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Deafferentation Pain in Man and Animals as it Relates to the DREZ Operation

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As a resident of Dr. Penfield, I was impressed by his clinical analysis of each patient's complex medical problem. This always included a detailed history and physical examination by the "Neuro" staff with added information gathered by Dr. Penfield during his personal interviews with each patient. This clinical information was later reinforced by extensive operative notes and hand drawn pictures by Dr. Penfield along with photographic studies of the operative site. I soon realized how important it was to collect complete documentation on each patient.

Penfield's major contribution to neurology and neurosurgery was his extensive observations and surgical treatment of patients with epilepsy, but if one looks through his scientific bibliography, he had wide interests in the problems of neurological disease, including pain.

In 1925 Penfield published a paper in the *Bulletin of Johns Hopkins Hospital* on the "Surgical Aspect of the Sympathetic Nervous System in the Work of Rene Leriche".¹ Penfield personally visited Leriche in France and spent several hours discussing the problems of pain as related to sympathetic nerve dysfunction. Penfield published a written record of his interview with Leriche and as a result of this visit he then published his own observations on the "Neurological Mechanisms of Angina Pectoris and its Relation to Surgical Therapy".² Although Penfield devoted most of his career to the treatment of epilepsy, it was obvious that he always had a distinct interest and concern about the perplexing problems of pain. It is also of some interest that the logo at the entrance to the Montreal Neurological Institute is "dedicated to relief of sickness and pain and to the study of neurology." After I left Montreal, the surgical treatment of epilepsy also occupied my interest, but later I became interested in the clinical problems of chronic pain, especially pain caused by deafferentation. I have used the same clinical methods taught to me by Penfield to analyze and study these complex pain problems.

Pain is a universal signal of "something wrong". The pain "signal" may vary from species to species and each creature's reactions to this "painful signal" also varies. It is these variations and differences that make analysis of pain difficult both experimentally and clinically. Acute and chronic pain differ both in origin and pathophysiology, making it difficult to develop animal models that may reflect the human situation. Acute pain in man can often be resolved quickly without serious consequence, but the establishment of long term chronic pain poses one of the most difficult pathophysiological therapeutic problems for the physician and surgeon.

Deafferentation pain is one of the most difficult to understand and treat. How does the physician explain to himself or his patient with a phantom limb syndrome the reasons for the pain in a missing or completely analgesic arm or leg? It may not be difficult for the physician or surgeon to recognize deafferentation syndromes such as phantom limb pain, thalamic pain and post cordotomy dysesthesia to name a few. Our understanding of the pathophysiological process behind these syndromes and developing appropriate treatments pose the difficult problem. Deafferentation pain is not clearly defined clinically or neurophysiologically. Tasker,³ a Canadian neurosurgeon, defines the term "deafferentation pain" as discomfort arising in any part of the body once the flow of afferent nervous impulses have been partially or completely interrupted. Tasker goes on to say, "While theoretically also resulting from injury to receptors, in practice it is caused by lesions of nerves, dorsal roots, spinal cord, brain stem or cerebral cortex, interruption at any anatomical level being capable of inducing pain." As one can see, injury or alteration to the sensory system at any point in the nervous system can result in a deafferentation pain syndrome — a very global concept. Neurophysiologists such as Wall⁴ express it as a dysesthetic pain due to "not only a loss of pain input but actual degeneration so that spinal cord cells were free to act in a

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pathologic way.” It is the defining of this “pathologic way” experimentally that continues to defy the neuroscientist and clinician.

In the neurosurgical treatment of deafferentation dysesthesia, I have designated three clinical types: 1) dysesthesia with involvement of spinal nerves up to but not including spinal cord (the causalgia of Weir Mitchell) or minimal damage to nerve roots and dorsal ganglia, 2) dysesthesia with peripheral nerve injury or involvement and invasion of the dorsal roots plus the spinal cord such as found in post-herpetic pain of herpes zoster, 3) dysesthetic pain with central involvement including the dorsal horn and the secondary sensory tracts originating in the dorsal horn which project to the brain stem and the thalamus as well as the downstream projections from these latter areas to the dorsal horn. Whether or not the cerebral cortex can be involved in this process is a moot point, and I have excluded it because of a lack of definitive clinical evidence of cortical involvement. It is not possible to discuss all the variety of clinical syndromes and their ramifications. I would like to concentrate on one well known clinical deafferentation syndrome and that is the spinal nerve root avulsion injuries of the brachial plexus and the intractable pain that occurs in about 10% of these patients. This is a total sensory disconnection pain syndrome, both the dorsal and ventral roots are usually avulsed from the spinal cord (arm C5-T1, leg L1-S5).^{5,6} The victim of this injury is left with a completely paralyzed analgesic arm or leg. This is an unfortunate experiment of nature brought about by modern life and due to accidents caused by the rapid movement of individuals from one place to another via automobiles, motorcycles, speedboats or snowmobiles. Accidents involving such vehicles have resulted in this type of injury. Brachial plexus avulsion can be simulated in animals under experimental conditions. The focus of the injury and possible site for the origin of pain may be within the deafferented dorsal horn of the spinal cord resulting in abnormality of the associated secondary neurons which are deprived of their peripheral input.⁷ I will describe the most recent neuroanatomy, neurophysiology and neurochemistry of the dorsal horn as it is related to dorsal root avulsion and the development of a treatment strategy known as the DREZ (dorsal root entry zone) operation in which localized thermal lesions made in the dorsal horn following avulsion injuries result in pain relief in over 60% of the patients.

Post Mortem Findings in Two Patients with Brachial Plexus Avulsion Following the DREZ Procedure

Prior to the first DREZ operation for pain of brachial plexus avulsion, there were few reports in the literature on post mortem examination of the cervical cord following brachial avulsion. The reports mainly dealt with the arachnoidal scarring and the gross nerve root disruption with little attention to the nature of the pathological lesions within the spinal cord.

Before I describe the experimental results of the deafferentation syndrome in animals, it is necessary to know the extent of the traumatic avulsion injury in the human spinal cord. Several questions must be considered. What is the extent of the spinal cord injury following avulsion injury? Is this a focal injury confined mainly to the structures of the spinal cord dorsal horn or does the injury extend beyond this limited area? What are the distant effects both anatomically and physiologically in the CNS? It is not possible to give an exact answer to these questions at this time, since there are few pathological examinations

of the spinal cord in patients with avulsion injuries. I will present two post mortem examinations of my colleagues where the spinal cord was examined after the DREZ operation.^{8,9} The pathological data is complicated by the trauma produced by the avulsion lesions and the later DREZ lesions. It appears that in these two patients the extent of the original traumatic injury involved mainly structures in the dorsal horn and its central spinal connections. The extent of the central neural degeneration of these pathways is still unknown.

Two patients have died in the immediate postoperative period following the cervical DREZ operation. The first patient was reported by Richter and Schachemmayr at the First International DREZ Symposium in Mainz, Germany in 1984.⁸ He was a 68-year-old man who suffered from deafferentation pain due to brachial plexus avulsion of ten years' duration. A preoperative cervical myelogram revealed a traumatic pseudomyelocele at C8-T1 and at the DREZ operation the C8 and T1 dorsal roots were avulsed. Twelve DREZ lesions were made over the avulsed region. The immediate postoperative course was uneventful with a 90% reduction of pain. The patient began to ambulate, but, on the fifth postoperative day he became acutely ill and during an abdominal exploration blood was found in the peritoneal cavity. The patient died suddenly of a massive myocardial infarction 24 hours later. At post mortem examination, both the ventral and dorsal roots from C8 to T1 were avulsed. Microscopic examination of the spinal cord revealed a pseudocyst with involvement of Rexed layers I-V. In the region of the cord adjacent to the Rexed lamina there was evidence of the recent DREZ thermal lesions — neuronal and axonal swelling, degeneration, and demyelination. Above the level of the lesion were signs of old degeneration with complete destruction of the Lissauer's tract. The authors concluded that “because the patient was almost pain free after operation and because Lissauer's tract and substantia gelatinosa had been destroyed by the primary trauma, it was concluded that other anatomical structures must at least in addition to these have been responsible for the positive effect of the DREZ lesion on the patient's deafferentation pain”.

The second patient was reported at the Second DREZ Conference at Duke University in 1987 by Iacono and Aguirre.⁹ The patient was a 56-year-old male with lower extremity pain related to a war wound in 1952. This resulted in paraplegia at the L3 level with partial involvement of the conus. At surgical exploration for the DREZ operation, the conus medullaris was exposed and there was marked arachnoiditis surrounding the conus associated with atrophy of the spinal roots. A series of 48 DREZ lesions were placed on the left side of the conus beginning at about L2 and about 35 lesions on the right side very near the tip of the conus. It was difficult for the surgeon to make an absolute anatomical localization on the conus because of the severe arachnoidal scarring. During the immediate postoperative period the patient was completely relieved of his pain with no change in his motor function but a slight elevation of his sensory level. On the 28th postoperative day the patient experienced a fainting spell, some back pain and suddenly died of cardiac arrest. Post mortem examination revealed severe disease of the right coronary artery and the lower part of the spinal cord was removed and studied. The DREZ lesions were found to involve the portions of the dorsal horn including Rexed layer V and parts of layer VI. There appeared to be total necrosis of the neurons within the dorsal horn in this region with a clear

border of demarcation along the edge of the dorsal horn where the white matter interfaced with the other spinal cord structures. A small syrinx was also noted. It was concluded that there was almost total destruction of the dorsal horn by the DREZ lesions with minimal damage to the nearby adjacent spinal cord structures (pyramidal tract, posterior columns and spinocerebellar tract). It was felt that the syrinx of the spinal cord was related to the patient's original trauma. The post-mortem studies in these two patients illustrate that the thermal DREZ lesions are confined to the most superficial layers of the Rexed lamina — in the first case I-V and the second case I-VI. In the first case the pathology was complicated by the previous avulsion trauma and to some extent the second case also showed evidence of the old trauma with cyst formation. It becomes difficult to separate out the original traumatic pathology and the effects from the DREZ lesion. It would be valuable to have neuroanatomical studies of the degenerated neural pathways and tracts in the spinal cord following the DREZ lesions, but this information is not yet available. We hope that neuroanatomical studies may be undertaken in the second patient. In conclusion it appears that the DREZ lesions produced by the Radionics thermal electrode were confined to the superficial Rexed layers I-VI of the dorsal horn. Interpretation of the pathological effects of spinal cord lesions must await future studies.

Experimental Dorsal Root Nerve Injuries

There is a large body of research on the neurophysiology of acute pain but less data on experimental chronic pain. It seems evident that the neurophysiology of acute and chronic pain are quite different, and there are obvious differences between these two types of pain in the human. We first began to explore the neurophysiology of experimental avulsion injuries in the 1970's in the Paris Lab of Professor Madame Albe-Fessard and, later, in the Duke Neurosurgical Laboratory with Dr. Jan Ovelmen-Levitt.^{10,11} It seemed to me from observing and talking with patients following a brachial plexus avulsion injury that certain temporal events were associated with the development of the pain syndrome and that it would be possible to reproduce the avulsion injury in experimental animals and study it using various neurophysiologic techniques. In the human, after traumatic avulsion of the dorsal roots and indeed in most instances of deafferentation pain in man, the onset of pain occurs shortly after the injury (days) and persists for long periods of time (years).¹² Only 10% of patients with a deafferentation injury develop pain (brachial plexus avulsion, spinal cord injury, post-herpetic pain). As yet there are no clues that set aside this group of patients with pain from those who do not experience pain with what appears to be similar pathologic insults. The patient who suffers a brachial plexus injury or a paraplegic begins to experience pain immediately after the injury. Prior to the DREZ operation the pain could persist for a lifetime. There seemed to be few changes in the character of the pain over long periods of time although the intensity of the pain could fluctuate and sometimes worsen with time. This worsening is probably due to the psychologic and physiological deterioration that occurs in these patients under siege from long term chronic pain. The verbal descriptors used by the patient to describe the pain are similar in that the pain is described as intense, localized to the analgesic or injured area with severe exacerbated bouts which the patient will describe as "electrical", "electrical shooting" or intense "burning". The pain may build up to an almost

explosive level and then subside to some extent with the patient dreading the onset of the next severe bout. External sensory stimuli, such as intense light, sound, changes in environmental temperature and touching certain skin areas outside the area of injury will set off the paroxysms of pain. One unusual phenomenon noted in the patients with brachial plexus avulsion and paraplegia is the presence on the surface of their skin, usually at some distance from the level of injury, of the so-called "trigger spot" or "trigger zone". This is usually a localized area of skin that when it is touched, activates the pain. In brachial plexus avulsion the skin area around the head, neck and shoulders will often harbor these "trigger spots" and in the paraplegic they can be found in normal dermatomes some distance from the level of spinal injury. The patient is often aware of these "trigger spots" and avoids touching them. After the DREZ operation, these "trigger spots" disappear. This suggests the alteration produced by deafferentation lesions often set up abnormal neural communication at distant normal spinal segments that result in intensification of the painful phenomenon. These lesions alter the anatomy, physiology and neurochemistry of the dorsal horn. What follows is an effort to relate these changes in the experimental animal to the patient and deafferentation pain.

Neuroanatomy of the Dorsal Root Entry Zone

In general all the dorsal horn afferent fibers terminate in the dorsal horn of the spinal cord. These afferent fibers make connections with secondary sensory neurons which form the ascending somatosensory tracts. The spinothalamic and spinoreticular tracts are two major examples. The dorsal horn or dorsal root entry zone of the cat was originally subdivided by the neuroanatomist Rexed into ten divisions based on its architectonic characteristics.¹³ These same divisions with some variations occur in the human dorsal horn and it is the first five Rexed divisions that are of the most interest to us because the pain afferents terminate in layers I and V.¹⁴ Basically there are three types of dorsal horn neurons. One type of neuron sends its axon ventrally into lamina IX. A second type of neuron forms long ascending axons destined to higher cephalic levels while a third type of axon is a true interneuron sending its axons into adjacent Rexed layers. It may be these interneurons which are reacting abnormally following deafferentation. The first five layers of Rexed in the dorsal horn can be described as follows. Lamina I contains nociceptors and thermal receptors in the marginal zone. Lamina II is divided into outer-inner zones which correspond to the "substantia gelatinosa". These two zones are made up of nociceptor, thermoreceptors and mechanoreceptors (C), and this is the region where a portion of the neurons contribute to the formation of the spinothalamic tract. Laminas III and IV contain hair (D type) and hair (G type) plus rapid and slow adapting mechanoreceptors (AB). Lamina V contains additional neurons contributing to the spinothalamic tract. It is these superficial five layers of the dorsal horn that we attempt to destroy by the DREZ operation in order to eliminate lamina I and V which contain the major second order neurons into the pain afferent pathways. Lissauer's tract is a longitudinal pathway which years ago Ransom designated as a pain pathway. It is made up of small diameter primary afferents and fiber contributions from both the dorsal horn as well as certain intrinsic spinal cord fibers which act to interconnect three or four spinal cord segmental levels. Certain portions of the Lissauer tract may exert inhibitory or excitatory influences on the dorsal

horn neurons. The fate of the Lissauer's tract following dorsal nerve root avulsion is not known, but in human avulsion injuries it is completely degenerated.

Neuropharmacology of the Dorsal Horn

The finding of peptides and endogenous opiates in the central nervous system and their relationships to sensory function and especially pain represents a major advance in the neuropharmacology of pain.

The question arises: what happens to these neuropeptides in the dorsal horn of an animal after an experimental deafferentation such as avulsion or section of the dorsal roots? Bennett Blumenkopf, at the time a neurosurgical resident at Duke Medical Center, investigated this question and reported on the experimental results which have already been published in the First International DREZ Conference held in Germany in 1985.¹⁵ Before detailing his experimental results, I will briefly describe his observation on the neuropeptides in this study, namely substance P, somatostatin and methionine-enkephalin. It should be remembered that these neuropeptides represent only a small fraction of the active pharmacological substances found in the dorsal horn.

In 1931 substance P was isolated from intestinal tissue. Its importance and presence in the dorsal horn of the spinal cord has only recently been recognized. It is concentrated in the dorsal roots and may be a transmitter released by primary afferent neurons. High concentrations of substance P occur in the dorsolateral portion of the spinal cord dorsal horn. It is reduced in this area after a dorsal rhizotomy. Rexed laminae I and III have large numbers of dense fibers positive for substance P and substance P is transported from the dorsal ganglion into the dorsal horn. A variety of CNS neurons are excited by substance P. Substance P levels in the spinal fluid are reduced in patients suffering from diseases of the nerve roots, dorsal horn and spinal cord. Excitation produced by substance P is slow in onset and continues for long periods of time. There is experimental evidence of selective effects of substance P on neurons with which A-delta and C fibers synapse in Rexed laminae I and III. Neurons associated with non-nociceptive stimuli were minimally affected by substance P. Two weeks after an experimental unilateral dorsal rhizotomy, it was found that the deafferentated spinal cord neurons were more sensitive to the application of substance P. Substance P appears to exert a strong effect on the afferent neurons and their connections in the dorsal horn of the spinal cord and because of this Dr. Blumenkopf examined its role in experimental deafferentation in avulsion injuries.

Somatostatin is found in terminals of Rexed lamina II of the dorsal horn as well as in the dorsal root ganglion. It exerts an inhibitory action and may inhibit noxious sensory neurons located in Rexed laminae I, II and V while not affecting the other sensory neurons.

Methionine-enkephalin (ME) is found in high concentrations in certain cells and their terminals of the spinal dorsal horn with dense networks of neurons concentrated in Rexed laminae I and II, and with moderate concentrations in Rexed laminae V and VII. Dorsal rhizotomy does not appear to alter these concentrations, suggesting that M-E is either intraneural or propriospinal in its location. Enkephalin terminals are primarily axosomatic and axodendritic and this suggests these terminals may modulate nociception. It is obvious that opiates are

important in the modulation of transmission of nociceptive information from the periphery to the central nervous system.

Drs. Blumenkopf and Jan Ovelmen-Levitt developed an experimental pain model in cats with dorsal lumbosacral nerve root avulsion and studied the density of the neuropeptides in the dorsal horn of the avulsed animals at intervals ranging up to 16 weeks.¹⁶ They used an indirect immunohistochemical technique to study the amounts of methionine-enkephalin (ME) somatostatin (SS) and substance P (SP). Early after the injury (one week) on the avulsed side, there was a moderate decrease in capsule ME terminals in Rexed laminae I and II. SP was reduced in these regions as well as in Rexed lamina V. In Rexed lamina II SS was reduced. Later (2 weeks) SP was completely absent from Rexed lamina V, but SS and SP showed slower declines in the appropriate lamina. Activity began to return in about 10 weeks but was more apparent at 16 weeks. In Rexed lamina II SS positive terminals recovered with SP noted in Rexed laminae I and V. In Rexed laminae I, II and V from the 6th to the 16th week there was complete loss of ME. In conclusion, these three neuropeptides were altered differently in the dorsal horn after experimental avulsion injury in the lumbosacral region of the cat. There is a distinct temporal difference in the disappearance of these substances. There appears to be an initial decrease in SS and SP followed at a later stage (16 weeks) by return of these neuropeptides in contrast to the terminals containing ME which remained relatively intact initially but later completely disappear.

Abnormal Physiology of the Dorsal Horn After Experimental Deafferentation

In 1976 I began to work with Professor Albe-Fessard and Madame Lombard in Paris.¹⁷ Our goal was to study the physiological and behavioral events that occurred in animals after an experimental deafferentation syndrome. Experimental avulsion injuries of dorsal roots were produced in rats and later in cats. It was noted that the behavioral changes occurred if four or more dorsal roots were avulsed or sectioned in the fore or hindlimb of the animal. Within hours the animal began to bite the deafferentated extremity and would scratch the skin, producing skin lesions in the dermatomes adjacent to the analgesic limb. At times the animal would scratch the intact limb contralateral to the deafferentated limb so the behavioral effects were bilateral. The deafferentation syndrome and the behavioral changes also occurred in cats and of great interest was the occurrence of abnormal electrical activity in the contralateral sensory thalamus of the cat 18 months following spinal cord deafferentation. These experimental results have already been reported in detail.

Later, after my return to Duke University Medical Center, the experiments were continued under the direction of Dr. Ovelmen-Levitt.¹⁸ The experimental observations were extended carrying out deafferentation studies in the lumbosacral segments of the cord of both cats and rats. Single unit electrophysiological studies were done at L6-L7 dorsal horn of the cat with special reference to the neurons situated in the Rexed lamina V. It was found that there were changes in the spontaneous cellular activity, modalities and receptive fields at various times after deafferentation. Experimental studies were also carried out on the effect of various pharmacological agents on the experimental animal mode.¹⁹

In cat dorsal horn, after deafferentation, we found bursting electrical activity in the cells of Rexed lamina V began within 24 hours which increased over successive weeks. The bursting neuronal activity was often preceded by one or two hours of sporadic spontaneous single and multiple action potentials. There were differences in the time course and pattern of the spontaneous neural activity in Rexed lamina V, dependent on whether deafferentation was the result of an avulsion or a multiple rhizotomy. In the rhizotomized animal, the bursting activity continued for several months in Rexed lamina V and the upper lamina. In the avulsion injury, the upper Rexed lamina remained relatively silent while high frequency regular activity was noted in lamina V. The onset for the high frequency regular neuronal firing was about 3 weeks.

Changes in the receptor cutaneous fields of the animal was also noted by Ovelmen-Levitt. Under normal conditions the cells in Rexed lamina V have a small receptive cutaneous field confined mainly to the lateral portion of the foot. After deafferentation the cells of Rexed lamina V are influenced by stimuli from wider cutaneous areas such as the adjacent flank, abdomen and occasionally the thoracic region. There was even some crossed effect from the contralateral limbs on the abnormal neuronal activity coinciding with the behavioral responses noted in the Paris animals. Excitatory effects from the distant receptive fields were most common, but inhibition was also noted. In the animals with avulsion injury and deafferentation there were less unilateral effects on the receptive field but a greater influence of contralateral inhibitory effects. Examination of the spinal cord showed evidence of direct trauma to Lissauer's tract, especially the medial portion. On the basis of findings by Denny-Brown in studies of Lissauer's tract, one might consider that involvement of Lissauer's tract was responsible for the significant differences between the avulsion and rhizotomized animals. This did not seem to be entirely the case as there was considerably more degeneration in the deeper layers of avulsed dorsal horn. It appeared that the intersegmental fibers in the dorsolateral fasciculus and ventral dorsal columns were in the main preserved in both types of deafferentation. After a time it was noted that there was a reduction of myelinated fibers within the dorsal horn.

The occurrence of the trigger spots in patients with spinal deafferentation (avulsion injury and paraplegia), was of great interest and may be explained by the observations of Ovelmen-Levitt.²⁰ Recordings made on the surface of the spinal cord showed strengthening of the input from distant normal innervated areas into the cells in the deafferented segment of the spinal cord. This may indicate a reorganization and increased projection of the pain afferents centrally following this type of deafferentation injury.

CONCLUSIONS

At present there is an intense effort by neurophysiologists and neurochemists to understand the normal and abnormal function of the dorsal horn. The development of a chronic animal pain model of deafferentation pain has been an important advance. The preliminary studies reveal profound electrophysiologic and neurochemical changes in the injured dorsal horn over the long term. The inter-relationship of these chronic

changes in the experimental animal model are still to be related to the clinical situation in man.

Clinical studies in man similar to those carried out by the basic neuroscientist are more difficult to come by, but we must be guided and inspired by the work of Dr. Penfield who, with his colleagues at the Montreal Neurological Institute, established our modern understanding of epilepsy and its surgical treatment in man. My hope is that the clinician and the basic scientist involved in studying pain will have the same inspiration as the Penfield group in order to alleviate untold suffering in some of our patients.

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