neuronal plasticity.

In addition, Baliki et al[25] used in vivo structural MRI to compare global, local, and architectural changes in gray matter properties in patients suffering from chronic back pain (CBP), complex regional pain syndrome (CRPS) and knee osteoarthritis (OA), relative to healthy controls. They found that different chronic pain types exhibit unique anatomical 'brain signatures'. Only the CBP group showed altered whole-brain gray matter volume, while regional gray matter density was distinct for each group. Voxel-wise comparison of gray matter density showed that the impact on the extent of chronicity of pain was localized to a common set of regions across all conditions. When gray matter density was examined for large regions approximating Brodmann areas, it exhibited unique large-scale distribution networks for each group. Also, they showed that brain reorganization with chronic pain was 6 times slower and twice as large in CBP by comparison to CRPS. The results show an exuberance of anatomical brain reorganization peculiar to each condition and as such reflects the unique maladaptive physiology of different types of chronic pain conditions.

Brain reorganization associated with chronic pain has also been investigated by comparing morphology between chronic pain and healthy controls. Altered brain morphology was shown in many pain conditions, including fibromyalgia,[26-27] complex regional pain syndrome (CRPS),[28] osteoarthritis,[29] irritable bowel syndrome,[30] headaches,[31] chronic vulvar pain,[32] and in women suffering from menstrual pains.[33]

However, many of the gray matter changes observed in chronic pain patients subside with cessation of pain.[34,35] In addition, it has been shown that the observed morphological differences in chronic pain conditions often correlate to the duration of pain related suffering as well as its intensity,[36] thus suggesting that the brain morphological changes may be reversible in nature and are a consequence of pain perception.

Chronic pain impacts morphology of whole brain structures, and treatment, in order to be effective, must recognize the importance of cerebral reorganization, but, above all, must induce the return to the *status quo ante*, i.e. to the preexisting peripheral and central anatomical and functional neural state.

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INVITED COMMENTS: Chronic Pelvic Pain

It's always a thought-provoking exercise to read a paper on the topic of non-malignant chronic pain. Pain is, and always has been, a complex phenomenon to study and to manage. It has been one of the most misunderstood conditions in modern medicine. However, with time and increasingly sophisticated scientific methods of study, our understanding of chronic pain continues to evolve and new findings compel us to review existing protocols of pain management.

Many clinicians intuitively or by training associate pain with tissue trauma and search for pathology that may shed insight into its existence, but, unlike acute pain, most chronic pain syndromes exist in the absence of pathology that can explain their actuality and severity. In chronic pain there is no relationship or proportionality between pathology and pain. This gives rise to a fundamental question in the study of chronic pain, "where is the pain coming from?" Some clinicians have been inclined to suggest that the pain is psychological in nature or "in the head." Though patients feel slighted by such an aspersion, with recent scientific evidence, there could be another reasons why this proposition may yet be true. The rationale for such a hypothesis, while ironical is quite rational. Working definitions of pain identify it as a sensory and emotional experience, however, a growing number of investigators are of the view that it is a disease process shaped more by genetically inherited traits that predispose individuals to increased pain sensitivity than by peripheral factors. Greater emphasis is being placed on the neuroplasticity of the central nervous system, than on body regions where pain is reported. Rather then focusing on region specific syndromes greater emphasis is placed on centrally driven variables that give rise to hyperalgesic states. As the focus shifts from "peripheral" to "central" mechanisms of pain current protocols of pain management are being called into question.

There are many other anomalies in the study of pain. Unlike various physiological functions of the body, regulated by well-defined sites within each system, there is no localized center that accounts for the regulation of pain. From overviews of major pain syndromes chronic pain is difficult to localize and its origins are often unrelated to the regions where it is experienced. Furthermore, chronic pain being a very individual and subjective experience is difficult to quantify and appears to be fashioned by a range of unique and peculiar variables that necessitate individualized approach to management. As an anaesthetist, Dr Ezio Vincenti examines recent findings based on functional magnetic resonance imaging studies, and highlights the interaction between peripheral and central factors, in particular the interaction between the immune and nervous systems and how these impact on the temporal experience of pain. His conclusions rightly emphasizes the need to shift from the historically mechanical perspective to one, which recognizes the intrinsic relationship between mind and body and enables the use of more effective pharmaceutical pain management protocols. As a clinician I would agree with such a proposition, but would emphasize that therapies focusing on the peripheral mechanisms of pain, such as dysfunctional pelvic muscle states, can also be an effective means of impacting and modulating the centrally-driven mechanisms of pain.

Whenever I listen to patient account of their symptoms and the various pain management strategies trialed I'm often reminded of a cogent statement made by a former chronic pain specialist, Daniel Brookoff, who in the context of chronic urogenital pain foresaw the need for a shift in our concepts when he said,

> "One factor that has made urogenital pain disorders particularly difficult to manage is that many of the traditional treatments – ranging from caustic bladder instillations to short-lived denervation procedures to the excision of the presumptively "diseased" end-organs in the form of unnecessary hysterectomies, prostatectomies, and cystectomies - often do more to ingrain and accelerate these painful conditions than to relieve them. Recent insights from the study of these syndromes suggest that we should be directing our treatments toward modulating the neurologic generators of nociception and dysfunction rather than removing or destroying the visceral organs that were once presumed to be responsible for chronic pelvic pain or the nerves that innervate them."

He then goes on to say,

> "I tell my patients with chronic urogenital pain that I have two equally important obligations to them. On the one hand, I must make sure that they get all the treatments they need, but on the other hand, I must often expend just as much effort to make sure that they are not subjected to treatments they do not need."

In concluding he makes an important statement that so poignantly reflects the point made by Dr Vincenti of a need to change our thinking on chronic pain,

> "One of the most difficult tasks that we as physicians need to accomplish in reconsidering our treatment of painful urogenital disorders involves the "unlearning" of long-held beliefs rather than the acquisition of new knowledge. Many of the assumptions we have carried with us for years… have contributed to the iatrogenic propagation of pelvic pain syndromes."[1]

If we are to assist our patients and meet their expectation, there is much that needs to be unlearnt before new findings and new insights into the mechanisms of chronic pain can be meaningful applied. It is then, and only then, that our approach to pain management will be truly evidence based and individualized.

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This is a wonderful erudite summary of the history, philosophy, physiology, microanatomy and biochemistry of pelvic pain. It was interesting to read about altered brain morphology shown in many pelvic pain conditions and how many of the gray matter changes observed in chronic pain patients subside with cessation of pain, suggesting that the brain's morphological changes may be reversible in nature and are a consequence of pain perception.

My perspective is confined to female pelvic pain which we have found can be cured in up to 80% of cases with a posterior sling.

This direction (outlined more fully below) has been ignored by Cochrane review,[1] which confines current approaches to treatment to counseling, psychotherapy, laparoscopic uterine nerve ablation, presacral neurectomy, hysterectomy with or without removal of the ovaries. A neuromodulation reports 40% improvement in pelvic pain symptoms and 26%improvement in their urinary symptoms (UDI-6) at 15 months mean follow-up.[2]

The European Association of Urology (EAU) Guideline Group for CPPS[3] presented a broad classification and a large and complex algorithm for pelvic pain, diagnosis of which was essentially organ based.

In 1993, Ulmsten and I reported CPP as a referred pain caused by laxity in the uterosacral ligaments, as part of the posterior fornix syndrome (urgency, nocturia, abnormal bladder emptying).[4] As such, it was potentially curable , along with other posterior fornix syndrome symptoms, by reinforcing the uterosacral ligaments.

The pelvic pain component of this syndrome was addressed more systematically a 1996 study which included diagnostic laparoscopy: *"In its acute state of manifestation, the pain was invariably severe, frequently one-sided, situated low in the right or left iliac fossa, usually relieved on lying down, frequently relieved by insertion of a ring pessary, reproducible on palpating the cervix and displacing it posteriorly, patient in supine position. Although the pain was chronic in nature, it varied considerably from time to time as concerns intensity. There was a history of deep dyspareunia which only occurred on deep penetration, or in specific positions. Frequently the patient complained of a constant lower abdominal pain the day after intercourse. Half the patients complained of low sacral backache which was also cured by the surgery. Six patients, 2 of whom were nulliparous, entered the study through Emergency".*[5]

85% of patients were cured at 3 months (falling to 70% at 12 months) by plication of the uterosacral ligaments (USL). Further deterioration in cure rate over time necessitated insertion of a posterior sling in the position of the USLs, whose effectiveness was later confirmed by other investigators.

Farnsworth[6] reports the following cure rates at 12 months: apical prolapse 87%; urgency 80%; nocturia 81%; chronic pelvic pain 79%, in a cohort of 90 patients who had undergone prior hysterectomy. Goeschen[7] reported 71% cure of pelvic pain in 59 patients.

A practical test for USL causation. Gently insert the posterior blade of a bivalve vaginal speculum into the posterior fornix of the vagina. Frequently this relieves the pain.[8] Alternatively, a large menstrual pessary inserted into the back part of the vagina can also alleviate CPP.

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