Nociceptive Pain
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Nociception

Pain is defined as: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."l Between the site of tissue damage and the perception of pain lies a complex series of electrophysiologic events, collectively termed nociception. Four physiologic processes are involved in nociception2 (Figure 1):

1. *Transduction* denotes the process whereby noxious stimuli are translated into electrical activity at the sensory endings of nerves.

2. *Transmission* refers to the propagation of impulses throughout the sensory nervous system.

3. *Modulation* is the process whereby endogenous analgesic systems can modify nociceptive transmission. These endogenous systems (opioid, serotonergic, and noradrenergic) exhibit their inhibitory influence at the dorsal horn of the spinal cord.

4. *Perception* is the final process whereby transduction, transmission, and modulation interact with theuniqueness of the individual to create the final subjective and emotional experience that we call pain.
The Gate Control Theory of Pain and Balanced Analgesia

Knowledge of the neuroanatomy and the neurophysiology of nocieption forms the basis for a rational approach to the treatment of postoperative pain by manipulation of thediscreet processes involved. The physiologic processes of transduction, transmission, and modulation converge upon and impact upon discharge of nociceptive neurons in the dorsal horn of the spinal cord. Thus, the dorsal horn is the foval point of "gate" for the intergration and modulation of nociception. Nociceptiona is therefore a dynamic process capable of modification at discreet levels by highly specific phamacologic agents (Figure 2). The dorsal horn should be conceptualized as a "gate" that can be "closed" by polyphamacologic manipulation of transduction, transmission, and modulation. the concept of " balanced analgesia" (polypharmacologic intervention of nociception at discreet points in the nociceptive pathways and processes) forms the underlying philosophic tenet for the effective management of acute pain.

The Neuroendocrine Stress Response

The global, linked, endocrinologic, immunologic and inflammatory effects that occur in response to surgery or pain are collectively termed "the stress response" (Table 1). The neuroendocrine response to surgery is largely undesirable and results in reduced body mass and tissue reserve, immunosuppression, increased myocardial oxygen demand with vulnerability to ventricular fibrillation, impaired respiratory function, enhanced risk of thromboembolism, and a general increase in postoperative morbidity and mortality.4-7 While certain modalities may provide profound pain relief, analgesia per se is not necessarily synonymous with abolition of the neuroendocrine stress response to surgery and improved outcome.

Even when provided through a patient-controlled paradigm (PCA), systemic opioids have little effect upon the neuroendocrine stress response.4,8 Despite provision of good analgesia and improvement in certain outcome measures such as pulmonary function, neuraxial (epidural and subarachnoid) opioids have no major effect upon the stress response. Trends toward reductions in the correlates of the stress response do occur, but fall far short of the magnitude and extent seen during continuous administration of epidural local anesthetics.9,10

Numerous clinical trials document that neuraxial administration of local anesthetics (and in particular, epidural anesthesia/analgesia) inhibit the stress response.5,6,11 Peripheral neural blockade (infiltration analgesia, intercostal nerve blocks, interpleural analgesia, ect.) does not. The improved patient outcomes associated with neuraxial regional techniques have been attributed to suppression of the neuroendocrine stress response.5,6,11 The clearest inhibitory effects are seen with operations occurring below the umbilicus. On the other hand, use of epidural anesthesia/analgesia for procedures of the upper abdomen

and thorax have failed to inhibit the stress response (despite provision of excellent analgesia). 10,12 This observation is explained by the persistence of evoked potential responses to somatic stimulation during thoracic epidural anesthesia.13

In summary, there appears to be a relationship between improved outcome after surgery and inhibition of the surgical stress response. Intraoperative neuraxial regional techniques with continuous postoperative epidural analgesia inhibit the neuroendocrine response (at least for lower abdominal and lower extremity surgery) and may be associated with improved outcome.

Tachyphylaxis

While epidural analgesia with local anesthetics is a powerful technique for the elimination of postoperative pain and suppression of the stress response, the phenomenon of tachyphylaxis has been reported during intermittent epidural injections of local anesthetics as well as during continuous epidural infusions. Simply stated, tachyphylaxis signifies the development of acute tolerance. 14 A given dose of local anesthetic becomes less and less effective in providing anesthesia/analgesia with repeated use. In clinical practice, this is observed as: (a) the production of anesthesia/analgesia in fewer and fewer dermatomes after repeated epidural injection (despite administration of identical volumes and identical concentrations of local anesthetic),14 or (b) the regression of a previously stable anesthetic/analgesic dermatomal level during continuous epidural infusion.15 Thus, tachyphylaxis represents a major obstacle to the maintenance of continuous postoperative analgesia with the administration of epidural local anesthetics alone.

Central Hypersensitization ("Wind-Up") and Neuroplasticity

Laboratory experiments have demonstrated increased nociceptive transmission (i.e., an afferent "barrage" of nociceptive impulses to the spinal cord),16-19 and peripheral, 16 and central sensitization of nociceptors17 after peripheral trauma. Such increased afferent input to the spinal cord can expand the receptive fields of dorsal horn neurons18 as well as induce a progressive "wind-up" (central hypersensitization) of dorsal horn neuronal discharge.19 Besides these electrophysiologic changes within the cord, postsynaptic morphologic changes also occur.20

A similar afferent "barrage" with concomitant neuroplastic changes within the cord should also occur in the postoperative period.21 Such enhanced afferent input and hyperexcitability of dorsal horn neurons would be antagonistic to the neural blockade of local anesthetics. Such antagonism would manifest itself as a reduction in sensory analgesia in the most distant parts of the neural blockade where the concentration of local anesthetic and the intensity of blockade are least.22 Such a mechanism (though one of many) would explain the genesis of the phenomenon of tachyphylaxis. What makes this mechanism so compelling is its corollary: nociceptive transmission and attendant neuroplastic changes (and thereby tachyphylaxis itself) could be ablated by combinations of analgesics affecting the individual physiologic processes of nociception (balanced analgesia).

Analgesic Synergy

The continuous epidural coadministration of morphine and bupivacaine for postoperative pain relief (a balanced analgesic regimen) has been found to inhibit the regression of sensory anesthesia/analgesia for protracted periods of time.23 Such combinations are thus able to retard the development of tachyphylaxis to bupivacaine.23 This synergistic effect of morphine has led to the more widespread use of combinations of epidural opioids and local anesthetics in lieu of continuous administration of local anesthetics alone. The benefits of the synergistic interaction between epidural opioids and local anesthetics are multiple: (a) reduction of dosage of individual drugs with a decreased incidence of side effects attributable to opioids and/or local anesthetics, (b) stable hemodynamics, (c) improved intensity of analgesia, (d) prolonged duration of analgesia, (e) equivalent or superior analgesia as compared to epidural local anesthetics or opioids alone, and (f) improved functional ability. 24

Not all studies of the coadministration of epidural local anesthetics and opioids demonstrate all the aforementioned benefits of analgesic synergy, however. Compared with administration of local anesthetics alone, combinations of epidural local anesthetics and opioids have uniformly been shown to enhance

analgesic efficacy. 12,23 In contrast, studies comparing coadministration with administration of epidural opioids alone have demonstrated equivalent analgesia.25,26 However, pain during activity or mobilization was not assessed during any of these studies.

In a double-blind randomized study by Dahl et al,27 combinations of epidural bupivacaine and morphine were shown to provide superior analgesia as compared with epidural morphine during mobilization after abdominal surgery .Only equivalent analgesia was discernible at rest. As defined by Dahl et al,27 different analgesic modalities have differential effects on pain at rest and during mobilization. Future comparisons of analgesic regimens must assess pain during rest and mobilization in order to account for these differential effects.

In summary, while continuous epidural anesthesia/analgesia can inhibit the stress response, tachyphylaxis reduces its prolonged effectiveness. The "balanced" epidural administration of a local anesthetic and opioid will prevent tachyphylaxis as well as achieve analgesic synergy with improvement in the quality and duration of pain relief. The enhanced analgesia commensurate with coadministration of epidural local anesthetics and opioids is best seen during postoperative mobilization.

Preemptive Analgesia

As discussed previously, surgical trauma creates a barrage of nociceptive transmission that induces both electrophysiologic and morphologic changes within the spinal cord. The sequelae of these alterations may long outlast the initial noxious stimulus.28

Enhanced Nociceptive Transmission: The Afferent Barrage and the " Priming " Mechanism

While the patient is unconscious under general anesthesia, the spinal cord still receives massive nociceptive input from the surgical site. On the other hand, regional anesthesia prevents this afferent nociceptive barrage from reaching the spinal cord. By administration of local anesthetic28-3l and/or opioid30-32 before surgical incision, such preemptive analgesia may prevent neuroplastic changes and their attendant physiologic sequelae within the cord. (The question as to the superiority of preemptive administration of local anesthetic versus neuraxial opioids is unresolved at present.)

By inhibition of neuroplastic changes within the cord, the effects of preemptive analgesia may long outlast the initial neural blockade.28-32 Such observations have led to the surgical incision being viewed as a "priming" mechanism.28 Once established in a hyperexcitable state, the spinal cord would respond excessively to afferent input. Analgesic administration prior to surgical incision would prevent the "priming." The electrophysiologic and morphologic neuroplastic changes associated with the afferent barrage would be prevented. Taken to its extreme conclusion, a single preoperative dose of analgesic could conceivably prevent postoperative pain.28 Unfortunately, many practitioners associate preemptive analgesia with such results by definition.

The Role of Balanced Analgesia

What conclusions regarding preemptive analgesia can be drawn from the literature? No current study *definitively* proves its existence in humans. Assuming that preemptive analgesia exists as a phenomenon, do we radically define it as the complete eradication of pain with a single preoperative administration of an analgesic? It is difficult to imagine how the*single* preoperative administration of an analgesic could *completely* eradicate pain over several subsequent days. This is especially true during postoperative mobilization of the patient when nociceptive transmission to the spinal cord is certainly increased. Furthermore, the development of tachyphylaxis during continuous infusions of local anesthetics suggests that continued nociceptive transmission reaches the spinal cord after completion of the surgical procedure.

It is perhaps better to state that some benefit does accrue from the preoperative administration of analgesics, particularly regional anesthetics and neuraxial opioids. Such benefits *may* be the result of prevention of neuroplastic changes within the cord. However, such assertions do not obviate the need for continuation of the analgesic (and more importantly the regional anesthetic/analgesic) into the postoperative

period. Thus, continued afferent barrage of the spinal cord may be prevented by extended use of regional anesthesia/analgesia into the postoperative period.

What is the best analgesic regimen for the management of postoperative pain? Balanced analgesic techniques would seem the obvious answer. The concept of balanced analgesia signifies the administration of agents that selectively affect the physiologic processes involved in nociception: transduction (nonsteroidal anti-inflammatory agents [NSAIDs]), transmission (neuraxial administration of local anesthetics), and modulation (neuraxial administration of opioids). Such combined or balanced analgesic regimens can almost completely eliminate postoperative pain, not only at rest, but also during mobilization27 Balanced analgesic techniques offer the tantalizing possibility of prevention of neuroplastic changes within the cord, prevention of the development of tachyphylaxis, suppression of the neuroendocrine response to pain and the possibility of shortened convalescence. Because of the tangible and potential benefits of the "balanced" administration of epidural local anesthetics and opioids (along with NSAIDs), combinations of such drugs are rapidly becoming the *sine qua non* of effective postoperative analgesic care.

References:

• Reflex Sympathetic Dystrophy, Causalgia and Chronic Regional Pain Syndrome
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INTRODUCTION

Ordinarily acute pain is not treated in a Pain Center simply because usually acute pain is relieved by treating or removing the cause. However, there are certain types of acute pain which should be referred to a Pain Center as early as possible after its onset, because these types of pain, if untreated or allowed to persist, become progressively worse and even self-perpetuating; and thereafter they become difficult, if not impossible, to treat successfully. Such is the case with reflex sympathetic dystrophy and acute herpes zoster. After an all-too-brief window of therapeutic opportunity, both of these syndromes become progressively difficult to treat successfully.

REFLEX SYMPATHETIC DYSTROPHY (COMPLEX REGIONAL PAIN SYNDROME)

Perhaps the group of patients who benefit most from the diagnostic and therapeutic modalities offered by a Pain Center are those patients who ultimately are found to be suffering from one variety or another of reflex sympathetic dystrophy. The causalgias, perhaps the most devastating form of reflex sympathetic dystrophy, must have occurred from the earliest of times; and because these syndromes resulted from injuries of peripheral nerve trunks or of tissues in close proximity to nerve trunks, descriptions of what we now call sympathetically maintained pain almost invariably appeared during or following times of war(1): Ambroise Paré apparently encountered them during his service as surgeon to the Kings of France during the 16th century: It is recorded that Paré was called upon to treat the persistent pain experienced by King Charles IX, pain which was described as "persistent and diffuse"(2). Sir Percivall Pott, in the latter part of the 18th century, mentioned that severe, persistent, and diffuse pain sometimes followed partial, rather than complete severance of a nerve(3). Denmark, in 1813 described some of the features of causalgia in a patient who sustained a musketball wound of the arm, stating that the pain "was of a burning nature ... and so violent as to cause a continual perspiration from [the patient's] face"(4). Sir James Paget in 1864 described fully the "glossy fingers, which are usually tapering, smooth, hairless, almost void of wrinkles, pink ... always associated with distressing and hardly manageable pain and disability" that followed some injuries to the peripheral nerves"(5). In the same year there appeared the monumental treatise by Weir Mitchell and his associates, G.R. Moorehouse and W.W. Keen on *"Gunshot Wounds and Other Injuries of Nerves"*(6). Their description is so classic and vivid that all who participate in pain management should read it at one time of another.

Because very few nerve injuries were seen in civilian practice, little or no mention was made of this syndrome subsequent to Mitchell's classic treatise until the German invasion of France in 1915 left a trail of patients with nerve injuries. Impressed by the similarity of the resultant pain syndromes to those described by Mitchell, René Leriche, the great French surgeon demonstrated that peri-arterial sympathectomy provided dramatic relief in soldiers suffering from causalgia, and after many years of clinical experience and

scientific investigation, Leriche, the modem day French counterpart of Mitchell, wrote his own classic treatise entitled *"The Surgery of Pain"*(7).

While causalgia and/or major reflex sympathetic dystrophy are not as frequent in civilian practice as in military medicine during war times, it is not widely recognized that the so-called minor reflex sympathetic dystrophies are not uncommon in civilian practice, and particularly in the clientele of a large, busy Pain Center. To anyone who has worked for a significant period of time in such a Center, it is readily apparent that a great variety of seemingly unrelated disorders, which in the past have been considered as distinct clinical entities, have strikingly similar clinical features, and are really manifestations of different types or degrees of the same fundamental disturbed physiology. The term usually applied to these conditions, namely, reflex sympathetic dystrophy, is an excellent one, semantically because it denotes the basic, underlying pathophysiologic process: The term "reflex" indicates that all of these syndromes represent a response to a primary, exciting mechanism, whether that mechanism is traumatic (mechanical), medical, infectious, or vascular; the term "sympathetic" indicates the neurological pathway subserving the development and maintenance of these syndromes; and the term "dystrophy" indicates the fact that if allowed to persist, these syndromes uniformly result in trophic changes as a result of the persistent and sometimes self-perpetuating sympathetic response.

As may be seen in Table 1, the reflex sympathetic dystrophies have been divided into major and minor reflex sympathetic dystrophies on the basis of the presence or absence of actual neural injury and/or neurological deficit: The major reflex sympathetic dystrophies, characterized by constant, spontaneous, severe, burning pain, usually follows partial but more rarely complete injury to or severance of a peripheral nerve trunk, and is usually associated with hyperalgesia, hyperesthesia, and hyperpathia, along with vasomotor and sudomotor disturbances that, if allowed to persist, result in trophic changes. The minor reflex sympathetic dystrophies, characterized by similar, though perhaps, less severe symptomatology, are not associated with overt damage to the nerve trunks; and while similar vasomotor, sudomotor, and trophic changes indicate a similar reflex neurovascular disturbance, minor reflex sympathetic dystrophy can be initiated by a multitude of agencies (Table 1) (8). However, whether major or minor, in general, all of these conditions are manifested by a triad of pain, vasomotor disturbances, and trophic changes. The pain is usually constant and diffuse, unlike neuralgia, it does not have a segmental or peripheral nerve distribution, and it is almost invariably associated with hyperesthesia. And while the initiating etiologic factors may be very different, the underlying pathophysiologic mechanisms producing the symptornatology are probably extremely similar, if not identical, in all of these disorders. It appears that the common etiologic denominator is local tissue damage, whatever the agency that produces it might be; and this tissue damage apparently initiates a reflex response which in some way involves the sympathetic nervous system. Furthermore, the pain and the vasomotor disturbances produced, with minor exceptions, are improved, cured, or otherwise dramatically modified by interruption of the involved sympathetic pathways.

Usually the diagnosis of either major or minor causalgia is not a difficult diagnosis to make, both because the initiating mechanism is usually related to obvious trauma, i.e., gunshot or stab wound, with damage to major nerve trunks or to tissues in close proximity to major nerve trunks, and because the resultant syndrome, and particularly the burning pain which gave rise to the term "causalgia", is so characteristic. However, the minor reflex sympathetic dystrophies, not having the same obvious evidence of injury or other etiologic agency, is frequently misdiagnosed, and hence, often mismanaged or neglected. In many of these cases, which are much more common in civilian practice than the major reflex sympathetic dystrophies, the signs and symptoms are so bizarre in their distribution and apparently so unrelated to any precipitating factor that not infrequently the physician doubts there being any organic basis for them whatsoever and tends to attribute them to psychogenic factors. It is to be emphasized that severe degrees of pain and/or vasomotor changes may occur following a seemingly insignificant injury, and in the absence of any infection or other post-traumatic sequelae. As a result, this group of patients is in danger of being misunderstood, discredited, and certainly misdiagnosed; and as a result they are frequently mismanaged or neglected for sufficiently long periods of time that the disease progresses from a completely reversible to an irreversible state.

ETIOLOGY

Reflex sympathetic dystrophy can be produced by any one of the etiologic agencies tabulated in Table 2(8). Trauma secondary to accidental (or intentional) injury is probably the most common cause of reflex sympathetic dystrophy, but what is peculiar about sympathetic dystrophy is that there is no correlation between the severity of the injury and the incidence or severity of the resultant syndrome. In fact, severe trauma causing fractures of long bones and total transections of nerves and blood vessels is rarely followed by reflex sympathetic dystrophy, whereas relatively minor injuries to those regions particularly rich in nerve endings, such as of the skin and pulp of the fingertips, the skin of the hands, and the periarticular structures of the interphalangeal, wrist, and ankle joints (all of which have more nerve endings than have the skin and soft structures of the rest of the extremity), are particularly likely to produce reflex sympathetic dystrophy. In the majority of these cases the precipating injury may be so minor and to the patient so insignificant that he may very well forget it until or unless he is questioned by the physician. On the other hand, while accidental injuries are no doubt the most common cause of reflex sympathetic dystrophy, surgical procedures are in reality "stab wounds", so they may also produce this syndrome, and both the patient and the physician may fail to consider surgery as an etiologic mechanism. Similarly, other therapeutic procedures may produce sufficient trauma to produce reflex sympathetic dystrophy. For example, this syndrome has developed following the application of casts, the accidental injection of drugs into nerves, the accidental extravasation of thiopental, and the (intentional) injection of alcohol into or around a nerve. And finally, a particularly insidious form of trauma is that of "chronic occupational microtrauma" such as may occur with the operation of a pneumatic hammer, sandblaster, or almost any tool which can produce repetitive, minor trauma.

The classic concept of reflex sympathetic dystrophy following some form of external violence has been so firmly established in the past that a history of trauma has always been expected or assumed when manifestations of reflex sympathetic dystrophy become apparent in an extremity. However, in recent years it has become obvious that while injury is, indeed, the most common cause, many visceral, neurologic, vascular and musculoskeletal disorders may also produce reflex sympathetic dystrophy, presumably by producing injury to nerves that initiates a physiopathologic response similar to, if not identical with, that produced by external trauma. Perhaps the most notable disease process which produces reflex sympathetic dystrophy is myocardial infarction, although other thoracic disorders such as pneumonitis, carcinoma, and embolism may be followed several months later by a full blown reflex sympathetic dystrophy of the upper extremity. Similarly, reflex sympathetic dystrophy may develop in patients with lesions of the central nervous system, particularly vascular accidents involving the brain, especially in the thalamic region, with consequent hemiplegia. However, the same syndrome may be produced by tumors and diseases involving the brain, brain stem, or spinal card. In a similar manner, infectious processes may be the inciting agency that results in reflex sympathetic dystrophy, almost without respect to the system involved in the infection; and finally, peripheral vascular diseases such as thrombophlebitis often produce the pain, edema, and vasomotor phenomena typical of reflex sympathetic dystrophy. In short, reflex sympathetic dystrophy can follow virtually every pathological process that can befall the body, regardless of the magnitude of that process.

SYMPTOMATOLOGY

Reflex sympathetic dystrophy is almost invariably manifested early by pain, hyperesthesia, vasomotor, sudomotor, and pilomotor disturbances, increased muscular tone, and later by weakness, atrophy, and trophic changes of the skin and its appendages, and of the muscles, bones, and joints. However, pain is certainly the most prominent and characteristic feature, and while it usually has a burning quality, occasionally the patient may describe it as an aching pain. It may vary in intensity from mild discomfort to excruciating and intolerable pain, such as that which occurs with classical causalgia. The pain is usually continuous, but with recurrent paroxysmal aggravations. Initially the pain is localized to the site of injury, but typically, with time it spreads to involve the entire extremity; and in certain cases, with the progression of time, the pain even spreads beyond the affected extremity to the contralateral or ipsilateral limb, or it may involve the entire side of the body. Hyperesthesia is almost invariably a part of the syndrome; and the patient characteristically protects the involved extremity in one way or another. Not infrequently, a patient will appear for treatment with the involved extremity wrapped in a cloth, cradling the arm in and protecting it with the other arm; and if the examining physician attempts to touch the affected extremity, the patient characteristically withdraws and refuses to allow anything to make contact with it.

Disturbance of vasomotor function is another common denominator of all of the various types of sympathetic dystrophy and may be manifested either by signs of vasoconstriction, which produces cyanosis and coldness of the skin, or vasodilatation, which results in a warm and erythematous extremity. In addition,

not infrequently edema, sudomotor, and pilomotor disturbances, usually hyperhidrosis, are also evident. As the disease progresses the trophic changes develop insidiously and include thin, glossy skin, atrophy of muscles, decalcification of bones, and usually the loss of hair. Usually the patient will also complain of marked weakness of the involved extremity as well.

The severity of the various signs and symptoms vary from patient to patient, and even within the same patient it varies during different phases of the disease. However, common to all cases of sympathetic dystrophy is the fact that the pain and physical signs do not conform to known patterns of nerve distribution, either segmental (dermatomes, myotomes, and sclerotomes) or peripheral (radial nerve, median nerve, ulnar nerve, etc.). Moreover, they have a tendency to spread proximally, so as to involve the entire limb, and occasionally, as stated earlier, to involve the contralateral and/or ipsilateral extremity. Another characteristic of this syndrome is that it continues after the etiologic mechanism has healed or disappeared. And of course, the most important characteristic common to all of these sympathetic dystrophies (important in terms of diagnosis and management) is the fact that the symptoms may be abolished by sympathetic block at an appropriate level; and if carried out prior to the development of irreversibility, repetitive interruption of the sympathetic pathways involved may result in resolution of the entire syndrome.

NATURAL COURSE OF THE DISEASE

The onset of reflex sympathetic dystrophy varies considerably: When provoked by external trauma, the onset is usually rapid, with signs and symptoms occurring several days to several weeks after injury. When the condition follows diseases, the onset may be slower and more insidious, and may remain unrecognized until it becomes an irreversible process. If untreated, reflex sympathetic dystrophy progresses sequentially through three stages, and the presenting signs and symptoms will vary somewhat depending upon the stage at the time the patient is first seen.

The first stage is characterized by constant pain, usually of a burning quality, or moderate severity and localized to the area of injury. The pain is aggravated by movement and is associated with hyperesthesia. The results are localized edema, muscle spasm, and tenderness. At this stage the skin is usually warm, red, and dry because of vasodilatation, although signs of vasoconstriction sometimes predominate. Towards the end of this stage the skin becomes smooth and taut, with decrease in or loss of normal wrinkles and creases. X-rays taken during this stage usually show slight, if any, osteoporosis. In mild cases the first stage lasts only a few weeks, while in severe cases this stage may last as long as six months. It is during this stage that the syndrome may be completely reversed by sympathetic blocks, and if so, the earlier this treatment is instituted, the fewer will be the number of blocks required to provide permanent relief.

The second stage is characterized by spreading of the edema and increasing stiffness of the joints, with muscular wasting. The pain may persist or may gradually decrease in intensity somewhat, The skin is usually moist, cyanotic, and cold; the hair is coarse, and the nails show ridges and are brittle. Signs of atrophy become more prominent; and x-rays begin to reveal patchy osteoporosis. During this stage, which usually lasts three to six months, sympathetic blocks may still be effective in reversing the process; so the longer the syndrome has persisted prior to treatment, the greater the number of blocks that will be required to provide permanent relief.

The third stage is characterized by marked trophic changes which eventually progress to irreversibility. The skin becomes smooth, glossy, and tight; its temperature is lowered; and it appears pale or cyanotic in color. While the hair has become long as this stage is entered, by the end of the third stage, the hair usually has fallen out. The subcutaneous tissues are atrophic, as are the muscles, particularly the interossei. There is extreme weakness and limitation of motion at virtually all of the involved joints, which finally become ankylosed. Contractures of the flexor tendons often occur at this stage, and osteoporosis becomes more advanced; and throughout this time the pain continues, aggravated by weight bearing, movement, and (frequently) by exposure to cold. At this point the syndrome becomes irreversible; and while interruption of sympathetic pathways by blocks may still provide temporary relief, repetitive blocks are no longer effective in terminating the process permanently. At this point neurolysis or surgical sympathectomy may still be effective, though in some cases, even surgery fails to provide prolonged relief, presumably because the pathophysiologic process has become "central".

MECHANISM

In spite of the numerous theories that have been proposed to explain the mechanism giving rise to reflex sympathetic dystrophies, none have succeeded in clarifying this unusual pathophysiologic state. Obviously, the sympathetic nervous system plays a central role in reflex sympathetic dystrophy, but it is not clear whether the pain is due to over activity of sympathetic efferents directly or if the sympathetic efferent over activity is an accompanying event. It appears that early in these syndromes the pain is associated with damage to A-delta and C-fibers. These fibers become "sensitized" or hypersensitive to the circulating catecholamines and light or repetitive touch. This produces spontaneous firing that results in pain through neural circuits that are not fully understood. The basic inexplicable fact is that the sympathetic nerves seem to be the pathways conveying the pain of the sympathetic dystrophies from the site of injury to the central nervous system. The presence of afferent sympathetic fibers would explain the pain and its relief by sympathetic interruption, but unfortunately, no positive proof has been brought forth to demonstrate their existence conclusively.

A concept first proposed almost forty years ago and still adhered to by many today (Figure 1) is that first proposed by Doupe(9) and later supported by Barnes(10) which suggests that as a result of injury, there is destruction of the biophysical insulation of nerves and a consequent anatomic interruption of nerve continuity, resulting in "shunting" or "short circuiting" of impulses (ephaptic transmission). This would result in cross stimulation of somatic afferent (pain) fibers by efferent impulses mediated by the sympathetic nerves within the injured nerve. Experimental work has demonstrated that the phenomenon of "cross talk" at an "artificial synapse" (ephapse) can occur between fibers that have become hypersensitive to the electrical fields of their neighbors. Those who adhere to this concept feel that it explains the clinical features of causalgia: They would point out that there is more or less constant activity in sympathetic fibers in response to the thermo-regulating needs, postural activity, and pilomotor activity of an individual. Moreover, sympathetic impulses to, for example, the palmar sweat glands and digital nerves are greatly increased by emotional stress. Therefore, the pain of sympathetic dystrophy would appear to be spontaneous and constantly present, but it would be greatly aggravated by emotional stress, anxiety, anger, or pain elsewhere in the body, and other peripheral stimuli which produce a physiologic disturbance, all of which are known to increase the pain in the sympathetic dystrophies and to increase efferent sympathetic impulses. Such a mechanism likewise would explain the diffuse character of the pain. Since pain and temperature fibers are thinly myelinated or unmyelinated and therefore have the least amount of insulation, they are particularly susceptible to sympathetic fiber interaction. If this concept were true, it certainly might explain the burning pain, and further, might afford a clear-cut explanation of the relief of the pain of the sympathetic dystrophies produced by sympathetic interruption. Those who do not feel that such a mechanism is valid point out that demyelination is a late consequence of nerve injury and would not explain the immediate occurrence of pain following neural injury. Moreover, the ephapse hypothesis does not explain the complete relief of spontaneous pain, allodynia, and hyperpathia achieved with nerve block distal to the nerve injury, nor that acheived with intravenous guanethicline regional block or with other adrenergic agents that block sympathetic function and terminals of post ganglionic sympathetic fibers. And finally, while these changes might be operative in reflex sympathetic dystrophy associated with peripheral nerve injuries, they are not relevant to those cases in which the nerve is not injured.

Perhaps the most widely accepted theory, and the one which offers the clearest understanding of the dynamics of the reflex sympthetic dystrophies is the theory proposed almost fifty years ago by Livingston(11): An important aspect of Livingston's theory is the concept of the "internuncial pool" originally proposed by Lorente de Nó(12), which indicated that the "connector elements" in the spinal cord, many of which are interposed between afferent and efferent neurons to take part in reflex activity are known as "internuncial neurons", which constitute the "internuncial pool" (Figure 2). This pool consists of an enormous number of interlacing or connecting pathways with numerous opportunities for the conduction of impulses over divergent routes. It does act as a receiving station which determines the routing of sensory impulses and the dispersal of the motor impulses to the periphery. Usually the status of the activity of the pool is such to ensure that the sensations which register into consciousness and the patterns of motor responses will be "normal". However, the activities of this beautifully functioning intricate network can be disturbed by a succession of abnormal sensory impulses, resulting in a state of imbalance. Livingston proposed that in the reflex sympathetic dystrophies an irritative nerve lesion, be it partial severance of a nerve as in classical causalgia, or injury to smaller nerves or nerve endings or in close proximity thereto, serves as a focus of chronic irritation from which an abnormal number of impulses arise and constantly bombard the spinal cord and upset the normal functioning of the internuncial pool (Figure 3-A). The path of the incoming impulses is

so altered by this abnormal activity of the pool that the pattern of excitation, is altered and is interpreted as pain. Moreover, the abnormal activity of the internuncial pool spreads upward, downward, and across to involve other neuron systems and also the anterior and lateral motor horn cells, resulting in excessive skeletal and smooth muscle activity (Figure 3-B). Consequently there is muscle spasm and vasospasm which produce hypoxemia and metabolites that serve to stimulate abnormally the sensory nerve endings and in this way furnish new sources for pain and reflex. This in turn aggravates the central disturbance in the cord thus setting up a vicious cycle. Finally, as the intensity of this process is increased, more and more neuron systems become involved, and the process becomes self-sustaining. There are thus, according to Livingston, three components leading to the establishment of this "vicious cycle": Incoming impulses from the periphery, the internuncial pool activity, and the motor impulses from the lateral and anterior horn cells that are brought within the influence of the pool. Obviously, if an important part of this vicious circle, such as the sympathetic component, can be eliminated, the process may subside and allow the establishment of the normal, physiologic status once again. However, the fact that once the process is firmly established the elimination of either of the peripheral components does not affect the cure, seems to point to the fact that the underlying central pathological activity is the most important component of the established process. Thus Livingston believes that this vicious circle, which sets in motion a chain of events that later has no further dependence on the afferent impulses from the peripheral focus that initiated it, is made possible by the closed self-re-exciting chains of internucial neurons. A single impulse initiates the reverberation of a neuron chain; additional impulses coming in and out of phase or in other positions would tend to disrupt, but continued impulses in the appropriate channels would tend to reinforce and maintain it. Such a reverberating network would constitute the maintained abnormal dynamic state of the spinal cord neurons.

The theory in no way negates the hypothesis of the artificial synapse. In fact, the latter concept compliments Livingston's theory, and both can be used to explain the pathologic process in reflex dystrophy. The obvious flaw in the Livingston theory is its failure to explain adequately the onset, the first and most basic neuropathologic error. In other words, it does not explain why causalgia occurs only occasionally following injuries to nerves and why one individual out of twenty with such injuries develops signs of sympathetic dystrophy while the others do not. This could very well be explained by the occurrence of a neuro-anatomical derrangement anywhere along the nerve which has sympathetic and sensory fibers within it. The ephaptic transmission ("cross talk") would then serve as a constant source of impulses which could produce abnormal activity within the cord. This, in turn, would produce the widespread disturbances that set up a vicious, self-perpetuating cycle.

It is interesting to note that the "Gate Control Theory" of Melzack and Wall(13) as modified later by Melzack and Casey(14) does not disagree with the concept of Livingston, but rather tends to reinforce it. The Melzack-Casey theory essentially states that the perception of pain depends on two factors, the balance between large and small fiber input, and the modulating functions of the higher centers in the brain (the "central biasing" mechanism). If the artificial synapse is a valid physiologic mechanism in reflex sympathetic dystrophy, then clearly the resultant small fiber input would maintain the "gate?' in the open position and enhance the reception of painful stimuli from the periphery. The complimentary extension of the "Gate Control Theory" introduced by Melzack and Casey is that under normal conditions the inhibitory influence, which usually shuts off the stimulus evoked activity in the sensory system as soon as the stimulus is removed, may under certain circumstances be abolished, so that a brief stimulus can result in prolonged spontaneous activity at several synaptic levels of the sensory system.

The model proposed by Melzack(15) to explain the pathophysiology of phantom limb pain can be paraphrased to, perhaps, explain sympathetic dystrophy: "First, there is a portion of the brain stem reticular formation which acts as a 'central biasing mechanism' by excreting a tonic inhibitory influence (bias) on transmission at all synaptic levels of the somatic projection system. When ... the amount of input to the reticular formation is decreased, inhibitory influence from the reticular formation then also decreases. This results in self-sustaining activity at all neural levels, and it can be triggereed repeatedly by the remaining fibers. Pain occurs when the output of the self-sustaining neuron pools reaches a critical level. Because this activity can recruit adjacent neurons, and because it occurs at several levels, trigger zones can spread to distant areas." What it is that decreases the amount of input into the reticular formation awaits additional neurophysiologic research, although Noordenbos(16) has postulated that, as in post herpetic neuralgia, in reflex sympathetic dystrophy there is widespread destruction of large fibers with the preservation of small fibers in a peripheral nerve, and the result of this "fiber dissociation" is predominant small fiber input to the cord.

Roberts(17)has recently reviewed the pathogenesis of reflex sympathetic dystrophy and has proposed an important hypothesis that helps to explain many phenomena observed in this syndrome (Figure 4): First, he pointed out that injury in some peripheral tissue activates unmyelinated C-nociceptors, which in turn activate and sensitize wide-dynamic-range (WDR) neurons in the dorsal horn whose axons ascend to higher centers. This sensitization persists, so that the (WDR) neurons now respond to activity in large-diameter A-mechanoreceptive afferents, which are activated by brushing or light touch. This state produces allodynia. Moreover, these sensitized WDR neurons respond to mechanoreceptive activity initiated by sympathetic efferent action on sensory receptors in the absence of cutaneous stimulation; and thus produce spontaneous pain or what he calls "sympathetically mediated pain" (SMP). While this hypothesis only focuses on central changes in sensitivity to afferent impulses, there is accumulating evidence that such changes takes place: Following peripheral nerve injury, large diameter myelinated axons sprout from their site of termination in lamina three 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. This accounts, at least in part, for the development of allodynia following peripheral nerve injury.

More recently emphasis has been on the peripheral responses to nerve injury, responses which are important since they would appear to indicate possible therapeutic measures that can be instituted to control sympathetically maintained pain. Following nerve injury there is an initial degeneration of the injured axon followed by efforts to sprout. Total axonal disruption is not a prerequisite for the sprout to develop, but the nerve injury does result in a breakdown of the blood-nerve barrier, to facilitate the entry of chemical mediators and/or blockers(19). These sprouts or "growth cones" seek to track down the original neural channels, but that regrowth is often thwarted, leading to local collections of sprout or "neuromas". Wall and his co-workers(20) have demonstrated that many myelinated and unmyelinated afferents that innervate these neuromas can be excited by epinephrine and norepinephrine, thus raising the question whether damaged sensory fibers expressed adrenergic receptors. That such is the case is indicated by the work of Devor and Jänig(21), who demonstrated that the afferent fibers from a neuroma are activated by sympathetic stimulation or by intravenous norepinephrine, and that this activation can be blocked by phentolamine. These findings have led to the hypothesis that nociceptors develop sensitivity to norepinephrine through expression of alpha-1 receptors on their terminals. Indirect mechanisms may include activation of alpha adrenergic receptors on mass cells, leukocytes, and platelets by norepinephrine, which then release chemical mediators (histamine, bradykinin, prostaglandins), which in turn activate nociceptive afferents(22). Subsequent work has demonstrated that norepinephrine released by activity of sympathetic postganglionic axons excites primary afferent neurons by activating alpha-adrenergic receptors.

DIAGNOSIS

The term "reflex sympathetic dystrophy" has been used to encompass an enormous number of pain disorders which appeared to involve some sort of "sympathetic hyperactivity", thus the diagnosis of RSD has been based on the improvement often obtained with sympathetic blocks. It was Bonica, in particular, who advanced nerve blocks as the standard diagnostic and therapeutic modality(18) the various techniques for producing sympathetic blockade (which will be discussed below) have become the mainstay of treatment, but RSD-like cases seen at Pain Centers worldwide yielded evidence of a large number of patients who were difficult to categorize into one or other of the various syndrome patterns, who did not necessarily respond to sympathetic blocks and who evidenced no physiological confirmation of sympathetic hyperactivity, Therefore, in 1993 a Special Consensus Workshop was held in Orlando, Florida to examine the terms RSD, causalgia, SMP, and SIP and to revise the IASP taxonomy. The group felt that the term "RSD" had lost usefulness as a clinical designation because it had been used so indiscriminantly that it was no longer clear what it meant. They felt that the link between nociceptive neurons and postganglionic sympathetic activity was in constant, with sympathetic blocks sometimes altering the syndrome, at least temporarily, and sometimes not at all; and they agreed that all adrenergic mechanisms in some form do appear to be involved in some of these conditions, measurements of sympathetic responses often showed normal results. Finally, they felt that the term "RSD" was used imprecisely, as it referred to changes in soft tissue which may or may not depend upon the sympathetic nervous system, may not be the consequence of a reflex, and may occur late in the disorder.

This group came up with the descriptive term "Complex Regional Pain Syndrome (CRPS)" and they drafted criteria for two types of CRPS, Type I (RSD), and II(Causalgia) (Table 3). The terms were chosen for

the following reasons: The word complex was used to denote the very clinical phenomena found in each group in addition to pain. The regional distribution of the symptoms and findings is the hallmark of these disorders in that they usually affect the distal part of a limb but rarely occur on the torso or face, and they may spread to other body areas. Pain, of course, is the cardinal symptom for the syndrome. It is noteworthy that the role of sympathetic blocks in making the diagnosis is minimized, though each of the categories under the umbrella term CRPS can be divided into patients responsive (SNIP) and unresponsive (SIP) to sympathetic blocks. The sole differentiating criterion between CRPS Type I and CRPS Type II is the presence of a known nerve injury in CRPS Type II.

Whatever terminology is used, the diagnosis of reflex sympathetic dystrophy is established by sympathetic blockade, regardless of whether that is carried out using regional sympathetic nerve blocks or systemic sympatholytic agents:

The classical sympatholytic test is a sympathetic ganglion block using a local anesthetic. However, it is important that the results of the block are interpreted carefully. It is important to know whether the sympathetic blockade is complete, especially in patients who do not experience significant pain relief If a patient does not obtain relief, is it because the mechanism is not sympathetic or because the block has been improperly placed? The efficacy of sympathetic blockade can be objectively assessed by evaluating the effects on sympathetic, sudomotor, and vasoconstrictor function, measuring changes in skin blood flow, skin temperature, and skin resistance. In patients who do obtain pain relief from a sympathetic block, it is important to do a careful sensory examination, since local anesthetic can directly spread to the nearby nerve roots, resulting in a somatic nerve block.

The sympathetic block can be produced by a pharmacologic differential nerve block, whether that be a differential brachial plexus block, differential spinal, or differential epidural. This approach has the advantage of indicating that the sensory block includes the painful area, thus indicating that the sympathetic block is also in the correct location.

The intravenous phentolamine infusion has recently been developed by Raja(23) as an alternative test to block sympathetic activity, and this simple technique avoids some of the potential pitfalls associated with sympathetic blocks. Phentolamine, an alpha-adrenergic blocker, is infused via a peripheral vein, and the patient's pain is evaluated using a visual analog scale as the infusion is continued. While the patient may exhibit the possible problems of hypotension and tachycardia, the test offers minimal risk and certainly very little discomfort to the patient.

Intravenous regional blockade with guanethidine (24) or bretylium (25) can be utilized as a diagnostic tool, though it is a painful technique to carry out in a patient with excruciating pain in the involved extremity. While thermography and a three-phase bone scan have both been advocated as diagnostic tools, their proper role is probably a confirmatory one to indicate the changes in blood flow from the disease and to document the response to sympatholysis.

A diagnosis of reflex sympathetic dystrophy may be obvious if (1) there is a history of recent or remote trauma, infection, or disease; (2) there is persistent, spontaneous pain, which may be burning, aching, or throbbing in character; (3) there are vasomotor and/or sudomotor disturbances; and (4) if there are obvious trophic changes. However, while the "typical" case of reflex sympathetic dystrophy can be diagnosed without difficulty, many "atypical" cases do not present with classical signs and symptoms, but with vague and confusing symptomatology that not infrequently simulates other diseases. For this reason, it is our opinion that if one does not routinely carry out some form of diagnostic sympatholytic procedure as a part of the workup of patients sent to a Pain Center by physicians who "can find no cause for the patient's pain", then the diagnosis will be missed in many patients, they will continue to suffer, and their disease will continue to progress until the stage of irreversibility is achieved(26).

TREATMENT

Clearly, from all that has been written so far, the primary treatment of reflex sympathetic dystrophy is sympatholysis, and traditionally this has been accomplished by sympathetic nerve blocks with local anesthetic. It is beyond the scope of the present discussion to describe in detail the various techniques of sympathetic blockade, but it is important to realize that the response to sympathetic blockade will vary with

the progression of the disease. If sympathetic blocks are carried out early in the disease, very few blocks ,vill be required in order to provide the patient with permanent relief The most important characteristic of the response to sympathetic blocks is that the relief afforded is significantly longer than the expected duration of the local anesthetic block. Typically, each subsequent sympathetic block provides relief that is longer than that provided by the previous block; and as long as this pattern persists, ultimately permanent relief can be achieved by sympathetic blocks with local anesthetics. If however, the relief provided by each subsequent block in a series of blocks is identical, then one must turn to neurolytic blocks or to surgical sympathectomy.

As an alternative to repeated sympathetic blocks, Hannington-Kiff (24) introduced the technique of intravenous regional sympathetic block with parenteral guanethidine. As compared with stellate ganglion blocks, this offers several theoretical advantages: The duration of a sympathetic local anesthetic block, even with bupivacaine, is only a few hours, while the intravenous regional block with guanethidine produces evidence of chemical sympathectomy for 3-5 days, meaning that a block is needed only every third day. The intravenous regional guanethidine block does not require an injection in the neck, which some patients find unpleasant, as does a series of stellate ganglion blocks. On the other hand, patients with acute reflex sympathetic dystrophy may not allow the manipulation of the painful extremity required to exsanguinate the extremity, place a pneumatic tourniquet, insert a needle or catheter into a vein, and inject the guanethidine, whereas they might allow injection into the neck, which is not involved in the pain syndrome being treated. Intravenous regional block may be used in anticoagulated patients, a situation that is a relative contraindication to stellate ganglion block. A major disadvantage of intravenous regional guanethidine is that this agent in the parenteral form is only available in the United States as "an experimental drug". Therefore, it must be approved by the Institutional Review Board of the facility in which it is to be used, and forms must be filed with the FDA for each patient in whom the drug is utilized. The patient must give informed consent for all procedures and must be aware that this is a limited-availability drug for the treatment of reflex sympathetic dystrophy.

The intravenous regional procedure is performed similarly to a local anesthetic Bier block. An I.V. catheter is placed distally in the affected limb and physiologic saline is placed in its bore to prevent clotting. When intravenous access has been secured in the other limb, a tourniquet is applied to the proximal limb (to be treated) and the extremity is exsanguinated, either by elevating it for at least one minute or with an Esmarch bandage. Following exsanguination the tourniquet is inflated to a pressure of 50-100 mm Hg greater than systolic pressure. Twenty to thirty miiligrams of guanethidine is diluted with 0.9% saline to a total volume of 30 ml for the upper limb and 50 ml for the lower limb. After exsuring that the tourniquet is functional and that the exsanguinated limb remains pale, the guanethidine is injected through the catheter. The tourniquet should remain inflated for a minimum of 20 minutes to allow the guanethidine to "fix" to the tissues. The tourniquet is then deflated but is left in place in the arm for 5 minutes in case reinflation is needed. Early tourniquet deflation may produce transient hypertension, because of guanethidine's initial inducement of norepinephrine release from post ganglionic neuronal storage sites. Other possible side effects of the block include orthostatic hypotension, usually prevented by adequate intravenous hydration and bed rest for two hours following the block. There are a few cases in the literature of transient syncopal episodes with apnea after tourniquet release that quickly respond to supportive measures(27) Application of the tourniquet may be painful enough to require sedation of the patient, addition of 20 ml of 0.5% lidocaine to the intravenous regional agent, or pre-exsanguination of a brachial plexus block.

The guanethidine has a biphasic action, initially releasing norepinephrine and then interfering with its re-uptake at the synaptic cleft as well as inhibiting further release. Since sympathetic activity depends on norepinephrine release, chemical sympathectomy results from its blockade. At larger doses this initial norepinephrine release may delay the maximal effect of the treatment until the day after the block. As a practical matter, 5-10 ml of 1% lidocaine should be added to the guanethidine when initially performing intravenous regional blocks in painful conditions such as reflex sympathetic dystrophy. This prevents the transient but intense worsening of pain from guanethidine-induced norepinephrine release. Blocks may be repeated after three days to maintain sympathectomy. Guanethidine has a high affinity for neural sites, and with serial blocks there is accumulation and prolongation of the sympathetic block.

Because of the unavailability of guanethidine, first reserpine (28) and more recently Bretylium has been used for intravenous regional block(25). Bretylium produces a sympathectomy by being taken up and concentrated in adrenergic nerve terminals. With initial uptake of Bretylium there is some displacement and release of norepinephrine as in the case of guanethidine. Bretylium releases much less norepinephrine compared with guanethidine, however. Later it prevents the release of norepinephrine when the adrenergic

nerve terminal is depolarized by an axon potential and sympathectomy results. Bretylium 100-200 mg diluted to a total volume of 30 ml with 0.9% saline is used for upper extremity block. The sympathectomy produced is shorter-lived than with guanethidine. Thus, intravenous regional blocks should be repeated on a daily basis. Potential side effects include postural hypotension. Early tourniquet release before 20 minutes have elapsed may result in nausea and/or vomiting as with rapid intravenous administration of Bretylium for arrhythmias. Until recently, the literature contains contradictory results with intravenous regional bretylium: While Ford et al,.(29) reported sustained relief after a series of IV regional bretylium treatments in four patients, Hanowell(30) and Manchikanti(31) obtained only transient relief in four patients in each of their reports. Ramamurthy et al.,(32) demonstrated that tourniquet induced analgesia could explain the short term relief, but riot the long term relief reported for both bretylium and guanethidine. The efficacy of bretyliurn was recently established by Hord et al.,(25) who carried out a controlled double-blind study comparing Bretylium 1.5 mg/kg in 40 ml of lidocaine 0.5% with 40 ml of 0.5% lidocaine alone in 12 patients with reflex sympathetic dystrophy. The intravenous regional bretyliurn provided a mean of 20.0 (± 17.5) days with more than 30% pain relief (range 3-69 days), whereas the corresponding result after lidocaine alone was 2.7 (± 3.7) days (range 0-12 days), a difference that was statistically and clinically significant.

Obviously, a more desirable form of treatment would be one that provides permanent (or at least long-lasting) relief, so intravenous regional sympatholytics may not ultimately play a significant role in the management of symathetically mediated pain (SMP). Nonetheless, the experience gained with intravenous regional guarethidine and Bretylium has led to the hypothesis that in SMP alpha-1 adrenoreceptors become expressed on primary afferent nociceptors such that the release of norepinephrine by the post-ganglionic sympathetic terminals lead to the activation of the nociceptors and pain. This hypothesis then led to the phentolamine test for SMP as a substitute for diagnostic sympathetic blocks(23) and, indeed, it is this line of thought that led several investigators to explore the use of oral phenoxybenzamine (33) and prazosin(34) for SMP.

A more novel approach was that recently reported by Vanos (35) who administered intravenous regional Ketorolac: to seven patients with reflex sympathetic dystrophy. They administered 60 mg of this agent in 40 ml of saline (or lidocaine to prevent burning), and all patients obtained significant pain relief from I to 45 days; and what is even more important (and hopeful) is the fact that a series of blocks with Ketorolac produced a progressively increasing duration of relief These authors pointed out that Ketorolac acts by inhibiting the enzyme cycloocygenase and reducing prostaglandin synthesis, suggesting that since prostaglandins sensitize pain receptors to both chemical and mechanical stimuli(36-38), reduction of prostaglandins should reduce this sensitivity. As pointed out earlier, according to Roberts' theory(17), A-fiber mechanoreceptors may be activated by sympathetic efferents in the periphery, so one possible mechanism by which this occurs may be the presynaptic release of prostaglandins(39). Ketorolac may also produce benefits by interfering with the vasoconstriction produced by thromboxanes. Reduction in prostaglandin levels may lead to the inhibition of norepinephrine release, and in addition, may result in direct vasodilation. Finally, these investigators suggested that since the mechanism of action of Ketorolac is distinct from that of sympathetic nerve blocks or intravenous regional guanethidine (or Bretylium), it may be especially useful in combination.

When reflex sympathetic dystrophy has become truly irreversible, even neurolytic blocks of the sympathetic or sensory nerves as well as sugical sympathectomy may be without effect. Presumably, at this point, the central component of the disease has become self-perpetuating, and removal of the peripheral component is without effect. An interesting approach to this previously hopeless stage of the disease is that described by Boas(40) recently in which he utilizes a "xylocaine test": He injects 50 mg increments of lidocaine intravenously up to the point where early toxic effects might be anticipated. If the patient obtains pain relief presumably due to the inhibition of spontaneous firing of cells in the central pool, therapeutic benefit might be derived by a series of such injections, and if not, by the use of "anticonvulsant agents" such as Carbamazepine or Gabapentin, either with or without supplemental anti-depressant agents.

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An entrapment neuropathy is a focal mononeuropathy caused by mechanical impingement at a vulnerable anatomical site (1). Peripheral nerves are commonly entrapped while passing through fibrous or osteofibrous tunnels and when traveling over a fibrous or muscular band. The incidence of compressive neuropathies is increased in malnutrition, alcoholism, diabetes, renal failure, or the Guillain-Barre syndrome. In patients with a rare familial disorder consisting of multiple compression neuropathies, a generalized neuropathy has also been documented electrophysiologically and histologically in nerves not subject to pressure (2). Experimental support for the concept that generalized neuropathies is predisposed to compressive neuropathies also comes from the observation that guinea pigs kept in cages with mesh wire floors develop localized distal demyelination. These changes occur more quickly than normal in animals with experimentally induced diphtheritic polyneuropathy and are prevented if these animals are suspended above the floor. Damage to a peripheral nerve by pressure results in a compression neuropathy (3). This may occur at any point along the course of the nerve although there are certain sites where individual nerves are anatomically vulnerable. The source of the pressure may be external such as an ulnar neuropathy resulting from habitually leaning on the elbow or a peroneal palsy due to pressure from a cast or brace. Alternatively nerves may be compressed or angulated by adjacent tissues within the body such as bony callus, synovial thickening, ganglia, tumors, fibrous bands, or normal or aberrant muscle. The compression may be acute, continuous or intermittent (3).

Mechanisms of chronic nerve entrapment and compression may be: 1) Compression in a fibro-osseous tunnel, for example: carpal tunnel syndrome or cubital tunnel syndrome. 2) Angulation and stretch, for example: ulnar lesions associated with gross deformity of the elbow joint ("tardy ulnar palsy") or cervical rib syndrome. 3) Recurrent compression by external forces, for example: some ulnar nerve lesions at the elbow, or lesions of the deep branch of the ulnar nerve in the hand (3).

The symptoms of an entrapment neuropathy can be sensory, motor or mixed depending on the fiber types involved in the affected peripheral nerves. Most clinical entrapments involve mixed nerves so both motor and sensory complaints are common. Sympathetic or parasympathetic dysfunction can occur if there is involvement of autonomic fibers (1). For the pain specialist, the harbinger of entrapment neuropathies is generally pain which may radiate proximally as well as distally. The usual pathology of entrapment neuropathy is a focal segmental demyelination and based on animal studies plus the very few pathological studies in humans, the sequence of events postulated by Ochoa (3) is that the initial stages, asymmetry of the myelin sheath leading to retraction from one end and thus to paranodal demyelinating. At a later state myelin loss from the complete internodal segment will occur, or in the most severe cases, complete degeneration of the fiber. Single teased fibers undergoing these changes have been seen not only in the median nerve of the guinea pig but also in the plantar nerves when these animals are kept on wire mesh floors to produce a plantar neuropathy. In man they have been found in median nerve fibers at the wrist and ulnar nerve fibers of the elbow and in the lateral cutaneous nerve of the thigh at the anterior end of the inguinal ligament. These changes are of considerable theoretical interest as they suggest that the demyelination and nerve fiber degeneration are the result of mechanical deformation rather than ischemia. However, this interpretation is by no means generally accepted and other factors such as altered capillary permeability and endoneurial pressure have also been considered. Entrapment neuropathies can be obvious or obscure and may occur as a common or rare phenomenon. They may require electrodiagnostic evaluation for diagnosis or may be clinically diagnosable. Some entrapment neuropathies are not clear cut and there is doubt that the syndrome exists at all or it's limits are poorly defined, or the cause is disputed, or the therapy is unknown efficacy, or the frequency is so variable from one medical center to another as to cast doubt on diagnostic criteria. Unfortunately those cases clinically most obscure are also those cases in which the diagnosis is least confirmable by electrodiagnostic measures.

UPPER EXTREMITIES:

The common upper extremity entrapment syndromes are carpal tunnel syndrome and ulnar neuropathy at the elbow (2). Numbness, painful tingling or weakness may be the result.

Carpal tunnel syndrome (4,5,6) is produced by compression of the median nerve at the wrist. Affected patients report numbness, tingling and pain in the hand which often worsens at night or after use of the

hand. The pain may radiate proximally into the forearm and arm. Examination in the early stages often reveals no abnormality. With more severe nerve compression, the patient will have sensory loss over some or all of the digits innervated by the median nerve, ie., thumb, index finger, middle finger, and radial half of the ring finger with weakness of thumb abduction.

Clinical assessment (2) includes Phalen's test (appearance or worsening of paresthesias with maximal passive wrist flexion for one minute) and Tinel's sign (paresthesia in the median territory elicited by gentle tapping over the carpal tunnel). Tinel's sign has a sensitivity of 60% and a specificity of 67% corresponding to values for Phalen's test of 75% and 47%. When conducted in the proper setting, these tests can provide useful information. There have been scattered attempts to quantitate the sensory function and improve it's diagnostic yield such as quantitative sensory testing and "inching technique."

The carpal tunnel syndrome is most common in middle aged women. There is pain radiating into the fingers and often retrograde up to the arm. This has been grouped into three groups. Symptoms include numbness, pain and weakness. There are several reports in the literature describing it in association with Raynaud's phenomenon. The weakness is usually in the opponens pollicis and abductor pollicis brevis. In addition to the Tinel's and Phalen's sign, the finger pulp sign, a woodiness in the median nerve musculature, and the blood pressure compression test or reverse Phalen's test may also be useful.

The etiologies of carpal tunnel syndrome (5) are various and can be as diverse as nonspecific flexor tenosynovitis, rheumatoid flexor tenosynovitis, traumatic conditions including colles fracture, epiphyseal fracture of the distal radius, fracture of both forearms or dislocations or fracture dislocations of the carpus. There may be space occupying lesions including tumors (giant cell, lipomas, hemangiomas, ganglia, and osteoid osteoma.) Metabolic conditions have been implicated including amyloidosis, myxedema and acromegaly. Vitamin deficiency has been invoked as well as estrogen deficiency, granulomas and familial neuropathy. Polymyalgia rheumatica has also been suggested. Electrodiagnostic testing is important for the accurate diagnosis of carpal tunnel syndrome and should be carried out in most cases. The electromyographer uses sensory fibers (2) to measure the nerve conduction velocity or distal latency from the finger or palm to the wrist and motor conduction velocity or distal latency from the wrist to the thenar eminence. The sensitivity of sensory conduction testing can be improved by making sequential measurements of short distances over the course of the nerve in the palm - the palmar serial sensory study. Approximately half of the patients with carpal tunnel syndrome have abnormalities of contralateral median nerve. Electromyography of thenar muscles innervated by the median nerve is also usually done.

Electrodiagnostic testing is particularly useful to the differential diagnosis of the presence of co-existing disease. Radiculopathy, a disease of the cervical spine, diffuse peripheral neuropathy or proximal median neuropathy can pose clinical questions soluble by electrodiagnostic testing. No other test has a higher diagnostic accuracy in patients with a final diagnosis of carpal tunnel syndrome. Most electromyographers consider the following results abnormal: An absolute sensory latency of more than 3.7 milliseconds, a difference of more than 0.4 milliseconds between values obtained for the median nerve and those obtained from the radial or ulnar nerve, and a motor conduction latency of more than 4.0 milliseconds and an incremental change of 0.4 milliseconds in the palmar serial sensory study (2). Magnetic resonance imaging has been used for the carpal tunnel (2).

The differential diagnosis includes cervical radiculopathy, ulnar neuropathy, and thoracic outlet syndrome. Overuse syndrome (cumulative trauma syndrome) is a common diagnostic problem in occupational settings.

The pathophysiology includes an increase of pressure in the carpal tunnel and chronic focal compression of a nerve trunk can cause focal demyelination by mechanical stress deforming the myelin lamellae. Ischemia has a role in carpal tunnel syndrome. It can account for the intermittent paresthesias (2).

Treatment: The mainstays of nonsurgical treatment (2) are avoidance of the use of the wrist, placement of a wrist splint in a neutral position for day and night use, and anti-inflammatory medications. These treatments are especially useful in patients with acute flare-ups and in those with minimal and intermittent symptoms. There has been no recent perspective trials of the effect of splinting alone. A study of the response of a group of patients to splinting plus injections of local steroids into the carpal canal indicated

that only 22% were free of symptoms at the end of the year long trial, although steroid injections have had a good record of success during short-term treatment with good or complete relief in 81% of patients.

Surgical treatment consists of sectioning the volar carpal ligament based on failure to respond to splinting, steroid injections and oral anti-inflammatories; the symptoms limiting the patient's activity and a diagnosis based on clinical examination and nerve conduction tests. If the patient does not respond to carpal tunnel surgery, it is important to verify that the distal ligament has been properly sectioned. Sometimes a separate branch to the thenar eminence is left untouched.

Ulnar neuropathy: Ulnar nerve entrapment (2,5,6) usually occurs at the elbow. The usual findings are intermittent hypesthesia in the distribution of the ulna. The amount of pain and paresthesias is variable. The sensory examination reveals the ulnar nerve to be involved on the ulnar border of the hand and occasionally up into the elbow. Froment's sign or weakness of adduction has been described. If the lesion has a chronic course, the interossei and lumbricales may be involved. Pain may be referred to the thorax posteriorly and even to the opposite side of the body. As the ulnar nerve passes through the ulnar groove at the elbow it is subject to several types of compression. Even with the most careful electrophysiologic techniques and with surgical exploration, it may be difficult to localize or precisely explain the neuropathy. Potential causes of ulnar entrapment in approximate order of frequency are as follows: cubital tunnel syndrome, external compression, previous fracture and scarring, recurrent subluxation of the nerve, and entrapment. A cubital tunnel syndrome can occur where the nerve passes the aponeurosis of origin of the flexor carpi ulnaris. In certain persons the aponeurosis is drawn taut over the nerve particularly with elbow flexion. The point of constriction is 1.5 to 3.5 cm distal to the epicondyle. External compression can occur from repeatedly resting the elbow on a flat surface especially if the ulnar groove is shallow. The comatose or anesthetized patient is at risk for prolonged pressure of the ulnar nerve. Previous fracture can damage the elbow and scarring can constrict the nerve. Recurrent subluxation of the nerve which can roll anteriorly over the medial epicondyle may contribute to ulnar neuropathy. However, nerve subluxation also occurs in asymptomatic persons. Finally, entrapment may occur distal to the cubital tunnel more than 4 cm below the epicondyle in the flexor pronator aponeurosis.

Patients with ulnar nerve compression typically note numbness in the little finger and medial side of the hand often times in the ulnar side of the ring finger. Pain and tenderness may occur at the elbow and radiate toward the hand. An increase in paresthesias with elbow flexion is a reliable sign of ulnar entrapment neuropathy. Weakness, if it occurs, may affect many functions of the hand including finger abduction, thumb abduction, pinching of the thumb and forefinger, and eventually power grip. The techniques used for electrodiagnostic testing resemble those used for carpal tunnel syndrome. Usually both motor and sensory testing are conducted. The location of the abnormality is sought by assessing conduction velocity across the elbow segment. The intrinsic muscles of the hand are used to determine the motor velocity and the little finger is used for sensory testing.

Although the presence of an ulnar lesion is commonly established, the exact location of the lesion is unclear in one-third to one-half of the cases, especially less severe cases (2). If the site can be established by careful sequential measurements over short segments, there are therapeutic implications since the nature of the surgical approach may depend on exact localization.

Differential diagnosis of several other entities need to be considered. The ulnar nerve can be compressed at the wrist rather than at the elbow by repeated trauma to the palm or by a ganglion or tumor. Rarely the brachial plexus is involved by a metastatic tumor (Pancoast's tumor) or by the thoracic outlet syndrome. Compression of the cervical nerve root can cause radiation and paresthesias in the hand. The C8 nerve root can best be differentiated from the ulnar nerve by the pattern of muscle weakness.

Treatment: Conservative treatment for ulnar nerve compression is limited. Steroid injections and oral anti-inflammatory agents are not useful. If there is a source of external trauma it must be eliminated. Frequent or prolonged flexion of the elbow should be avoided. The patient may try wearing a loose bivalve cast at night to prevent elbow flexion.

A surgical approach is reserved for those with disability, particularly weakness (7,8). If the weakness is early and mild, especially if a Tinel's sign is present, a simple release may be performed. There is no consensus regarding the procedure of choice. Some prefer epicondylectomy whereas others favor nerve transposition. Generally the results are satisfactory but the results are more commensurate with the degree of preoperative motor or sensory loss than with the choice of procedure.

Proximal medial nerve lesions: There are three general areas in which the median nerve can become entrapped (4,7) in the forearm about the elbow. The most proximal point and the least frequent is the ligament of Struthers, an aberrant ligament found immediately above the elbow. Pain is described above the elbow and local tenderness is noted in the region of the ligament. The diagnosis is established by the discovery of a supracondylar process on x-ray. Exploration and release of the aberrant ligament and neurolysis should alleviate the symptoms.

Pronator syndrome: The most frequent symptom is a mild to moderate aching in the proximal forearm, sometimes described as tiredness or heaviness. Paresthesias in the median nerve distribution may be reported but generally are not as severe or well localized as carpal tunnel syndrome. A wide range of physical findings may occur including Tinel's sign or a palpable or even measurable enlargement of the pronator teres muscle.

The anterior interosseous nerve syndrome is present when the median nerve is impinged upon at it's last major branch, the anterior interosseous muscle. The patient's describe acute pain in the proximal forearm or arm lasting hours to days. Examination typically shows absence of flexion of the interphalangeal joint of the thumb and distal interphalangeal joint of the index digit due to paralysis of the flexor pollicis longus and flexor digitorum profundus of the second digit.

Ulnar nerve entrapment at the wrist (5,7,8): Ulnar nerve entrapment of the wrist may be compression of the deep palmar nerve which is usually painless and does not cause sensory loss or involve the hand. There may be external trauma causing ulnar nerve compression: long distance cycling, using the palm as a hammer (Karate player's palsy), chronic pressure from a screwdriver or pliers has also been described as well as "silver beaders' palsy". The treatment depends on the origin. For mild conditions, avoidance of the chronic trauma and conservative treatment is indicated.

Radial nerve entrapment (7): High radial nerve entrapment is rare and trauma counts for the majority of traumatic lesions. Posterior interosseous nerve compression may cause a dull ache in the dorsum of the forearm and the patient may also have partial or complete paralysis of dorsiflexion. The radial tunnel syndrome may be difficult to differentiate from so-called resistant tennis elbow.

Thoracic outlet syndrome: Neurogenic thoracic outlet (2) syndrome with measurable neurological deficit is very rare. The patient may note tingling in the hands with shoulder abduction or elevation are relatively common. Neurogenic thoracic outlet syndrome is caused by abnormal bands crossing the brachial plexus often inserting on a rudimentary cervical rib. The pathogenesis of reversible, positionally dependent paresthesia is unknown. Often the symptoms occur after a whiplash injury and cervical muscle spasm may have a role.

Assessment: Weakness of all the intrinsic muscles of the hand and sensory loss over the ulnar side of the hand and forearm are the classic features of neurogenic thoracic outlet syndrome. A change in pulse volume of the arm abduction is found in 15% of normal persons and is not a reliable indicator of the syndrome. Electrodiagnostic testing usually shows no abnormalities in patients with the more common reversible paresthesias and no evidence of focal demyelination in the rare patients with neurogenic thoracic outlet syndrome.

Treatment: Patients with reversible paresthesias usually respond well to a program of physical therapy which increases the range of motion of the neck and shoulders, strengthens the rhomboid and trapezius muscles, and induces a more erect posture. Exploration of the brachial plexus carries some risk and should be reserved for rare patients with documented worsening of neurologic functions.

Entrapment of a digital nerve: Digital nerve entrapment (5) in the hand especially in the thumb ("cheiralgia paresthetica") is not uncommon. It occurs in people who use ring-like devices, bowling balls, pinking shears,

or tin snips habitually. With the cessation of activity usually in six weeks to two months the condition which is self-limited resolves spontaneously.

LOWER EXTREMITY:

Peroneal nerve entrapment: Peroneal nerve entrapment (1,5,7) or compression occurs at the head of the fibula. It was common caused by casts because before it was generally recognized as a risk. Involvement of the lower portion of the leg on the lateral aspect is common. If it progresses far enough, it can produce a foot drop.

Sciatic nerve syndrome: Sciatic nerve syndrome or entrapment at the piriformis (9) is a controversial and difficult entrapment neuropathy. Patients who were explored had unimpressive findings and none had anatomic anomalies. In some of the more recent accounts of the piriformis syndrome, it is correctly assumed that neurologic deficits due to sciatic nerve damage are a syne qua non of this disorder but others have argued that the absence of such signs is an essential criterion for the diagnosis. If there is indeed a specific syndrome due to compression of the proximal sciatic nerve by the piriformis muscle it should meet five specific criteria: 1) Symptoms and signs of sciatic nerve damage should be present. 2) There should be electrophysiological evidence of damage to the nerve and the paraspinal EMG studies must be normal ruling out a lumbar radiculopathy. 3) Imaging of the lumbosacral roots and of the paravertebral and pelvic areas must be normal to exclude nerve root compression, lower lumbar and/or sacral plexus infiltration or damage. Imaging of the sciatic notch must show absence of mass lesions there. 4) Surgical exploration of the proximal sciatic nerve should confirm an absence of these lesions. Ideally compression of the sciatic nerve at the piriformis muscle should be identified. 5) Relief of symptoms and improvement in neurological abnormalities should follow surgical decompression. In a book entitled Tunnel Syndromes, Pecina (9), et al., listed several differentiating symptoms and signs of the piriformis syndrome. In the piriformis syndrome there is: 1) No pain in the lumbosacral region, 2) a peripheral nerve distribution irritation not radicular in origin, 3) irritability on palpation of the greater sciatic foramen, 4) palpable mass or swelling over the region of the piriformis muscle with exacerbation of pain, 5) piriformis muscle spasm appreciated by rectal exam, 6) positive Laseque-Lazarebic sign at 25 degrees, 7) increased pain with internal rotation of the hip or hip flexion with an extended knee, and 8) decreased pain with external rotation of the hip.

Treatment: Treatment consists of conservative therapy, physical therapy, corticosteroids and anesthetic injections and anti-inflammatory medications. Surgical therapy must be initiated within six to eight months of presentation.

Lateral femoral cutaneous nerve: Meralgia paresthetica (1) is one of the most common and painful nerve entrapments. It occurs as the lateral femoral cutaneous nerve comes up through the pelvis and through the fascia. Numbness and pain usually with recruitment occurs on the lateral aspect of the thigh.

Ilioinguinal, genitofemoral and other inguinal neuropathies: These neuropathies may occur following herniorrhaphy on either side or a low McBurney's incision for an appendectomy on the right side (1,5,6,7). There is pain coming down into the groin from the anterior superior iliac crest. This can be palpated three fingerbreadths medial to and one fingerbreadth inferior to the anterior superior iliac spine. There has been a recent tendency to group these conditions under the rubric of inguinal neuropathy as a sensory neuropathy of the syndromes tends to overlap.

Tarsal tunnel syndrome as well as plantar neuropathy: The tarsal tunnel is formed by the flexor retinaculum and the posterior tibial nerve traverses it and divides into three branches. These are the lateral medial and calcaneal branches. Any one or all of these branches may be involved with numbness of the foot (1,5,6,7).

Morton's neuroma and Joplin's proper neuroma: These are lesions which occur either between third and fourth toes, in the case of Morton's neuroma (7), or in the great toe, in the case of Joplin's proper neuroma.

Rare neuropathies include femoral and obturator neuropathy (1).

Reference

• Headaches: Mechanisms and Management
Bernard M. Abrams, M.D.
Pain.com

1. Describe evaluation and management of a headache patient.

The goals of any headache evaluation are two-fold: 1) the recognition of common syndromes for which treatment is available, and 2) the recognition of syndromes which constitute a threat to life or function. The headache evaluation consists of a detailed history, pertinent information from the physical examination and pertinent diagnostic laboratory studies. Of these far and away, the most important element is the headache history. The late Dr. A.L. Sahs stated, "If you have thirty minutes to see a patient, spend twenty-nine on history, one on the examination".(1)

Mechanisms of head pain

The mechanisms of head pain include:

1. Traction on intracranial structures: i.e., intracranial mass, post lumbar puncture headache.

2. Dilatation of cranial arteries (today it is felt that both tension type and migraine or vascular headaches have a central brainstem pacemaker which affects structures in the trigeminal nerve selectively).

a. Intracranial, i.e., cluster headaches, anoxia, CO2 intoxication, pheochromocytoma.
b. Extracranial, i.e., migraine or cluster.

3. Inflammation

a. Intracranial, i.e., meningitis,
b. Ex:tracranial, i.e., temporal arteritis

4. Contraction of the striated muscles of the head or neck (this concept has been called into question by the recent discovery of central type pacemaker on PET scans), i.e., contraction headache.

5. Cranial neuralgias.
6. Diseases of the eyes, nose, sinus, ears, or teeth.

The major categories of headache disorders are given in Table 1

GENETIC MECHANISM

Migraine is well known to be a familial disorder with the risk factor of migraine 50% more likely in relatives of migraineurs than in controls. But the patterns of inheritance are complicated and, as a result, the role of inheritance of migraine is unclear.

Rapid molecular biological technological advances are being applied to analysis of migraine. Specific mutations leading to an increased risk of rare forms of migraine have been identified in both mitochondrial DNA and a calcium gene channel. Approximately one-half of the families known to have familial hemiplegic migraine, including all families with FHM and progressive cerebellar ataxia show genetic linkage to chromosome 19p 13. This type of migraine appears to be caused by a mutation in a subunit of neuronal P/Q-type Ca++ channels.

BIOLOGICAL BASIS

There are 2 fundamental theories concerning the genesis of migraine: (1) vascular and (2) neurogenic although it is now believed that both are involved in the migrainous process.

A number of studies have shown that the aura phase of migraine is associated with posterior cerebral hemisphere reduction of cerebral blood flow and positron emission tomography (PET) scanning shows a process of cortical spreading depression.

Aminergic brainstem nuclei (locus coeruleus, raphe nuclei) regulate cerebral blood flow, influence cortical neuron excitability, and modulate endogenous pain control mechanisms. A discharge from these nuclei has been hypothesized to initiate parts of the migrainous process. PET during acute migrainous attacks consistently show increased activation in medial brainstem structures contralateral to the headaches side. (Weiller, C, May A, Lirnmroth V, et al., Brainstem activation in spontaneous human migraine attacks. *Nat Med* 1995;1:658-660)

Data indicate that the trigeminovascular system may constitute the anatomic substrate responsible for migraine pain. The pain is thought to result from neurogenic inflammation, produced by the antidromic release of neuropeptides by trigeminal nerve endings and associated with the release of other algesic substances from plasma, platelets, and mast cells (e.g., Histamine, prostaglandin, serotonin). This release of neuropeptides and algesic compounds induces the vasodilatation and extravasation of plasma proteins, as well as the sensitization of trigeminal nociceptive nerve endings.

The messenger molecule, nitric oxide, has also been impliced in the pathophysiology of migraine pain. Data show that in both normal volunteers and migraine sufferers headache is induced by intravenous infusions of glycerol trinitrate (an exogenous nitric oxide donor) and histamine (which liberates nitric oxide from vascular endothelium); it has been hypothesized that nitric oxide released from either blood vessels, perivascular nerve endings, or brain tissue is a molecular trigger for migraine pain.

Serotonin has been implicated as a catalyst responsible for the genesis of migraine attacks. But the locus of the changes in serotonin activity that could initiate the process is still unknown. In addition, it is still not known where serotonin acts.

In cluster headaches there are three major elements: (1) trigeminal distribution of the pain; (2) autonomic features; and (3) the inherent periodicity of the attacks. The pain of cluster headache is very much a first division trigeminal phenomenon, and many of the autonomic features are the result of seventh cranial nerve activation. It is likely that a trigeminal-autonomic reflex underlies the pain expression of cluster headache. Changes have been observed in the cranial circulation consisting of the release of both calcitonin gene-related peptide and vasoactive intestinal polypeptide during cluster headaches. It has been proprosed that several syndromes, including cluster headaches and paroxysmal hemicrania, may be considered to be trigeminal-autonomic cephalgias. For cluster headache a crucial aspect of the dysfunction appears to lie within the ipsilateral hypothalamic grey and it's clear that the carotid flow changes are driven by the ophthalmic division of the trigeminal and are not produced by the cluster headache per se.

It is also noted that testosterone levels are altered during an attack of cluster headaches.

Acute cluster headaches triggered by nitroglycerine have been studied by PET scan. The activated areas fall into 3 categories: (1) areas generally associated with pain; (2) an area that seems specific to cluster headache; and (3) vascular structures.

The anterior cingulate was significantly activated, as would be expected, because activation of the anterior cingulate by pain is observed in most human PET studies. Activation was also noted in the frontal cortex, insulae, and ventroposterior thalamus contralateral to the side of the pain. In addition, activation in the ipsilateral basal ganglia was observed.

The only activated area that is unique to cluster headache is the ipsilateral hypothalamic grey matter in the region of the base of the third ventricle. Activation of the hypothalamic grey matter is not seen in migraine, nor in experimental first trigeminal division head pain. This region is not activated when the patient is not having a bout.

During acute cluster headache attacks, activation is observed in the region of the cavernous sinus and has been shown using MRA to be caused by internal carotid artery vasodilatation. Similarly, during experimental head pain induced by injection of capsacin, the same region is activated. This finding implies that the activation of the carotid does not relate specifically to cluster headache, but it is a trigeminovascular autonomic reflex caused by first division pain. The flow changes are, therefore, an epiphenomenon of the trigeminal activation. This mimics Ekbom's classic observation made during angiography of a patient suffering from an acute cluster headache that there are changes in the internal carotid artery.

<u>Headache evaluation</u>

A. Detailed history
B. Pertinent information from the physical examination
C. Pertinent diagnostic laboratory, neurophysiologic, and radiographic studies

Little guidance is offered for the headache history by standard textbooks of neurology (2) because major attention is usually directed toward entities producing headaches which leaves the questioner to evolve his own set of headache questions based upon diverse information from a wide variety of conditions. While headache history guidelines and lists are available, (3,4) the author has evolved a list of twenty questions in order to elucidate the headache history.

Because the classification of headache has recently undergone revision (5) and there has been a rapid flux in the current conceptions of the pathogenesis of various types of headaches with what was formerly known as muscle contraction (presently called tension type), and migraine being conceived of as much more of a unified disease rather than two diseases. (6) The present author has chosen to classify headaches as:

1. Acute life threatening
2. Chronic life threatening
3. Chronic benign non-life threatening

The acute life threatening include but are not limited to: subarachnoid hemorrhage, meningitis, and space occupying lesions. The chronic life threatening include but are not limited to: space occupying lesions and chronic meningitis. The chronic benign non-life threatening include but are not limited to: migraine, cluster, contraction type headache, sinusitis, trigeminal, and other facial neuralgias, cervical spondylitis, benign exertional headache, and orgasmic headache.

In the headache evaluation, factors that cause concern are:

1. Headaches associated with neurologic dysfunction,
2. Exertional headache,
3. Headaches which peak rapidly,
4. Nocturnal headaches,
5. Headaches associated with systemic symptoms,
6. Focal headaches,
7. Recent headaches, and
8. A recent change in headache.

This is not an all-inclusive list, and will be alluded to under each of the twenty questions to be propounded. The twenty questions are as follows:

1. Where am I?
2. What's the matter?
3. Has this ever happened before?
4. If this has happened before, is it progressive?
5. If this has happened before, for how long, and has it changed?
6. If it is the same, what is the pattern of occurrence?
7. What is the character and location?
8. What is the onset to peak time?
9. What is the usual time of day it occurs and the total duration?
10. Are there any associated and/or residual neurological phenomena or sequelae?
11. Is there an aura?
12. What makes the headache worse?
13. What makes the headache better?
14. Is there a family history?
15. Were there headaches in childhood?
16. Was there motion sickness, cyclical vomiting, dizziness, or unexplained fever in childhood?
17. Were there any prior diagnostic tests?
18. What were the results of prior medication?
19. Are there any other medical illnesses?
20. Are there any psychiatric illnesses, history of alcohol or substance abuse, and what is the quality of the individual's life?

The order selected for these twenty questions is definite, and the reason for it is that it accomplishes in the briefest period of time and most economically the goals of separating headaches first, into those which may present an acute life-threatening situation, and second, those which are chronic or benign.

QUESTION 1: WHERE AM I?

While on the surface this may seem like a frivolous question designed to test the examiner's own sense of orientation, it is on the contrary the beginning of a separation of headaches into one or two types. One finds oneself in the emergency room seeing a patient in two types of situations: 1) an acute life threatening situation, or 2) the first chronic benign headache which is severe. Life-threatening headaches present as either headaches of great severity associated with meningeal signs, and immediately suggest the need for contrast studies, usually an immediate CT scan followed by a lumbar puncture, or hemispheric type syndromes giving unilateral signs, symptoms, and perhaps signs of increased intracranial pressure.

Confusion arises with the first chronic benign headache, such as a migraine headache in a l5-year old young lady. Therefore one may have to go through the entire differential diagnosis and also do everything required of an acute life threatening headache in order to rule out any life threatening problem. The first headache of a chronic benign sequence which is severe enough, migraine cluster muscle contraction headache, trigeminal neuralgia, sinusitis and many other types of headaches may lead the first time sufferer to the emergency room, whereas with repeated familiarity the patient would simply seek the appropriate treatment.

If the physician is in the hospital called as a consultant, then one may be dealing with an acute or chronic life threatening situation which has gone beyond the emergency room stage. Presumably in the emergency room, all immediately demonstrable life threatening headaches will have been resolved so that the CT scan will have shown a subarachnoid hemorrhage, tumor, or cerebral edema, and the lumbar puncture will have ruled in or out any type of meningeal syndrome, most likely infection or subarachnoid hemorrhage. (7) Chronic headaches, either life threatening or benign will often warrant hospitalization, especially if associated with a systemic illness such as fever, leukocytosis, weight loss, claudication and joint manifestations, or if the patient is particularly emotionally labile. The entities of chronic meningitis, developmental abnormalities such as platybasia or Arnold-Chiari malformation, subdural hematoma or emotional disorders suggest themselves. In the office, most headaches are chronic benign headaches. Rarely they are chronic and life threatening. At a social event one approached by a headache sufferer will almost always be dealing with a chronic benign headache.

QUESTION 2: WHAT'S THE MATTER?

This is an open-ended question, and tends to eliminate most of the complaints while not leading the patient. It compromises between an economy of time and a freedom for the patient in allowing the patient to tell his/her own headache history. If the patient begins to delineate a headache history, he/she should be allowed to do so freely. However, at the conclusion of this period of the questioning, the patient should be asked if there is a second type of headache, or perhaps even a greater number that has been experienced by the patient previously.

QUESTIONS 3 & 4: HAS THIS EVER HAPPENED BEFORE AND IF SO, IS IT PROGRESSIVE?

If the patient has never had a headache of the type suffered at present before, it is a definite warning sign that one may be dealing with an acute life threatening headache. The "sentinel" headache of subarachnoid hemorrhage is well known and may be a minor feature. It is far more reassuring to hear that a patient has suffered the same headache before than to find out that the headache is occurring for the first time. Part of the interpretation depends upon how old the patient is. Obviously a 50-year old male who has never suffered a headache before and suddenly experiences a severe headache is much more at risk for an acute life threatening headache than is a 15-year old girl who has never experienced a headache before of similar type and who has a strong family history of migraine. Both of them demand a workup, but the index of suspicion is much higher with the older patient. By the same token, a headache which is relatively nondescript, but progressively increases in severity and decreases in the interval between headaches, also suggests the possibility of life threatening type situation. One must beware of chronic life threatening

headaches such as that associated with slow-growing tumors, subdural hematoma or chronic meningitis. Oftentimes these headaches are relatively diffuse in their location and relatively nondescript in their character. Further, they may go away for periods of time which are variable, but may be up to several days or even weeks allaying one's suspicions that they are life threatening. Obviously the situation in which one finds oneself makes a great deal of difference. For example, if a patient had a severe head injury with unconsciousness three or four weeks before, then a headache which comes and goes may be of greater significance than a headache in a non-head injured patient under severe and episodic stress at work or at home.

QUESTION 5: IF THIS HAS HAPPENED BEFORE, FOR HOW LONG, AND HAS IT CHANGED?

This question again points to the differential between acute or chronic life threatening and chronic benign. If a headache is a single episode in a sequence of recurrent headaches, then one can be more confident that it is a chronic benign, recurrent syndrome. The headache which has been present for many years off and on, or even many years continuously suggests a more benign process. However, again if that headache changes in character, for example, lasts longer, is of greater intensity, or is associated with neurological sequelae, then attention must be drawn to the possibility of it as a life threatening situation.

QUESTION 6: IF THE HEADACHE IS THE SAME, WHAT IS THE PATTERN OF OCCURRENCE?

By this time one can be fairly confident that he has differentiated between acute or chronic life threatening situations and chronic benign headaches. This question tends to differentiate between recurring vascular headaches versus chronic tension type headaches. Recurring vascular headaches tend to be episodic and associated with headache free periods, while chronic tension type headaches tend to be headaches which occur every day or at least frequently. There is of course a mixed type headache, in which chronic tension type headaches are interspersed or punctuated by vascular type headaches.

QUESTION 7: WHAT IS THE CHARACTER AND LOCATION?

A vascular headache is generally pounding in type, sometimes synchronous with the pulse. It can be diffuse or holocranial or unilateral. The classical migraine headache is unilateral, giving rise to its name of hemicrania. The tension type headache is a steady headache, usually generalized over the head, sometimes beginning in the neck muscles or suboccipital region, and then becoming holocephalic and sometimes beginning in the frontal regions. A cluster headache is a stabbing type headache often described as a "hot poker" and is almost always unilateral and focal through the eye. Trigeminal neuralgia is focal, usually in the 2nd or 3rd division, and a flashing type pain of extremely high intensity. The headache associated with tumor, while focal, is generally nondescript. The patient with psychogenic headache will describe a generalized headache, usually with some bizarre features either as to the character of the headache or other features to be described below. In the patient with subarachnoid hemorrhage, if the patient retains consciousness it is not unusual to hear the headache described as tearing, bursting, exploding and certainly the worst headache the patient has ever experienced if they have experienced other types of headaches.

QUESTION 8: WHAT IS THE ONSET TO PEAK TIME?

Migraine headaches of the classic variety take thirty minutes to an hour to peak. The more common type takes one to two hours to peak. Muscle contraction or tension type headaches take two to four hours to peak. Cluster headaches may awaken the patient with the first REM, and then of course the patient has an "instant headache". If the patient is awake at the time of onset it takes five to ten minutes. There has been a tendency to regard the rapid onset to peak time as carrying a bad prognosis and import, and more often than not this is not true. Orgasmic headache, benign exertional headache, trigeminal neuralgia and the perceived onset of ice cream headache are almost instantaneous. Nonetheless, any patient who has a very rapid onset to peak time must be viewed with some concern.

QUESTION 9: WHAT IS THE USUAL TIME OF DAY IT OCCURS AND THE TOTAL DURATION?

Migraine occurs at any time, although probably more characteristically in the morning than any other time. The duration is between six and seventy-two hours and especially until sleep can be induced. Cluster headache occurs with the first REM, usually ninety minutes after the patient retires for bed. There is a tendency when medication is started for cluster headache to be "chased around the clock", and to occur then early in the morning and then with increasing medication, later in the day. Usually the common cluster headache occurs with a duration of twenty to forty minutes. Muscle contraction headache occurs usually from 4 pm on, and lasts somewhere in the neighborhood of six hours, although this is not inviolable.

QUESTION 10: ARE THERE ASSOCIATED AND/OR RESIDUAL NEUROLOGIC PHENOMENA OR SEQUELAE?

Sonophobia or noise intolerance is nonspecific. Photophobia occurs in vascular headaches. A stiff neck or meningeal signs requires workup for subarachnoid hemorrhage, and if a CT scan is normal, demands a lumbar puncture. Scotomata hemisensory defects, cranial nerve palsies preceding the headache suggest the possibility of a vascular type headache. Myosis and pseudoptosis or ipsilateral Horner's syndrome suggest cluster headaches. Any residual neurological deficit raises the possibility of complicated migraine headache on the basis of subarachnoid or intracerebral hemorrhage, cerebrovascular disease, meningitis or space occupying lesion. Fever associated with the headache suggests the possibility of infection.

QUESTION 11: IS THERE AN AURA?

Repeated headache preceded by scotoma, hemianopsia, cranial nerve palsies, hemisensory phenomena are almost always vascular, and represent classical migraine.

QUESTION 12: WHAT MAKES THE HEADACHES WORSE?

Vascular headaches are worsened by alcohol, tyramine containing foods, MSG (a common food additive), Nutrasweet, birth control pills, drugs containing vasoactive properties such as vasodilators. Stress or neck position usually implies muscle contraction headaches; bizarre things, psychogenic headache. Exertion generally implies benign exertional headache and the headache associated with intercourse if repeated more than once is almost undoubtedly an orgasmic headache.

QUESTION 13: WHAT MAKES THE HEADACHES BETTER?

Migraine headaches are made better by sleep, by ergot and by any pain medications. They are often improved by pressure over the side that is throbbing. Cold compresses are relatively nonspecific, and may improve migraine or muscle contraction headache. Heat usually improves muscle contraction headaches as does alcohol. A history of oxygen inhalation improving the headache suggests cluster headache. A history of nasal drainage followed by relief of headache suggests the possibility of sinus headaches.

QUESTION 14: IS THERE A FAMILY HISTORY?

A family history is present in migraine headaches in 75-85 percent, and in muscle contraction headaches, 50 percent.

QUESTION 15: WERE THERE HEADACHES IN CHILDHOOD?

While tension type headaches do occur in childhood, most childhood headaches have a vascular basis.

QUESTION 16: WAS THERE MOTION SICKNESS, CYCLICAL VOMITING, DIZZINESS OR UNEXPLAINED FEVER?

These are childhood antecedents of migraine and oftentimes produce puzzling type syndromes for the pediatrician and only in retrospect is it noted that the patient has become a migraineur in adulthood. (8)

QUESTION 17: WERE THERE ANY PRIOR DIAGNOSTIC TESTS?

The implications of this almost seem too obvious to be discussed, but it is fairly clear that if a patient has had a workup including CT scan or MRI within the past year or two, that the possibility of a structural lesion is considerably diminished. The question of when to repeat studies comes up and it is the author's personal conviction that any change in the headache should militate in favor of a contrast study of the head, most usually CT scan or MRI regardless of the time of the last CT scan or MRI, but it is the author's practice that if a patient is not responding to treatment to repeat these studies if they have not been done within a one year period of time.

QUESTION 18: WHAT WERE THE RESULTS OF PRIOR MEDICATION?

The results of prior medication should then be ascertained for two reasons. 1) as a "therapeutic test", and 2) as a guideline to future treatment. The results of analgesics are nonspecific and avoidance of narcotic medication in a patient with chronic headache is mandatory . At this point it may become evident that the patient if not previously known to the physician is drug-seeking. One of the surest signs of this is the specification of a powerful narcotic as the only drug which will stop the patient's headaches. Drugs which have no pain reducing qualities in and of themselves such as ergot, midrin, oxygen, steroids and non-steroidal anti-inflammatory drugs generally indicate that the patient has vascular headaches if they are efficacious. Drugs with mild sedatives such as butabarbital in Fiorinal or Esgic plus are useful in patients who have tension type headaches.

Prophylactic medications include lithium, Sansert, steroids for cluster headaches; an older drug that has been used for cluster is Periactin. Inderal or beta blockers, amitriptyline, Prozac, calcium channel blockers and more recently Depakote have been used in prophylaxis for migraine. There is a definite overlap between amitriptyline as a drug for muscle contraction headaches and vascular headaches. Oftentimes a patient will dismiss a drug as, "I'm allergic to it", and closer inquiry will reveal that the patient received too much of the medication over a short period of time and developed dose-related side effects, or that the medication was "not efficacious" which generally means that the medication has not been slowly and judiciously pushed to its limits.

QUESTION 19: ARE THERE ANY OTHER MEDICAL ILLNESSES?

This is especially important for ascertaining if the patient may have been given medications which may trigger headaches. For example, if the patient has heart disease, vasodilators may give headaches and the institution of estrogen therapy in a menopausal woman may also start up a new skein of headache. However other medical conditions such as polymyalgia rheumatica (usually given not as a diagnosis, but as a group of symptoms), rheumatoid arthritis which may give cervical spine disease, cancer which may give metastatic manifestations or immunosuppressive diseases should be clues as to the possible substratum on which serious and life threatening headaches may arise.

QUESTION 20: IS THERE ANY PHYCHIATRIC ILLNESS, HISTORY OF DRUG OR SUBSTANCE ABUSE AND WHAT IS THE QUALITY OF THE PATIENT'S LIFE?

A history of psychiatric illness does not necessarily mean the patient's headaches are psychiatric, but it is well to suggest the possibility that headaches may be stress related before having the patient undergo extensive testing. If extensive testing fails to yield an etiology for the patient's headache and then psychiatric consultation or psychiatric diagnosis is suggested, the patient may view the physician's suggestion as punitive.

A history of substance abuse or drug addiction or alcoholism should militate very strongly against using narcotic drugs, benzodiazepines or other drugs with a potential for cross addiction.

Sometimes the etiology of a headache will appear to be most obscure. It is the author's practice then to ask the patient to describe in full detail the circumstances of life under which the patient's headache started. If the patient states, "Nothing was going on", at the time the headaches began then it is the author's practice to inquire specifically about the patient's job, any deaths in the family, the state of health of other family members, any life transitions, and this will often reveal what was going on.

Finally, it is the author's habit to ask the patient to describe a typical headache if they have many, and a headache in great detail if they have few, beginning with the circumstances the day before, if these can be identified, and proceeding through the entire headache plus the next day.

THE TARGETED HEADACHE PHYSICAL EXAMINATION

The headache patient will commonly show no abnormalities on examination if he has a chronic benign type of headache. Incidental abnormalities may be encountered which are not germane to the patient's situation. However in all patients, a careful general physical and neurological examination should be carried out. In addition to the general examination, the skull and spine should be examined. The patient should have a complete examination of the head, eyes, ears, nose and throat for sinus disease, temporomandibular joint disease and even dental disease. Oftentimes pain referred to the head will come from the teeth and while sensitivity to cold is nonspecific, sensitivity to warmth such as using a warm test tube on a tooth, tapping a tooth or having a patient hold a warm liquid in their mouth may be specific for an abscessed or diseased tooth. In the general examination attention should be pain to the possible existence of cafe au lait spots or other stigmata of the phakomatoses. Examination of the range of motion of the neck should be carried out as well as a complete neurovascular examination. In the elderly with any suspicion of temporal arteritis, examination of the joints of the body plus the temporal arteries is mandatory.

The general configuration of the body especially a short neck or a low hair line may suggest congenital anomalies which may lead to headaches. The presence of obesity should be considered as a risk factor for the development of pseudotumor cerebri.

While there are numerous texts on the neurological examination ranging from those which are short and easily mastered (9) to those that are exhaustive (10) the author prefers the following scheme because of its thoroughness, but efficiency.

STEP 1: Check the patient's gait, noting his arm swing. Check tandem walking and walking on heels or toes. Remove any high heeled shoes.
RATIONALE: This portion of the examination is most conveniently performed with the patient totally dressed. This allows ambulation in hallways and allows for fuller observation of the patient over a longer period of time and a greater distance. It gives a general idea as to whether or not there is any hemiparesis, any limp, any postural abnormalities, and will quickly reveal any extrapyramidal or cerebellar signs.
STEP 2: Check the patient's posture with his feet together then have him close his eyes (Romberg test). This again is performed with the patient fully dressed and it gives a general idea of the posture of the patient plus the posterior column.
STEP 3: Have the patient step up and down alternatively with either leg onto a stool. This is a gross test of the strength ofthe lower extremity plus the patient's balance.
STEP 4: Test the motor power of the patient, his fine finger movements and alternating hand movements. Checkthe strength at the shoulder, elbow wrist and individual fingers. Check the strength of the hip, knee,ankle and foot. Check the heel to shin movementsand toe tapping and heel pivoting.
RATIONALE: This is a test for both upper and lower motor neuron disease.
STEP 5: Check the reflexes starting with the jaw jerk and for the presence of a snout reflex. Check the biceps, triceps, brachioradialis reflexes, knee and ankle jerk and check the foot for possible Babinski. Also check the abdominal reflexes.
STEP 6: Check sensation starting with the face, first with a wisp of cotton, then with a pin. Use a cotton pledget to test corneal reflexes. Under no circumstances use a Wartenberg wheel or another device which cannot be discarded. All safety Pins and other material used in the test which may breech the patient's skin must be discarded. Check vibration and position sense in both upper and lower extremities as well as the pin prick sensation in both upper and lower extremities. If there is any suggestion of a cortical problem check finger writing, point localization, two point discrimination, stereognosis and for extinction (the face-hand test, or double simultaneous stimulation).
STEP 7: Next: return to the cranial nerves. The first cranial nerve can be checked with common substances such as coffee, perfume, etc. Do not use spirits of ammonia or other substances which may volatilize and irritate the trigeminal nerve. The second cranial nerve should be checked by the pupillary light response, optic fundus and field by confrontation. The eye movements in all directions check the third, fourth and sixth cranial nerves. The sensory part of the fifth nerve has already been checked under sensation, so the strength of the temporalis and masseter muscles should be checked as well as that the jaw is protruded in the mid line.

The seventh cranial nerve is conveniently checked by having the patient close his eyes tightly and bare his teeth. He can also elevate his eyebrows and flare his nostrils. At this point, tongue movements can be checked including whether or not the tongue is protruded in the mid line. The tongue then should push the examiner's finger away in each cheek. The eighth cranial nerve should be checked already when the vibration is checked during the sensory exam. The ninth and tenth cranial nerves should be checked by observing the palate, the palatal movements and touching the back of the throat on either side with a cotton swab. The eleventh cranial nerve is checked by resistance of the patient to attempts to turn his deviated head from right to left, and left to right. At this point, the strength of anterior flexion and extension of the neck should be checked. Finally shoulder shrugging should be checked.

This entire scheme of the neurological exam should not take more than five to seven minutes in a healthy, normal adult. Obviously any portion of the neurological exam which is abnormal should be followed up.

CONCLUSION

If one goes about the headache history and physical examination in a systematic way, one can rapidly exclude acute or chronic life threatening headaches and decide on which patients require immediate or at least further diagnostic testing. One can then separate out into the most likely type of common headache syndrome. Further, with these type questions in mind, when one is confronted with a new type of headache, one can then try to fit that headache into the framework or these questions so as to develop as "data bank" of questions for future delineation of any new syndrome.

HEADACHE: FACTORS THAT CAUSE CONCERN

Clues to headaches which are life threatening and which cause concern come from the history, the physical examination and the diagnostic tests which are ordered. Saper (11) lists four key factors distinguishing physiological (primary) from secondary (organic) headache. These are:

1. Abruptness on onset.
2. Progression of the headache pattern.
3. The presence of abnormal neurological of physical findings.
4. The nature of the proviking and alleviating factors.

Diamond and Dalessio (12) make no specific allusions to danger signs.

A list of "danger signs" in headache pain patients that suggest the need for immediate attention are: (13)

1. Headache is a new symptom for the individual in the past three months, or the nature of the headache has changed markedly in the past three months.
2. The presence of any sensory or motor deficits preceding or accompanying the headache other than the typical visual prodromata of migraine with aura. Examples include hands or feet, aphasia or slurred speech.
3. Headache is one-sided and has always been on the same side of the head.
4. Headache is due to trauma, especially if it follows a period of unconsciousness (even if only momentary).
5. Headache is constant and unremitting.
6. For a patient reporting tension type headache-like symptoms:

A. Pain intensity has been steadily increasing over a period of weeks to months with little or no relief.
B. Headache is worse in the morning and becomes less severe during the day.
C. Headache is accompanied by vomiting.

7. Patient has been treated for any kind of cancer and now has a complaint of headache (to this may be added any patient who is immunosuppressed).
8. Patient or significant other reports a noticeable change in personality or behavior, or a notable decrease in memory or other intellectual functioning.
9. The patient is over 60 years of age, and the headache is a relatively new complaint.
10. Pain onset is sudden and occurs during conditions of exertion (such as lifting objects, sexual intercourse or "heated" interpersonal situation).

11. Patient's family has a history of cerebral aneurysm, other vascular anomalies or polycystic kidneys.

An extensive list of headaches of acute type is included in Wiener. (14)

Certain types of headaches may be difficult to diagnose even with a high index of suspicion and some situations which on the surface would appear ominous are more benign than commonly thought.

The evaluation of factors which cause concern begins with the initial site of contact with the patient (Question 1). In the emergency room generally the patient has a severe headache although the first chronic benign headache which is severe, should be excluded.

Questions 3 and 4: Has this ever happened before, and if so, is it progressive? If a patient has never had a similar headache before or the headache is progressively increasing in severity it raises the concern that the patient may have an ongoing process such as brain tumor or infection. A special case of headache which has never happened before is the so-called sentinel headache in subarachnoid hemorrhage. This has been extensively written about, and remains a subject of controversy. (15-26) It has been claimed (27) that sentinel headaches occur in the 40% of patients prior to aneurysmal rupture and that these warnings are very intense and abrupt in onset, "Like an unexpected clap of thunder", giving rise to the term thunderclap headaches. This conclusion however has been challenged by others. (28)

Question 5: Similarly any headache which has happened before but has now changed is cause for concern. Patients who develop migraine headaches generally develop them before the age of 25 if not earlier. If the headache has occurred before but is changing in pattern, that is a concern.

Question 7: The character and location of the headache may be quite nondescript even in a space occupying lesion.

Question 8: The onset to peak time is a cause of concern if the headache peaks rapidly especially with exertion or coughing or sneezing. However the entity of benign exertional headache or onset of a neuralgia is an exception.

Question 10: Associated and/or residual neurological phenomena or sequelae unless associated with well established migraine headache are a cause for concern. Exacerbating factors such as coughing, sneezing, straining or emotional excitement imply the possibility of space occupying lesions and/or aneurysm.

Question 19: Any medical condition suggesting spread to the central nervous system such as prior history of cancer, especially lung, breast or kidney, history of HIV infection or chronic diabetes mellitus or other immunosuppressing conditions such as lymphoma must be viewed with alarm.

Any headache which is associated with systemic symptomatology especially in the elderly should be considered for either spread of malignancy or systemic disease, or collagen vascular disease.

Question 20: Any history of substance abuse should be viewed with suspicion. History of chronic daily intake of medications whether they be opiates or ergots should be considered for chronic daily headache.

In the physical examination obviously papilledema, signs of surgical scars which could indicate prior cancer or other neurological abnormalities suggest the possibility of severe disease.

Finally there is a subset of patients with uncommon syndromes (29) which should be considered. Ref. 29 also contains a table distinguishing subarachnoid hemorrhage from benign exertional headache. (Table 2)

All patients with headache should be considered as having potentially serious intracranial or systemic disease. With attention to the targeted headache history, factors which cause concern can be delineated and confirmed by an appropriate physical and neurological examination as well as appropriate ancillary studies.

An algorhithm has been included for summary purposes. (Figure 1)

MANAGEMENT

Headache mechanisms provide a clue both as to when to be alarmed with headaches and what might possibly help headaches. All of the danger signals in headaches point to mechanisms of head pain which are fairly obvious. Assuming that there are indications that this is a primary headache, then there are five papers which are evidenced based treatment guidelines. These are:

Campbell JK, Penzien D, Wall EM, Evidenced-based guidelines for migraine headache: behavioral and physical treatments. *Neurology*, January 2000.

Frishberg B, Rosenberg JH, et al. Evidenced-based guidelines in the primary care setting: neuroimaging in patients with nonacute headaches. *American Academy of Neurology*.

Matchar DB, Young WB, Rosenberg, JA et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. *American Academy of Neurology*, January 2000.

McCrory DC, Matchar DB, Rosenberg JH, Silberstein SD, Efidenced-based guidelines for migraine headache: overview ofprogram description and methodology, *Neurology*, January 2000.

Silberstein SD, Rosenberg J, Multispecialty consensus on diagnosis and treatment of headache. *Neurology* 2000; 54(8): 1553.

Acute Treatment for migraine headaches in patients to moderate or severe migraine, DHE, or Triptans (Serotonin 1B/1D receptor agonists) should be used. Naratriptan, Risatriptan, Sumatript, and Zolmatriptan are effective and relatively safe. Ferrari MD, et at. Oral triptans (serotonin 5-HT 1B/1D agonists) in acute migraine treatment: a meta analysis of 53 trials. The *Lancet*, 358:1668-1675,2001.

Anti-emetics such as Reglan may be useful as well as Compazine. Non-steroidals are not recommended. All the oral triptans appear to be equally effective. Sumatriptan by nasal spray or in subcutaneous injection may be faster acting. DHE appears to be less effective. Toradol while frequently used is not particular effective. Combinations such as acetaminophe, aspirin, and caffeine may be useful in mild cases. Opiate analgesics including nasal Stadol, appear to be more effective than oral opiates. Corticosteroids IV, plus anti-emetics are reasonably effective. Nasal lidocaine does not appear to be effective.

As far as preventative treatment is concerned, the only FDA approved treatments are sodium valproate, amitriptyline, and Sansert. Nortriptyline appears to be useful. Other drugs used, but not proven include Doxepin, and Imipramine, mono amino oxidase inhibitors, and SSRI's. Inderal is the most useful of the beta blockers and while others like Timolol are useful they are not proven. Calcium channel blockers are often used but are not proven. Sansert is an effective drug with frequent side effects. Other drugs include Feverfew, magnesium, and B2 are unproven. For cluster headache, for the acute attack 100% oxygen at 10 to 12 liters per minute by mask for 20 minutes is useful. Injectable Imitrex has been useful also. DHE is sometimes effective. Locally applied Lidocaine nasal drops have been reported to be effective. Preventative treatments of limited courses of oral corticosteroids or Sansert can be very effective. Verapamil has been suggested and compares favorably with Lithium. Lithium may be used in the prophylactic treatment of chronic cluster headache. Valproic acid has been suggested but not proven. Topamax has been used in a number of cases and Neurontin in a single case. A surgical procedure in intractable cases is radiofrequency thermocoagulation of the trigeminal ganglion.

Chronic daily headache (Spierings, Egilius L.H., Review Article, Chronic daily headache, *Headache Quarterly*, 2000; 11 : 181-196.) Many of these patients are rebound type patients. When treated with Amitriptyline there is a 30% improvement, but the with the withdrawal of analgestics, 72% improvement.

When not treated with Amitriptyline and analgesics were continued there was an 18% improvement with analgesics withdrawn at 43% improvement. Hospitalization may be necessary for headache control in chronic daily or rebound headaches.

References:

• Herpes Zoster and Post-herpetic Neuralgia
Alon P. Winnie, M.D.

Pain.com
Introduction

While the pain of herpes zoster usually disappears with or shortly after the healing of the skin lesions, the most common (and dreaded) complication of the disease persistent pain, termed post-herpetic neuralgia. Post-herpetic neuralgia can vary in degree from a mild, bothersome discomfort to severely debilitating and agonizing pain. Severe post-herpetic neuralgia, most frequently described as a burning pain, is unique in that it may occur spontaneously and continuously without stimulation, though it is exacerbated by light tough and/or temperature changes. Post-herpetic neuralgia produces significant physical, mental, and emotional incapacitation, and is associated with a height rate of drug addiction and suicide(1).

The therapeutic benefit of sympathetic blocks in herpes zoster was discovered by coincidence by Rosenak(2), who was utilizing lumbar paravertebral sympathetic blocks to treat a patient with severe peripheral vascular disease. The patient also had developed painful, acute herpes zoster in the gluteal area two days earlier, and following the blocks the patient had dramatic relief of the zoster pain with drying and crusting of the vesicles within 48 hours. Startled by the seemingly illogical but dramatic effect of sympathetic blocks on acute herpes zoster, Rosenak undertook further trials of this therapeutic modality, and in 21 subsequent patients he obtained relief of pain in 19, with prompt drying and crusting of the vesicles. In one case the sympathetic block was incomplete on the first attempt; and when it was repeated, the patient obtained complete relief. Rosenak's only failure was a patient who had a six year history of recurrent neuralgia which was frequently accompanied by a rash, and it may be that this patient had zosteriform herpes simplex(3) rather than repetitive episodes of acute herpes zoster. Nonetheless, Rosenak still achieved a 95% success rate in his series, an impressive finding in a disease for which there had previously been no treatment whatsoever.

Since Rosenak's original publication a multitude of reports concerning the use of sympathetic nerve blocks for the treatment of acute herpes zoster have appeared sporadically in the literature(2.4-27). Because most of these studies were uncontrolled, Tenicela(28) reconfirmed the efficacy of sympathetic blocks in terminating acute herpes zoster in a double blind, randomized study. It is important to realize that the data presented in most of the studies cited were obtained in patients treated within one month of the onset of their pain; and Colding, who has the largest series of cases in the literature(12,14), has stated that it would appear from his data that the earlier this treatment is started, the more successful it will be. In fact, in his second paper(14), Colding reported that 90% of those patients treated before the eruption was two weeks old exhibited a dramatic response to sympathetic block, whereas only 40% of those treated more than two weeks after onset, responded to this treatment. Anyone with significant experience treating acute herpes zoster with sympathetic blocks is certainly aware that there is, indeed, a time after which the blocks cease to be effective in terminating acute herpes zoster and preventing post-herpetic neuralgia. The present study was undertaken to determine the more precisely relationship between the time of treatment of acute herpes zoster and the prevention of post-herpetic neuralgia and to utilize this clinical data to support our theory as to the mechanism by which sympathetic blocks provide their therapeutic benefit(20).

Methods and Materials

The charts of 122 patients treated in the University of Illinois Pain Control Center for pain related to herpes zoster were reviewed retrospectively. Only the records of patients with complete follow-up, whether by personal or telephone interview, were utilized for the study; and all patients with complete follow-up were included, regardless of their response to treatment. The technique by which sympathetic blockade was provided, of course, depended on the location of the patient's pain: Patients who had trigeminal, cervical, brachial, or high thoracic nerve involvement received stellate ganglion blocks by the anterior approach; while patients with a thoracic, lumbar, or sacral distribution receive epidural blocks. In a few cases where the herpetic lesions did not extend all the way to the midline, intercostals blocks were utilized for thoracic involvement. The local anesthetic agents utilized in the epidural (and intercostals) blocks were administered

in a sufficient concentration to produce sensory as well as sympathetic blockade in order to confirm that the level of the blockade was appropriate for the level of the patient's pain. The agents utilized for the blocks included bupivacaine, mepivacaine, lidocaine, and 2-chloroprocaine, all without epinephrine.

In order to assess the importance of time of treatment of the efficacy of sympathetic blockade In terminating acute herpetic pain and in preventing post-herpetic neuralgia, great care was taken to accurately determine the duration of the patient's symptoms prior to the initial treatment and to note carefully the timing of subsequent treatments. Thus, patients were grouped according to the duration of their symptoms prior to the initiation of treatment as follows: Group A consisted of those patients whose treatment occurred less than two weeks following the onset of symptoms; Group B represents those patients treated at least 2 weeks but less than 1 month after the onset of symptoms; Group C patients were treated at least 1 month but less than 2 months after the initial onset of symptoms; the patients in Group D were treated at least 2 months but less than 6 months following their first symptoms; Group E patients were treated at least 6 months but less than 1 year after the initial symptoms; and the patients in Group F were all treated at least 1 year after the onset of their symptoms. In all cases the first sympathetic block was administered on the first visit to the pain Control Center. The patient was told to return immediately if and when their pain returned for a second block. If a second block was carried out, again the patient was told to return if and when their pain recurred for a third block. If their pain returned after a third block, with rare exceptions, further sympathetic blocks were not administered.

Similarly, the various responses to treatment were grouped as follows: a Type I response indicates complete and permanent relief was achieved after a single block. A Type II response indicates that the first treatment provided pain relief, but though the relief outlasted the effect of the anesthetic (by as long as several days), the pain subsequently returned. However, when it returned, it was significantly less severe, and with this type of response repeated blocks (usually two or three) did provide permanent pain relief. A Type III response indicates that temporary pain relief was provided by each treatment; but the relief only lasted as long as the local anesthetic, and when the pain returned, the intensity was the same as before the block. However, in this type of response subsequent to the series of blocks these patients had a slow, gradual improvement in their pain until they were ultimately (and permanently) pain free. It is significant to note that all of those who exhibited a Type I, II, or III response ultimately became and remained pain free, unlike those exhibiting a Type IV or Type V response: A Type IV response, like the Type III response, indicates that temporary pain relief was provided by each treatment, relief which only lasted as long as the local anesthetic. But unlike the Type ill response, patients exhibiting a Type IV response, though improved, still had residual pain at the time of follow-up. A Type V response indicates no apparent improvement whatsoever with treatment and residual pain at the time of follow-up. So all patients exhibiting a Type IV or V response continued to have pain in spite of the treatment.

All patients included in this study were followed up by telephone. In addition to the data concerning age, sex, distribution of lesions, duration of symptoms prior to treatment, number of treatments and response to treatment, information was obtained concerning any complications of the treatment, any co-existant diseases and any medications being taken concomitantly. The results of this study were analyzed using a contingency table (Table1), which gives the Number of patients in each group (A-F), and within each group, the number exhibiting each type of Response (I-IV). This table was then analyzed by a chi-square approximation(29)

Results

The results of this study are tabulated in Table 1 and presented graphically in Figure 1, which indicates dramatically the relationships between the type of responses to treatment and the time interval between the initial symptoms and the initiation of treatment. Of the 21 patients in Group A, all twenty-one (100%) had complete relief of their pain at the time of follow-up: seven in this Group demonstrated a Type I response, eleven demonstrated at Type II response, and three a Type III response.

Of the thirteen patients in Group B, twelve (92.3%) were pain free at the time of follow-up, and one was improved, though he did still have some residual pain: three of the patients in this Group exhibited a Type I response, seven a Type II response, and two a Type III response, and one a Type IV response.

Of the fifteen patients in Group C, twelve (80%) were pain free at the time of follow-up, while three had residual pain; of the patients who were pain free at the time of follow-up, none exhibited a Type I response, ten exhibited a Type II response, and two a Type III response. Of those who still had pain at the time of follow-up, one represented a Type IV response, while two exhibited a Type V response.

Of the twenty-eight patients in Group D, five (18%) were pain free at the time of follow-up, while twenty-three still had pain: of the five who were pain free at the time of follow-up two had exhibited a Type I response, two a Type II response, and one a Type III response. Of those who had persisted pain at the time of follow-up, nine represented a Type IV response and fourteen a Type V response.

Of the nineteen patients in Group E, four (21%) were pain free, and fifteen had persistent pain: of the patientswho were pain free at the time of follow-up, two had exhibited a Type I response and two a Type II response. Of those patients with persistent pain at the time of follow-up, four represented a Type IV response and eleven a Type V response.

Of the twenty-six patients in Group F, only one (4%) was pain free, with all of the other twenty-five complaining of persistent pain: the patient who was pain free at the time of follow-up had exhibited a Type II response, while four of the patients with persistent pain represented a Type IV response and twenty-one a Type V response.

With respect to complications specifically related to the treatment, only three of the 134 patients who received epidural blocks developed hypotension, and in each case the hypotension responded promptly to intravenous fluid therapy and/or small doses of ephedrine without further sequelae. In two of the patients treated with epidural injections the dura was inadavertently punctured. Of these two, one had no sequelae and went home after remaining supine several hours, while the other experienced a severe spinal headache with nausea and vomiting and ultimately required an epidural blood patch to obtain relief. Interestingly, in spite of having had such a severe headache, this patient remained enthusiastic about the treatment, because it had provided complete relief from her herpetic pain. Of the 135 stellate ganglion blocks carried out, only one resulted in undesirable side effects, which in this case consisted of hoarseness, blurred vision, and nausea, all of which resolved spontaneously without treatment.

Discussion

Certainly this study corroborates Colding's impression that the earlier sympathetic blocks are initiated, the more successful they will be in terminating the acute phase of the disease and preventing post-herpetic neuralgia. As may be seen in Table 1 (I, II, III Combined column, far right), 100% of the patients in Group A were pain free at the time of follow-up. However, only 85% were pain free upon completion of their last sympathetic block. In Group B 92.3% of the patients were pain free at the time of follow-up, though again, only 77% were pain free at the time of their last block. In Group C, while the overall success rate decreased somewhat, nonetheless, 80% of the patients were pain-free at the time of follow-up, 67% of whom were free of pain following their last block. It is important to note that when the initial treatment was delayed beyond two months, as was the case in Groups D, E, and F, the overall success rate fell drastically to 18%, 21%, and 4% respectively Interestingly enough, at six months and beyond, it is only those patients who obtained relief at the time of the last treatment that are pain free at the time of follow-up, i.e., there are no Type III responses.

From these data it would appear that while success in terminating acute herpes zoster isgreatest when the patient is treated within the first few weeks, if treatment is begun within two months, the chance of preventing post-herpetic neuralgia is still almost 80%. To test statistically the difference between treatment before and after two months in terms of preventing post-herpeticneuralgia (i.e., whether 2 months is the latest that this therapy will provide a reasonable expectation of preventing post-herpetic neuralgia), the data were analyzed using a contingency table (Table 2) and applying the Fisher Exact test(30). Such analysis indicates the highest statistical significance ($P<0.000001$). Nonetheless, in spite of the low incidence of Type I and Type II responses to sympathetic blocks when they were administered more than 2 months after the initial onset of symptoms, this form of therapy should be tried no matter how late after the initial symptoms the patient is seen, since the occasional success achieved represents 100% success to that patient. And even if the treatment fails, it is innocuous in competent hands, as attested to by the fact that we experienced no serious complications in our entire study, in spite of the fact that most of the blocks were performed by residents and fellows.

Any theory as to how sympathetic blockade terminates the acute phase of herpes zoster must also explain how sympathetic blockade prevents the development of post-herpetic neuralgia if a patient is treated early enough and why it fails to do so when treatment is delayed. We feel that such a theory is as follows: It is well established that shortly after reactivation, the Varicella-Zoster virus moves rapidly out along the course of the involved nerve(s), producing an inflammatory reaction that is responsible for the initial hyperesthesia, dysesthesia, and pain, and ultimately, the characteristic vesicular eruption(31). Such an inflammatory response typically produces intense sympathetic stimulation, and Selander has recently demonstrated experimentally that sympathetic stimulation can reduce blood flow in the intraneural capillary bed by as much as 93%(32). Furthermore, Lundborg has shown that when such ischemia is prolonged, there is anoxic damage to the endoneurial capillary endothelium with leakage of albumen, and the formation of endoneurial edema. This edema, in and of itself, can cause increased intrafascicular pressure and result in even greater impairment of endoneurial blood flow and ultimately irreversible nerve damage(33). In addition to the production of hypoxic damage, such a reduction in blood flow results in glucose deprivation,

which like hypoxia produces preferential destruction of large nerve fibers with survival and/or recovery of the less metabolically active small fibers(34).

It would appear, then, from the available laboratory data that in the acute phase of herpes zoster the virus (or its toxin) is capable of producing severe sympathetic stimulation which results in ischemia of the involved nerves; and it would appear from our clinical data that after the first few weeks the reversal of the results of the ischemia (the hypoxic, hypoglucic, and toxic damage to large fibers) takes progressively longer and requires a greater number of sympathetic blocks. And finally, also from our clinical data, it would appear that after two months the ischemic damage becomes irreversible.

Both Fink and Lundborg have demonstrated experimentally in animals that, unlike large fibers, small fibers are able to survive prolonged periods of ischemia and still recover full function (33,35). That this is also true in man is supported histologically by the work of Noordenbos(36), who many years ago compared cross-sections of post-herpetic and normal nerves under the light microscope and found that in the post-herpetic nerve, the vast majority of the large nerve fibers have been destroyed and replaced by fibrous tissue. As a result, unlike the situation in a normal nerve, where the population of nerve fibers is predominatly composed of large fibers,(2A) Figure 2, Noordenbos found that in the post-herpetic nerve there was a predominance of small fibers,(2B) Figure 2, a phenomenon he referred to as "fiber dissociation II Correlating these histological findings with the clinical picture of spontaneous pain in the post-herpetic patient, Noordenbos postulated that large fibers tend to inhibit the entry of noxious impulses into the central nervous system, while small fibers tend to enhance such entry .Therefore, in the post-herpetic nerve, "fiber dissociation" abolishes the normal inhibitory effect of large fiber predominance with the result that not only is the entry of noxious impulses into the spinal cord enhanced, many impulses that are not ordinarily noxious are interpreted as noxious by the altered large/small fiber balance.

The similarity of Noordenbos' theory, (Figure 3), to the Gate Control Theory conceptualized by Melzack and Wall six years later(37) is remarkable in itself; but more importantly, it is critical to our hypothesis as to mechanism by which sympathetic blocks produce their therapeutic benefit. Since the characteristic lesion in post-herpetic neuralgia is the death and replacement of large nerve fibers within the nerve, clearly if the sympathetic response responsible for the ischemic state of the nerve is interrupted before the changes in the large fibers become irreversible, the symptoms of acute herpes zoster disappear, and the development of post-herpetic neuralgia is avoided. It would appear from the data obtained in the present study that this is precisely what has happened in those patients who had a favorable response to sympathetic blocks. It would also appear from this study that if this therapy is instituted within the first few weeks of the onset of the disease, in most cases, reversal of the ischemic changes is almost immediate, whereas if treatment is delayed, the changes secondary to the ischemia become progressively more severe; and after about two months, large fiber death and fiber dissociation make the process virtually irreversible.

Interestingly, the advent of acyclovir for the "specific" treatment of herpes zoster at first appeared to represent a replacement for the nerve block therapy of this disease. However, it now has been shown that while acyclovir is effective in terminating the acute phase of herpes zoster in a high percentage of cases, it does not prevent against the development of post-herpetic neuralgia(38). As a matter of fact, it may even enhance this possibility, since in those patients in whom acyclovir fails to terminate the acute phase of the disease, the time required for a course of acyclovir only serves to delay the institution of sympathetic blocks by several weeks. Thus, because the effectiveness of sympathetic blocks in terminating the disease process is related to the time of therapy, the delay to administer acyclovir could reduce the efficacy of the sympathetic blocks, once they are administered.

References:

• **Myofascial Pain and Its Management**
Bernard M. Abrams, M.D.

Pain.com

Myofascial pain syndrome (MPS) is a chronic pain syndrome that affects a focal or regional portion of the body. The sine qua non of myofascial syndrome is the finding of myofascial trigger pints on physical examination. Although these trigger points are generally localized to the regional part of the body affected the pain of myofacial pain syndrome is often referred to other areas. This referred pain is often misdiagnosed or attributed to other organ systems leading t extensive evaluations and ineffective treatment. The trigger point is the pathognomonic lesion of myofascial pain and is thought to be the result of microtrauma to the affected muscle. Stimulation of the myofascial trigger point will reproduce or exacerbate the patient's pain. (1) Substantial controversy revolves around both myofascial pain syndrome and fibromyalgia. (2,3,4)

There are large numbers of patients who have muscular pain diagnosed as myofascial pain syndrome or alternatively as fibromyalgia requiring diagnosis and treatment. The pain physician needs to be aware of the diagnosis, differential diagnosis and management of the complaints manifested by these patients. The pain physician needs to know the controversial nature of this class of illness or he may become the target of criticism for uncritically subscribing to the their diagnosis and treatment. Myofascial pain syndrome has an enormous legal and economic impact. Enormous sums are expended on the legal settlement of claims on myofascial pain syndrome (and fibromyalgia) said to be two hundred million dollars per year in Canada, (5) eight billion dollars per year in the United States (2), and the leading cause of disability in Norway and having led to near collapse of the disability/workmens compensation system in Australia. (6) The history of the development of the concepts of myofascial pain syndrome is a long one. Two excellent reviews (7,8) allow for some abbreviation here. In the 1700's the distinction between articular and muscular rheumatism arose in Germany, Scandinavia, and Great Britain with awareness increased by the prevalence of massage for therapy and diagnosis. In 1815 William Balfour of Edinburgh described nodules in rheumatic muscle which he ascribed to inflammation in the connective tissue.(9)

The history of this condition then becomes convoluted. In 1876, Helleday described a chronic myalgic condition characterized by pain and nodules in the affected muscles. In 1904, Gowers first used the word *fibrositis*. He described (10) as one of his suggested treatments, deep hypodermic injection of cocaine repeated daily for two or three weeks!

Stockman (11) erroneously perpetuated the concept of inflammatory nodules though he described edema without leukocytes in inflammatory lesions. Moldofsky in 1975, promulgated the concept of non-restorative sleep in fibromyalgia.(12)

During the 1930's Mixter and Ban published their article, "Rupture of the Intervertebral Disc with Involvement of the Spinal Canal," codifying the concept of the herniated disc. At the same time Kellgren in 1938 published, "A Preliminary Account of Referred Pain Arising from Muscle." He described patients with neck and back pain both traumatically induced and occurring spontaneously with local tender spots and referred pain which could be totally abolished with the local infiltration of novocaine. (13)

The first reference to the tender area in muscle was "tender zone," and in 1939, Otto Steindler, professor of orthopedics at the University of Iowa used the term trigger point and myofascial pain for the first time.

Myofascial Pain Syndrome: Janet Travell (14) formulated a theory that the cause of myofascial pain was a vicious cycle with muscle spasm leading to more muscle spasm. Electro-myography never produced evidence of spasm and in 1983 (15) Travell and Simmons revised their theory to include tissue damage in localized areas of muscle leading to a hypermetabolic-vasoconstrictive state resulting in an ischemia of the muscles.

The The diagnosis of fibrositis was generally discarded when no inflammatory changes were found in muscle. Criteria for the diagnosis of myofascial pain syndrome were suggested by Simons (16). Table 1.

Fibromyalgia was the term advanced by Yunus et al., (17) to replace "fibrositis" to acknowledge the lack of inflammation. Utilizing Smythe's description of fibrositis (18) they propounded initial criteria which reached fruition as the American College of Rheumatology Criteria for the diagnosis of fibromyalgia published in February 1990. (19) Table 2.

Controversy has been abundant (2, 3, 4, 6) about the entities of myofascial syndrome and fibromyalgia. Problems of nonreproducibility of trigger points (2) false positives with inability to differentiate patients and controls as well as circularity in training examiners who then selected the patients have been invoked as invalidating studies in which there is "no gold standard," i.e., a definitive test for the disease such as biopsy-obtained material, neurophysiologically distinct or clinical laboratory verifiable findings.

Fibromyalgia has lead to "preferred non-histologic terms" (2) such as *aches and pains, chronic pain syndrome, somatoform pain disorder, pain amplification syndrome, somatic dysthymia, hypervigilance syndrome, affective spectrum disorder, and diffuse suffering* portray the type of skepticism already described. Previous muscle pain syndrome such as myalgia, rheumatic myositis, pressure point syndrome,

myofibrositis, fibromyositis, myelogelosis, muscle hardenings, and non-restorative sleep syndrome (9) reflect previous confusion if perhaps a less harsh judgement. An effort to codify these syndromes under the rubric "tension myalgia" (9), a diagnosis which first appeared at the Mayo Clinic in about 1950 has failed to gain prominent support or representation. A recent report on fibromyalgia and disability (20) dealt with causality, disability and prognosis.

CLINICAL PRESENTATION, DIAGNOSTIC CRITERIA, DIFFERENTIAL DIAGNOSIS, AND RELATED CONDITIONS

Myofascial Pain Syndrome: Travell (15) defined a myofascial pain syndrome as "pain and/or autonomic phenomenon, referred from active myofascial trigger points with associated dysfunction. The specific muscle or muscle group that causes the symptom should be identified." The myofascial trigger point, according to this definition is intrinsic to the disease and is defined as a "hyper-irritable spot, usually within a taut band of skeletal muscle or in the muscle's fascia, that is characteristic on compression or that can give rise to characteristic referred pain, tenderness, and autonomic phenomena.

Myofascial pain syndrome is a regional pain syndrome accompanied by trigger points. (1) When a trigger point is palpated there is referral of pain. Common areas are the neck, shoulders, arms, head, and face, lumbar musculature and legs. The character of the pain varies from a pressure-like sensation to a sharp pain and is usually described as either dull, sharp, or burning. Associated symptoms include stiff joints and swelling, poor sleep, tinnitus, fatigue, paresthesias, nausea, dizziness, and global depression and anxiety. (1)

The physical sign most often described is a trigger point and manuals,(1,15) contain diagrams of characteristic trigger points with radiation of the pain in different body regions. No evidence of joint dysfunction nor neurological deficits are expected. There is "a lack of obvious organic finding" and "most of the regional rheumatic disorders cannot be defined radiographically or by laboratory tests and there is a lack of reproducible histologic studies on trigger points and a lack of routine EMG findings." (21) This has raised the claim (22) "that certain diagnostic criteria would also apply equally to conversion reaction and malingering."

In its most restricted form the myofascial pain syndrome is characterized by pain in a zone of reference, trigger points in muscle, occasional associated symptoms, and the presence of contributing factors. The so called "jump sign" is a general pain response of the patient who winces, may cry out, and may withdraw in response to pressure applied on a trigger point. (15) Trigger points can range from 2 to 5 mm in diameter and are found within a hard palpable band of skeletal muscle and fascial structures of tendons and ligaments and may be active or latent. (21) " A local twitch response" can also occur with palpation and this is elicited by placing the muscle in moderate passive tension and snapping the band containing the trigger point briskly with the film pressure from a palpating finger moving perpendicularly along the band at its most tender point. Affected muscles may show increased fatigability, stiffness, subjective weakness, and restrictive range of motion. (21) Contributing factors may include psychological problems, maladaptive behavior, poor muscle health, joint pathology, and of course trauma. (21) The controversy over the reproducibility of trigger points and their referral patterns has been alluded to above.

All routine clinical laboratory tests are generally normal as are biopsies, and electromyography. Sleep disturbances are reported but offer little help in diagnosis. Current criteria are listed in Table 1. The differential diagnosis includes all conditions peculiar to that region including arthritis, infection, malignancy and mechanical causes. (1) Also to be ruled out are chronic regional pain syndrome (CRPS I and CRPS II previously called reflex sympathetic dystrophy and causalgia), vascular syndromes, e.g., thoracic outlet syndrome, and claudication, and enthesiopathies, e.g., lateral epicondylitis, bursitis, scapulocostal syndrome (23), iliolumbar syndrome, (24) trochanteric bursitis (25), ischiogluteal bursitis (26), and well as visceral syndromes of the chest, abdomen, and pelvis. Also included are more obscure syndromes of the chest wall such as the slipping rib syndrome (27), or entrapment of the nerves in the rectus abdominus, or diabetic thoraco-abdominal neuropathy. (28,29,30,31) The differential diagnosis of myofascial pain syndrome is summarized in Table 3.

PATHOPHYSIOLOGIC MECHANISMS AND ETIOLOGY

There are no characteristic pathological anatomical features of either myofascial pain syndrome or fibromyalgia. Certain biochemical changes have been found in fibromyalgia including a lowered serum serotonin level as well as low tryptophane in the serum and spinal fluid of fibromyalgia patients. Substance p is elevated in the CSF of fibromyalgia subjects. Kynurenine is also increased in the cerebrospinal fluid of fibromyalgia subjects. The findings suggest that there is an increased likelihood that noceioceptive stimuli entering the spinal cord will be amplified or that non-nocioceptive stimuli will be interpreted as painful. There is also a suggestion that there is a diversion of tryptophane into the kynurenine pathway away from the production of serotonin.

Electromyographic changes in myofascial syndrome are at this point preliminary and speculative.

TREATMENT

The treatments of myofascial pain syndrome and fibromyalgia are multiple (9) attesting to the lack of proven efficacy for any single treatment. There is no doubt that reassurance and education of the patient is extremely helpful in assisting the patient. The Arthritis Foundation (1-800-207-8633) with Internet address www.@arthritis.org offers an informative brochure as does the fibromyalgia network (1-805-631-1950).

Elimination of contributing factors is essential for the success of treatment and prevention. Of these, the two most important contributing factors are motor dysfunction and disturbance of sleep.

Physical therapy consists of deep sedative massage, often preceded by superficial heat.(34) Gentle prolonged stretching of affected muscles as well as a combination of hot packs, high intensity galvanic stimulation, and progressive relaxation have been advocated. (9) Electromyographic feedback may help the patient become aware of postural stresses and habitual contraction of muscle. One of the major helpful therapies is exercise. It has been shown overall that a cardiovascular exercise fitness program is more effective than a flexibility exercise program in alleviating the symptoms of patients with fibromyalgia. (35)

Inactivation of trigger points can be done manually by ischemic or trigger compression. The muscle is stretched locally, the regional fascia is stretched, and the entire muscle is stretched. The patient must also be taught to self stretch affected muscles. Aquatic therapy is very helpful as a non-traumatic method of conditioning muscle and restoring movement pattern.

Trigger can also be inactivated either by local injection or by dry needling. Spray and stretch have also been utilized extensively. Botulinus toxin has been reported to be useful in patients with chronic myofascial pain syndrome involving cervical paraspinal and shoulder girdle muscles. (36,37)

PHARMACOTHERAPY OF MYOFASCIAL PAIN SYNDROMES

In both acute and chronic pain, pharmacotherapy is often indicated. Most studies on multidisciplinary biopsychosocial rehabilitation among working adults have shown no advantage over multiple treatments including physical therapy, manipulation and patient education have indicated no trend for improvement. (38, 39) A slight trend was noted with acupuncture in terms of improvement. In addition spinal manipulation, (46,41) injections of sterile, subcutaneous water for chronic neck and shoulder pain following whiplash injuries (42) and intra-articular corticosteroids have demonstrated no consistent or statistical improvement in patients. (43) A slight improvement was recorded for percutaneous radio frequency neurotomy for chronic cervical zygaphophyseal-joint pain. (44) Therefore, in most instances one is left with palliative therapies of the pharmacological type.

Analgesics:

Typically treatment may be begun with acetaminophen. It has the advantage of being non-irritating to the GI tract and has analgesic and antipyretic activity. Surprisingly, although acetaminophen is not generally considered to affect inflammation, when compared with nonsteroidal anti-inflammatory agents in osteoarthritis of the knee it faired equally well for relief of pain. (45) It is best administered on a regular basis avoiding prn status and doses above 3 gm per day are to avoided. In two trials tailored for low back pain patients treated with acetaminophen faired as well as those treated with an opioid (meptazinol-not available

in the United States) and an NSAID (difunisal) and a randomized comparison with another NSAID (mefenamic acid) demonstrated acetaminophen to be superior. (46) Patients with underlying liver disease or those who weigh less than 90 pounds as well as patients taking Coumadin will need tailored advice about acetaminophen dosing. (47) Concurrent use of acetaminophen and alcohol is to be vigorously discouraged because of the possibility of increased liver problems.

Skeletal muscle relaxants:

Skeletal muscle relaxants are generally more effective than placebo. (48) Side effects include sedation and the possibility of an addictive potential. (49,50) Skeletal muscle relaxant therapeutic effects are independent of sedative effects. (51) Skeletal muscle relaxants demonstrate a consistent advantage over placebo. Cyclobenzaprine has been shown to be superior to placebo for acute low back pain (52) and in particular methacarbamol and has been shown to be more efficacious than placebo in a double blind trial of patients suffering neck pain. (52) Individual preferences amongst musculoskeletal relaxants should depend upon the experience of the clinician. More extensive experience with a limited number of skeletal muscle relaxants is probably far more efficacious. There is some potential for abuse (Metaxalone accepted) and particularly caprisoprodol. Metaxalone appears to have the lowest reported incident of sedation. In patients needing night time sedation, more sedating agents such as cyclobenzaprine or methocarbamol may be employed at bedtime with a lesser sedating, e.g., methaxalone for daytime use. In particular methaxalone has a more versatile dosing pattern. Carisoprodol is currently a controlled substance due to its metabolism to Meprobamate. In addition a red flag should be raised when a patient insists on the brandname "Soma" because this particular drug has a very high street value. (Personal communication DEA)

Skeletal muscle relaxants are enhanced by combination with NSAID's and generally the use of skeletal muscle relaxants is as an "add on" to NSAID's. (54,55) Further report indicates that Cyclobenzapine and Naproxyn were superior to Naproxen alone in the treatment of acute low back pain and muscle spasm and by extension to cervical and shoulder pain and spasm. (56) There is apparently no difference between the efficacy of skeletal muscle relaxants plus opioids and NSAID's alone.

NSAIDs:

NSAIDs have been demonstrated to be effective for both pain relief and overall improvement in comparison with placebo. There is no evidence to suggest that one NSAID is superior to another or consistently better tolerated. Most patients develop a definite and strong preference for one agent over another. It has been suggested that Cox-2 NSAIDs or Coxibs have a superior safety profile. Platelet inhibition and gastrointestinal muscosal integrity breeches are felt to be mediated by blockade of Cox 1. The cost is much greater for the new generation Cox 2 inhibitors but significant morbidity from NSAIDs in general militate in their favor.

Opioid analgesia:

While cervical radiculopathy may produce excruciating pain and loss of sleep and daytime function, generally musculoskeletal complaints do not require opioid analgesia. In the case of cervical radiculopathy the pain is generally better treated with epidural steroids or high dose oral steroids ("the green protocol" a 12 day declining dose of Decadron starting with 64 mg daily and declining by 8 mg per day every three days). While the potential for opioid addiction in a previously non-addicted individual has been over stressed, it is well to avoid this medication except as a "rescue medication." (57)

Opioids available include: Codeine, Morphine, Oxycodone, Hydrocodone, Hydromorphone, Methadone, Butorphanol, Fentanyl, and Pentazocine. Preference should be given to starting with Hydrocodone/amphetamine combinations. Newer formulations combine 5,7.5, or 10 mg of Hydrocodone, with 325 mg of Tylenol, therefore decreasing the daily Tylenol load. Tramadol a non-opiate has modest activity at the mu opioid receptors and functions as a norepinephrine and seratonin re-uptake inhibitor. If other seratonergic agents are used tramidol should be used with caution and has a potential for producing seizures.

Other agents:

Topical analgesics including Methylsalisalate, capsaicin and topical NSAIDs may be used. Antidepressant medication in the form of amitriptyline, nortriptyline, and trazadone have been used mainly as an adjunct to sleep.

Chronic myofascial pain.

Chronic myofascial pain demand a re-evaluation of the patient and the adage that "diagnosis precedes therapy" is never more clearly demonstrated.

Pharmacologically NSAIDs are usually more beneficial than acetaminophen and one small randomized well controlled study demonstrated that chronic NSAIDs are more effective for reduction of pain than placebo. (58) This is particularly true in joint pain. Tolerance to NSAID's does not develop but GI toxicity more often limits their use. (59)

Chronic neck and shoulder pain antidepressants:

A variety of antidepressants including imipramine, trazadone, nortriptyline, doxepine, and clomiprame have produced conflicting results as far as reduction of pain. However, a controlled trial of amitriptyline versus acetaminophen found greater efficacy with amitriptyline. (60)

Adverse effects of amitriptyline include dry mouth, constipation, sexual dysfunction, orthostatic hypotension, sedation, weight gain, and prolongation of the QT intervals.

Other agents:

Skeletal muscle relaxants have not been extensively reported in trials for chronic myofascial pain. In one brief study (10 days) in chronic low back sufferers the anti -spasticity agent tizanidine which has central pain properties, the skeletal muscle relaxant tetrazapam was superior to placebo. (58) In general chronic skeletal muscle relaxant utilization is to be discouraged. Tizanidine, an antispasticity agent with central pain relieving properties has been used in chronic pain in the neck and shoulder with some anecdotal reports of efficacy however, no systematic study has been done to this point.

Chronic myofascial: The role of opioids

Chronic opioids in the form of Oxycontin, a long acting opioid analgesic, MS Contin, Methadone, or Fentanyl patches have been used and become an inevitable part of the patient for whom there is genuine concern over long lasting musculoskeletal or other nociceptive pain. Opioids are generally well tolerated with fewer side effects than non-steroidals, antidepressants and other agents. Certainly their efficacy is undoubted in controlled studies. In general large populations of patients with need for long term opioids have rarely become substance abusers due to opioid treatment unless they had a prior history of substance abuse. (61) The goal of treatment of chronic neck and shoulder pain is a return to function. Opioids are generally well tolerated with the exception of the adverse drug effect of constipation most users develop tolerance to all other adverse effects. A pain contract should be established with every patient who requires chronic administration of opioid analgesia specifying conditions under which medications will be refilled, dose escalation stipulations, and other conditions which individual clinicians feel are necessary to maintain a successful use of opioid analgesia.

BOTULINUS TOXIN

Type A in the management of myofascial syndrome. (36,37)

Since many of the treatments for myofascial syndrome are aimed at blocking the trigger to allow sustain muscle relaxation the use of botulinum toxin represents a logical extension of traditional therapies. Although not specifically approved for this indication botulinus toxin A has a long track record of efficacy in safety in the treatment of a variety of other conditions including strabismus and dystonias. Van Ermengen identified botulinum toxin as the causative agent of botulism in 1897. However, it was not until 1949 that it was demonstrated that botulinum toxin produced the clinical signs of botulism, i.e., facial weakness, ophthalmoplegia, dysphonia, dyspnea, and limb paralysis to blockade of neuromuscular transmission. This

finding provided the basis for the clinical use of botulinum toxin type A. After the safety and clinical utility of botulinum toxin was unequivocally demonstrated in the treatment of strabismus in non-human primates, in 1989 the Food and Drug Administration approved botox A for use in humans to treat strabismus, blepharospasm, and hemifacial spasm. Over the ensuing 9 years the promising clinical results and safety have lead to the increased and expanded use of botulinum toxin A for a variety of clinical conditions including the cervical dystonia, spastic dysphonia, spasticity and myofascial pain syndrome. Botulinum toxin A is synthesized as a single chain. The neuro-toxin activation requires cleaving of a single chain into a die chain molecule. Botulinum toxin A is a neuro-toxin which exerts its clinical affect by inhibiting acetylcholine at the neuro-muscular junction. In addition to the clinically useful botox A, the bacteria, clostridia botulinum produces 6 other paralytic toxins labeled B, C, D, E, F, and G. Blockade of neuromuscular transmission is by binding then internalization and subsequently blocking. First botulinus toxin A binds to the motor nerve terminal then it's internalized inside the nerve terminal and the light chain interferes with acetylcholine release and ultimately it blocks muscle contraction by inhibiting the release of acetylcholine from the nerve terminal. Clinically demonstrable weakness is usually observed within 24 to 72 hours. It has a duration of 2 to 6 months. Botulinum toxin is produced by growing clostridia botulinum and then purifying and titrating the potency of the harvested toxin. The measure of potency of botox A is the mouse unit. The injection of botulinum toxin A into myofascial trigger points is carried out in a manner analogous to trigger point injection by using a solution containing 10 units per ml with a total dose not exceed 400 units. The major side effect is excessive weakness of treated muscles with attendant functional disability. The effects of botox A may be potentiated by aminoglycoside antibiotic. The smallest possible dose should be used and the therapeutic dose is significantly less than the toxic dose.

FIBROMYALGIA: Fibromyalgia syndrome is a common form of generalized muscular pain and fatigue that is believed to affect approximately 2% of the US population or 5,000,000 people. It has been defined above as a form of non-articular rheumatism characterized by widespread musculoskeletal aching and stiffness as well as tenderness on palpation at characteristic sites called tender points. (1) Initially fibromyalgia was characterized as regional primary, secondary, and concomitant. Primary implies the absence of a significant underlying or concomitant condition. Secondary fibromyalgia is caused by an underlying condition such as active rheumatoid arthritis and hypothyroidism. Concomitant fibromyalgia is that in which the patient has the features of primary fibromyalgia as well as the concomitant presence of another condition which affects few parts of the body. No significant differences in clinical presentation have been shown between primary fibromyalgia and concomitant fibromyalgia. Secondary fibromyalgia must be causally related. Secondary fibromyalgia is further defined as a condition which would remit following the specific treatment of an underlying condition such as rheumatoid arthritis or hypothyroidism without specific treatment for fibromyalgia.(l)

Fibromyalgia is a disease which occurs predominantly among women 80 to 95% with the most common age of presentation 40 to 50. It has been described in all ethnic groups, most frequently in caucasians probably due to referral bias.

Symptoms include musculoskeletal pain at multiple sites (100%), stiffness and swollen feeling in tissues (30 to 70%), general and morning fatigue (75 to 90%), poor or impaired sleep (50 to 70%), paresthesias (20 to 70%) with associated symptoms of global anxiety, headaches, dysmenorrhea, irritable bowel symptoms, global depression (generally in the 30 to 60% range) as well as sicca symptoms (15%), Raynaud's phenomenon (13%), and the female urethral syndrome (12%). (1)

The criteria for diagnosing fibromyalgia syndrome are quite different from those employed in diagnosing MPS. They share the same necessity of muscle palpation; however FM is diagnosed by a physical examination with finding of 11 of 18 specific tender points in a person with widespread pain. (18) Table 4. The American College of Rheumatology has given the following criteria. Table 2. (32) Again as in myofascial pain syndrome the findings are limited to physical examination. The most significant findings are the presence of multiple tender points with skin fold tenderness. There is also cutaneous hyperemia, reticular skin discoloration, and rarely diffuse puffiness of the fingers. There are absent findings if there is not concomitant disease and these include joint swelling, loss of range of motion of the joints, abnormal muscle strength, sensory functions, or reflexes. The usual blood work consisting of a complete blood count, sed rate, muscle enzymes, thyroid function tests, rheumatoid factor, ANA, x-rays and bone scan, neurophysiological testing, and muscle biopsy are all normal. Sleep EEG studies and neuroendocrine tests may be abnormal. The clinical utility of these tests is highly questionable.

ASSOCIATED CONDITIONS: Irritable bowel syndrome, tension headaches, and primary dysmenorrhea symptoms have a high association with fibromyalgia. A link between chronic fatigue syndrome and fibromyalgia has been suggested. (33) The same problem exists with chronic fatigue syndrome. With its cause unknown it is difficult to classify it as a disease.

Treatment is highly problematical and physical therapy, (34) exercise (35) and pharmacology must be supplemented with reassurance and education.

Differences between myofascial pain syndrome and fibromyalgia are listed in Table 5.