Physiology and Pharmacology of Neuropathic Pain States

Tony L. Yaksh, Ph.D.

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A. Introduction.

Following soft tissue injury and inflammation, pain is a common symptom, the disappearance of which is considered to be a consequence of the healing process. In contrast, over time after a variety of injuries to the peripheral nerve, the animal and human will often reflect the appearance of a constellation of pain events. Frequent components of this evolving syndrome being i) on going incidences of sharp-shooting sensations referred to the peripheral distribution of the injured nerve and ii) abnormal painful sensations in response to light tactile stimulation of the peripheral body surface. This latter phenomenon is referred to as tactile allodynia. This composite of sensory events was first formally recognized by Silas Weir Mitchell in the 1860's. The psychophysics of this state clearly emphasize that the pain is evoked by the activation of low threshold mechano-receptors (AB afferents). This ability of light touch evoking this anomalous pain state is *de facto* evidence that the peripheral nerve injury has led to a reorganization of central processing, i.e. it is not a simple case of a peripheral sensitization of otherwise high threshold afferents. In addition to these behavioral changes, the neuropathic pain condition may display other contrasting anomalies, including on occasion, an ameliorating effect of sympathectomy of the afflicted limb and an attenuated responsiveness to analgesics such as opiates.

B. Morphological and functional correlates.

The mechanisms underlying this spontaneous pain and the miscoding of low threshold afferent input are not completely understood. As an over view, these events are believed to reflect i) an increase in spontaneous activity in axons in the injured afferent nerve and or the dorsal horn neurons; ii) an exaggerated response of dorsal horn neurons to normally innocuous afferent input.

Following peripheral nerve ligation or section, several events occur signaling long-term changes in peripheral and central processing. Thus, in the periphery after an acute mechanical injury of the peripheral afferent axon, there will be an initial dying back (retrograde chromatolysis) that proceeds for some interval at which time the axon begins to sprout sending growth cones forward. The growth cone frequently fails to make contact with the original target and displays significant proliferation. Collections of these proliferated growth cones form structures called neuromas

1. Spontaneous Pain State.

Under normal conditions, primary afferents show little if any spontaneous activity. Following an acute injury to the nerve, afferent axons will display
i) an initial burst of afferent firing secondary to the injury; ii) silence for an interval of hours to days, iii) followed over time by the development of a measurable level of spontaneous afferent traffic in both myelinated and unmyelinated axons. This ongoing input is believed to provide the source of the afferent activity that leads to spontaneous on going sensation.

a. Site of origin of spontaneous afferent traffic.

Single unit recording from the afferent axon has indicated that the origin of the spontaneous activity in the afferent arises from: the neuroma and from the dorsal root ganglia of the injured axon. Activity in sensory afferents originates after an interval of days to weeks from the lesioned site (neuroma) and from the dorsal root ganglion (DRG) of the injured nerve. (Figure 1).

b. Increased sodium channel expression.

Voltage sensitive sodium channels mediate the conducted potential in myelinated and unmyelinated axons. Cloning has emphasized that there are multiple populations of sodium channels, differing in their current activation properties and structure. Following peripheral injury there is an increase in the expression of sodium channels in the neuroma and the dorsal root ganglia. This increased ionic conductance may result in the increase in spontaneous activity that develops in a sprouting axon.

c. Changes in afferent terminal sensitivity.

The sprouted terminals of the injured afferent axon display a characteristic growth cone that possesses transduction properties that were not possessed by the original axon. These include significant mechanical

and chemical sensitivity. Thus, these spouted endings may have sensitivity to a number of humoral factors, such as prostanoids, catecholamines, and cytokines such as TNFa. This evolving sensitivity is of particular importance given that current data suggests that following local nerve injury there is the release of a variety of cytokines, particularly TNFa which can thus directly activate the nerve and neuroma. In addition, following nerve injury, there is an important sprouting of postganglionic sympathetic efferents that can lead to the local release of catecholamines. This scenario is consistent with the observation that following nerve injury, the postganglionic axons can initiate excitation in the injured axon (see below). These events are believed to contribute to the development of spontaneous afferent traffic after peripheral nerve injury.

2. Evoked Hyperpathia.

The observation that low threshold tactile stimulation yields a pain states has been the subject of considerable interest. As noted, there is considerable agreement that these effects are often mediated by low threshold afferent stimulation. Several underlying mechanisms have been proposed to account for this seemingly anomalous linkage.

a. Dorsal root ganglion cell cross talk.

Following nerve injury, evidence suggests that "cross-talk" develops between afferents in the DRG and in the neuroma (Figure 2). Here, depolarizing currents in one axon would generate a depolarizing voltage in an adjacent quiescent axon. This depolarization would permit activity arising in one axon to drive activity in a second. In this manner, it is hypothesized that a large low threshold afferent would drive activity in an adjacent high threshold afferent. Alternatively, dorsal root ganglion cells in vitro can release a variety of transmitters and express excitatory receptors.

b. Afferent sprouting

Under normal circumstances, large myelinated (A?) afferents project into the spinal Rexed Lamina III and deeper (Figure 3). Small afferents (C- fibers) tend to project into spinal laminae II and I. a region consisting mostly of nocisponsive neurons. Following peripheral nerve injury, it has been argued that the central terminals of these myelinated afferents (A-fibers) sprout into lamina II of the spinal cord. With this synaptic reorganization, stimulation of low threshold mechano-receptors (A? fibers) could produce excitation of these neurons and be perceived as painful. The degree to which this sprouting occurs is a point of current discussion and while it appears to occur, it is less prominent than originally reported.

c. Dorsal horn reorganization

Following peripheral nerve injury, a variety of events occur in the dorsal horn, which suggests altered processing wherein the response to low threshold afferent traffic can be exaggerated.

Spinal glutamate release.

There is little doubt that the post-nerve injury pain state is dependent upon an important role of spinal glutamate release (Figure 4). Recent studies have emphasized that after nerve injury there is a significant enhancement in resting spinal glutamate secretion. This release is in accord with i) an increased spontaneous activity in the primary afferent, and ii) with the loss of intrinsic inhibition that may serve to modulate resting glutamate secretion (see below). The physiological significance of this release is emphasized by several convergent observations.

i) Intrathecally delivered glutamate will evoke a powerful tactile allodynia and thermal hyperalgesia though the activation of spinal NMDA and non-NMDA receptors. ii) The spinal delivery of NMDA antagonists has been shown to attenuate the hyperpathic states arising in animal models of nerve injury. NMDA receptor activation mediates an important facilitation in neuronal excitability. In addition, the NMDA receptor is a Calcium ionophore which when activated leads to prominent increases in intracellular calcium. This increased calcium serves to initiate a cascade of events that includes the activation of a variety of enzymes (kinases) some of which phosphorylate membrane proteins (e.g. calcium channels and the NMDA receptors) while others such as the mitogen activated kinases (MAP kinases) serve to mediate intracellular signaling that leads to the altered expression of a variety of proteins and peptides (e.g. cyclooxygenase and dynorphin). This downstream nuclear action is believed to herald long term and persistent changes in function. A variety of factors have been shown to enhance glutamate release. Two examples will be further discussed below.

Non-neuronal cells and nerve injury.
Following nerve injury (section or compression), it has been shown that there is a significant increase in activation of spinal microglia and astrocytes in the spinal segments receiving input from the injured nerves (Figure 5). Of particular interest is that in the face of pathology such as bone cancer, such up regulation has been clearly shown. Astrocytes are activated by a variety of neurotransmitters and growth factors. While the origin of this activation is not clear, it will lead to an increased spinal expression of COX /NOS / Glutamate transporters / Proteinases. Such biochemical components have been previously shown to play an important role in the facilitated state.

Loss of intrinsic GABAergic / glycinergic inhibitory control.
In the spinal dorsal horn there are a large number of small interneurons that contain and release GABA and glycine. GABA / glycinergic terminals are frequently presynaptic to the large central afferent terminal complexes and form reciprocal synapses, while GABAergic axosomatic connections on spinothalamic cells have also been identified (Figure 6). According these amino acids normally exert an important tonic or evoked inhibitory control over the activity of A? primary afferent terminals and second order neurons in the spinal dorsal horn. The relevance of this intrinsic inhibition to pain processing is provided by the observation that the simple intrathecal delivery of GABA A receptor or glycine receptor antagonists will lead to a powerful behaviorally defined tactile allodynia. Similarly, animals genetically lacking glycine-binding sites often display a high level of spinal hyper-excitability. These observations led to consideration that following nerve injury that there may be a loss of GABAergic neurons. While there are data that do support a loss of such GABAergic neurons, the loss appears to be minimal. Recent observations now suggest a second alternative. After nerve injury, spinal neurons regress to a neonatal phenotype in which GABA-A activation becomes excitatory. This excitatory effect is secondary to a reduced activity of the membrane C1 transporter which changes the reversal current for the C1 conductance. Here increasing membrane C1 conductance as occurs with GABA-A receptor activation results in membrane depolarization.

Spinal dynorphin.
Following peripheral nerve injury, there is a wide variety of changes in the expression of dorsal horn factors. One such example is the increased expression of the peptide dynorphin. Nerve injury leads to a prominent increase in spinal dynorphin expression. Intrathecal delivery of dynorphin can initiate the concurrent release of spinal glutamate and a potent tactile allodynia; the latter effect is reversed by NMDA antagonists.

3. Sympathetic dependency of nerve injury pain state.
After peripheral nerve injury, there is an increased innervation of the peripheral neuroma by post-ganglionic sympathetic terminals. More recently, it has been show that there is an in growth of post-ganglionic sympathetic terminals into the dorsal root ganglia of the injured axons. These post- ganglionic fibers form baskets of terminals Neuroma around the ganglion cells. Several properties of this innervation are interesting (Figure 7).
i) They invest all size ganglion cells, but particularly Type A (large ganglion cells); ii) the innervations occurs principally in the DRG ipsilateral to the lesion, but In addition, there is innervation of the contralateral ganglion cell and iii) Stimulation of the ventral roots of the segments, containing the pre-ganglionic efferents, will produce activity in the sensory axon by an interaction either at the peripheral terminal at the site of injury or by an interaction at the level of the DRG. This excitation is blocked by intravenous phentolamine, emphasizing an adrenergic effect.

C. Pharmacology of nerve injury pain state.
The ability of low threshold stimuli to evoke pain behavior after peripheral nerve injury has been a subject of interest and led to the development of several models of nerve injury. Three commonly used models are the ones developed by Bennett and Xie (4 loose ligatures around the sciatic nerve), Shir and Seltzer (hemiligation of sciatic nerve) and by Kim and Chung (tight ligation of the L5/6 nerves just peripheral to the ganglion (Figure 8). The Bennett model is widely used to study thermal hyperalgesia, while the Chung displays a well-defined tactile allodynia. These models are of particular importance as they have been widely employed to investigate the pharmacology of the pain states associated with the particular nerve injury .As indicated in the accompanying table, spinal actions of drugs in ameliorating these pain states vary somewhat between the models. Of particular interest, both models show particular to NMDA antagonists alpha 2 agonists and anticonvulsants such as gabapentin and low doses of intravenous lidocaine. In contrast, while the thermal hyperalgesia in the Bennett model is sensitive to intrathecal morphine, the tactile

allodynia in the Chung models is not. This difference may reflect the fact that large low threshold afferents are not thought to possess opiate receptors and hence that terminal excitability is not altered by opiates.

CONCLUDING COMMENTS.

The above comments reflect upon a number of mechanisms that have been shown to occur after nerve injury .It is not at present clear to what degree some or all of these mechanisms are brought into play in any given post-nerve-injury state in humans. It is clear, for example, that not all post-nerve injury states possess sensitivity to sympathetic blockade. Moreover, some neuropathic states are opiate-sensitive and some are not. Similarly, it seems certain that after nerve injury a degree of sensitivity to NMDA receptor blockade may occur in humans as well as animals. Such observations provide support for the idea that at least some human states have mechanisms that appear in the preclinical model.

• Physiological Comments of Several Clinical Pain States
Tony L. Yaksh, Ph.D.
Pain.com

A. Postoperative Pain
B. Causalgia
C. Headache
D. Arthritis
E. Cancer Pain
1. Peripheral acute terminal activation
2. Tumor compression
3. Central mechanisms

A. Postoperative pain

The generation of local tissue injury will induce a wide range of effects, all of which mechanistically have been previously discussed.

In short, the injury itself generates an acute mechanical stimulus and a barrage of small afferent input. This barrage evokes activity in dorsal horn neurons that eventually project supraspinally. As long as the mechanical distortion occurs, the barrage will continue. In addition, the injury itself leads to the formation of active tissue factors that serve to both stimulate and sensitize the peripheral nerve endings.

The generation of a progressive discharge in the small afferents leads to a progressive sensitization of the dorsal horn neuron. This facilitation induced by the local activation of NMDA/NK1 receptors will result in an exaggerated response to subsequent input. In addition, the sensitization is associated with an increase in the receptive fields of the affected spinal neurons. The sensitization evoked by NMDA receptor activation also causes the cell to display an augmented response to low threshold input. Jointly, these effects will account for the evolution of a state of hyperesthesia and hyperalgesia.

A second important aspect of these events is that they occur in the presence of any small afferent input and processes of generating the facilitated state will occur under surgical planes of volatile anesthetics. In contrast, opiates and local anesthetics can markedly diminish this augmented sensitization and accordingly diminish the magnitude of the postoperative pain state.

B. Causalgia
Bennett, 1991; Campbell et al., 1992; Sato and Perl, 1991; Yaksh et al., 1992; Woolf et al., 1992; Todd and Sullivan, 1990; Yaksh, 1988; McLachlan et al., 1993

Following nerve injury, there is an intial degeneration of the injured axon followed by efforts to sprout. This intervention leads to a complex physiological state in which several characteristics are noted: i) low threshold afferent input may lead to a pain state, e.g., allodynia; ii) wherein a given noxious stimulus is reported as being more painful than would be anticipated, e.g. hyperalgesia; iii) a spontaneous sensation of dysaesthesia or pain; iv) dependency of all or part of the above phenomena on intact sympathetic terminal

function. In these conditions, the patient may develop states of prominent, spontaneous pains, as well as marked allodynia and hyperalgesia. There are several general mechanisms that may be associated with these marked changes.

1. Peripheral changes in terminal sensitivity.

The spouted terminals display a characteristic growth cone that possesses transduction properties that were not possessed by the original axon. These include significant mechanical and chemical sensitivity. Thus, these spouted endings may have sensitivity to a number of humoral factors, such as prostanoids, catecholamines, and cytokines. In addition, it is known that these regenerating terminals have significant densities of Na/K/Ca channels. This increased ionic capacitance may be responsible for the increase in spontaneous discharges that develop in the sprouting axon.

2. Central changes.

As reviewed previously, peripheral nerve lesions can give rise to changes in central spinal function and morphology.

i) Increased spontaneously activity in peripheral afferents will induce states of central facilitation, as reviewed in the preceding sections. Importantly, many of these activity-driven pain states can be "turned off" by blocking the triggering stimulus.

ii) There is a prominent increase in certain neuropeptides including galanin and VIP and a reduction in sP and CGRP. Early immediate genes such as c-FOS have been shown to display significant increases.

iii) Following peripheral nerve unjury, large diameter myelinated axons sprout from their site of termination in Lamina III or deeper into the upper lamina, a region normally only innervated by small diameter, high threshold afferents. Thus, low threshold afferents gain access to a pool of dorsal horn neurons involved in nociceptive processing that were originally accessed only by high threshold afferent input.

iv) After nerve injury, dark staining neurons are prevalent. While the specific significance of these changes is not understood, the clear alteration in biochemistry and morphology indicates the likelihood of a maintained alteration in spinal processing. As noted previously, the encoding of sensory information, particularly that of low threshold afferents, is strongly controlled by an active modulatory process involving GABA and glycine receptors. Loss of those dorsal horn interneurons may lead to a failure of such regulation of input and give rise to the pain states as associated with nerve injury.

v) The peripheral nerve injury leads to the elaboration of active factors that are transported centrally to evoke an increase in sympathetic tone at several levels of the injured afferent, including the dorsal root ganglia, where type-A cell bodies show an enhanced innervation by postganglionic sympathetic terminals. Increased sympathetic activity has been shown to increase activity originating in DRG cells.

The mechanisms whereby peripheral nerve injury leads to these central changes are not understood. However, several probable mechanisms have been proposed to account for these central alterations.

i) Increased afferent input, leading to neurodegenerative changes. Such mechanisms have been proposed to be mediated in part of by spinal NMDA receptors.

ii) Alterations in the central transport of growth factors. Peripheral nerve lesions obtund axon transport. The injury frequently gives rise to an increased in endoneurial pressure and this will produce blockade even in uninjured axons. There is a growing appreciation that trophic maintenance of postsynaptic function may involve the transsynaptic movement of factors brought from the distant terminal.

iii) Increased endoneurial pressure. DRG cells are known to be mechanically sensitive and may be influenced by the increased pressure with the perineureal sheath, leading to their activation.

The role of the sympathetic in many pain states is supported by the observation that sympathectomies can attenuate the anomalous pain states. This leads to the differential diagnosis of a "sympathetically dependent" pain. The observation that sympathetic innervtion increases in the ganglion after nerve injury and that afferent activity can be driven by sympthetic stimulation provides some linkage between these efferent and afferent systems and suggests that an overall increase in sympathetic activity per se is not necessary to evoke the activity.

These observations also provide a mechanism for the action of alpha antagonists (phentolamine) and alpha2 agonists (clonidine) that have been reported to be effective after topical or intrathecal delivery. This alpha2 receptors may act presynaptically to reduce sympathetic terminal release. Spinally, alpha2 agonists are known to depress preganglionic sympathetic outflow. In either case, to the degree that pain states were

driven by sympathetic input, these states would be diminished accordingly. Interestingly, this consideration provides some explanation as to why opiates do not exert a potent effect upon the allodynia observed after nerve injury. As summarized above and Figure 1 (See Figure 1), neither mu nor alpha2 agonists alter large afferent input. Yet, alpha2 agonists may reduce allodynia. This differential action may result from the fact that opiates, unlike the alpha2 agents, do not alter sympathetic outflow (as indicated by the lack of effect of spinal opiates on resting blood pressure).

The importance of these mechanisms is relevant to a large number of clinical phenomena. Several common syndromes may be considered as examples:

i) post-thoracotomy pain, where injury to intercostal nerves may lead to long-term pain states;

ii) cancer pain, increasing tumor bulk will lead to a progressive distortion of the sensory axon; radiation/chemical therapeutics ? neuropathy.

iii) Carpal tunnel syndrome where chronic compression may be associated with chronic pain states. Importanlty, characteristic of many of these states is that they are not uniformly sensitive to opiates. The alteration in sensory encoding and the progressive involvement of large diameter afferent input may account for this differential sensitivity.

C. Headache

Headache is a widely used general descriptor that encompasses a large number of clinically defined disorders. Aside from intensity, the varying characteristics of headaches make it clear that the mechanisms of these various pain states will also vary and be differentially sensitive to drugs having different mechanisms of action. Thus, syndromes classified as muscle tension headaches are particularly sensitive to aspirin, while migraines are not. With cluster headaches, syndromes classified as chronic paroxysmal hemicrania are said to be particularly sensitive to NSAIDs, while episodic or chronic cluster headaches are not.

For migraines, the incidence is female (15-18%) > male. They may be preceded by a visual / auditory aura. CBF may display a spreading oligoremia, then hyperemia.

Mechanisms of migraine reflect that the brain is insensate, but the meninges and cranial blood vessels, innervated by trigeminal (Vth nerve) nerve are mechanically sensitive. Early studies by Woolfe (1948) with direct stimulation in lightly anesthetized patients revealed such referred pain when specific intracranial surfaces were stimulated. This emphasizes that the pain likely arises from the meningeal afferents (See Figure 2).

Precipitating event for activating afferents is not certain. Some have argued for arteriovenous shunting leading to a local ischemia.

A correlated intervening variable may be the increased K+e concentration that is associated with cortical spreading depression. The anatomical distribution of the spreading depression correlates with the auditory visual areas of the cortex that would underlie the respective sensory auras (See Figure 4).

An alternative possiblility lies in the potential contribution of local neurogenic inflammatory reactions in the meninges that leads to sensitization of meningeal afferents. This sensitized nerve endings would then be sensitive to the distention of the meningeal blood vessels (much as a tooth pulp afferent becomes sensitized and correlates with a pounding sensation in conjunction with the heart beat) and leads to activation of trigemenial projections (See Figure 5).

In this regard, the meningeal terminals can release sP and CGRP leading to local plasma extravasation and perhaps contributing plasma products to the local sensitization.

A role for 5HT has been postulated in migraine, based on increased urinary 5-HIAA after migraine Ergotamines are effective in headaches and reduce arteriovenous shunting through a 5-HT- agonist like vasoconstriction. More recently, 5-HT1B/D receptors have been found on C-fiber terminal in meninges and 5HT1b/d agonist (sumitriptan) have been shown to reduce sP/CGRP release and will produce a block of migraine (See Table 2).

This mechanism is thought to represent the mechanisms of action of current ergotamine like anti-migraine agents. 5-HT-1 agonists are believed to act preterminally to inhibit activation of C-fibers. In addition, an important component is that during the development of the migraine, there is a large increase in the extracellular K and this leads to a local spreading depression that can physically encompass large areas of the cortical surface. The rate at which the spreading depression spreads has been shown to correspond to the evolving neurological consequence associated with the migraine. As to the initiating stimulus that evokes the above scenario, there is much controversy.

Caffeine abstinence in a person consuming significant quantities of daily caffeine can induce a headache state, and that sudden abstinence is accompanied by significant increases in blood flow in the frontal poles. The headache and changes in blood flow can be abolished by the usbsequent administration of caffeine. Given the widespread consumption of caffeinated beverages, it is generally appreciated that a a significant fraction of the incidence of headaches experienced in the population may be iatrogenic and this may account for ancidence of post-operative headaches.

D. Arthritis

The formation of a degenerative state within a joint leads to the formation of a variety of active factors that can directly stimulate and sensitized peripheral nerve endings. As noted, many axons innervating a joint are not activated by even extreme mechanical stimuli, but will develop low thresholds of activation in the presence of the "inflammatory soup" that appears following joint injury.

There is a growing belief that some of these factors may act through the local stimulation of the sympathetic terminals and inflammatory cells to release agents such as purines, prostanoids and catecholamines. These factors in the inflamed state may thus interact with the free nerve ending that is otherwise extremely high threshold. In addition, this activation of nerve endings will itself give rise to the local release of neuropeptides that yield plasma extravasation and capillary vasodilatation.

All of the mechanisms called into play by repetitive afferent input are also in play in the arthritic state. Thus, hyperalgesia and hyperesthesia would be important components of this pain state (See Table 3).

E. Cancer Pain

1. Peripheral acute terminal activation
Rapidly enlarging tumor burdens can provide acute mechanical stimulation of the periosteum and viscera. The pain relief that can derive from simple debbulking of a tumor is one indication that such mechanical distortion can account for a meaningful component of the tumor pain.

Many tumors also consist of hormone-secreting cells that respond, as do normal endocrine cells to a variety of secretogogues with the release of stimulatory agents. Prominent among these agents are the kinins (notably bradykinin), amines (5-HT; histamine) and the prostaglandins (PGE2).

It is at present not known to what extent these intermediaries play a role as a primary stimulus in the cancer pain state. Of further interest are the hyperalgesic effects of a variety of cytokines (such as IL1??and TNF?). Many of these agents share the property that they can be released upon activation from antigen-presenting cells of the immune system. Elevated levels of such factors in the presence of large tumor bulk can be

anticipated. One well-known example of the role played by these chemical imtermediaries is the surprising efficacy of nonsteroidal anti-inflammatory agents in controlling the pain secondary to bone metastases. Whether the cyclooxygenase products derive from the tumor or reflect an active response of the resident tissue to the tumor is not known.

2. Tumor compression:

A tumor may chronically compress a nerve fiber. Physiological studies have shown that compression of the dorsal root ganglion will give rise to a continuous afferent barrage and could thus represent a source of afferent input from an invading tumor mass. Such compression will lead to several events that could generate traffic on the peripheral nerve:

i) Blockade of endoneurial flow and local nerve ischemia. Over prologned circumstances, it appears that this may engender changes in peripheral nerve function that resembles diabetic neuropathy and is associated with an anomalous pain state.

ii) Local degeneration and the creation of spontaneous generators at local neuromas. In many instances, these neuromas have been shown to be pharmacologically sensitive to a number of the circulating (histamine/5-HT) or released (bradykinin) agents outlined above.

3. Central mechanisms.

There is an appreciation that prolonged injury to a peripheral nerve (like that which might occur with an encroaching tumor) can give rise to pain states that are dysaesthetic in character. The mechanism of the events leading to these anomalous pain states has been discussed previously, but is not specifically known. Following such peripheral nerve injuries, complex delayed transsynaptic changes in morphology and biochemistry in the dorsal horn have been readily identified. Thus there are increases in the expression of the peptides galanin and dynorphin. Such changes appear to reflect major changes in the organization of neuronal processinginthe dorsal horn.

Of particular interest has been the observation that is osteosarcoma, that there is a progressive increase in the activation of astrocytes in spinal cord (Figure 3). These glial elements play an important role in the regulation of parenchymal glutamate levels. Moreover, many of these cells possess glutamate receptors and can be activated by a number of cytokines. A third element of interest is that hey communicate by a spreading excitation mediated by GAP junctions. The net effect is that with osteosarcoma, there maybe persitent alteration in elements contributing to the excitability of spinal processing.

4. Iatrogenic events.

Radiation therapy can yield significant plexopathies that lead to dysaesthetic painstates. This likely reflects the same mechanisms as produced by physical lesions of the peripheral nerve. Many chemotherapeutic agents, such as cis-platinum, AZT and BCNU, among many others, can produce dysaesthetic states, allodynia and, with long-term exposure, neuropathies (Figure 3).

Jointly, the cancer state presents an exceedingly complex syndrome of events that can serve to produce the pain state. It is not surprising that the therapy for cancer pain appears to evolve as the state progresses. It is likely, given the development of neuropathies components that occur secondary to nerve injury (tumor compression, lytic processes, iatrogenic treatments), that opioid requirements may rise, which is consistent with a stronger small afferent activation and the developement of a facilitated state of processing, but the central changes in morphology may lead to the involvement of pain mechanisms that are not modulated efficaciously by opioids. The developement of novel insights into the pharmacology of these alternate states promises alternatives in the treatments for management of this difficult problem (Table4) .

COMMON FACTORS TO REMEMBER
a short list.....

Tissue Injury:	**Acute**
	Hyperalgesia

* **Factor activate /sensitize afferents**

* **C-fibers activate hard-wired circuit > pain report**
* **Persistent small afferent input > facilitation > "hyperalgesia"**

Nerve Injury: **Dysesthesia**
Allodynia
Hyperalgesia

* **Peripheral change: Sprouting**

Neuroma /DRG > SA / transduction
Sympathetic ingrowth

* **Central change: Cell loss / sprouting**

Ascending Projections:
Spinal outflow travels through several X-ed pathways
Anatomical map
Intensity encoded

(WDR Neurons- VB Thalamus
SST Cortex)

Sensory-discriminative

Nonspecific
All or none

(Marginal Neurons-medial
Thalamus - Ant Cingulate Cortex)

Affective-Motivational