Acute Complex Regional Pain Syndrome (type-1): *(Part A)*

Case Presenting Acutely after Anesthesia and Surgery *(Part B) (pages 22-23)*

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INDEX *(part A)*

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I. INTRODUCTION[1],[2],

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition representing nervous system dysfunction. The complete clinical picture features do no develop simultaneously. There is a consistent sequence of events and the fact some signs or symptoms are present at a moment in time, might not alert the clinician to the fact CRPS will finally develop. Two types of CRPS are differentiated. CRPS is clinically characterized by a triad of events;

(1) sensory disturbances,

(2) autonomic disturbances, with tissue changes,

(3) motor disturbances[3].

The very earliest recognition of this group of illnesses came from the American Civil war, when in 1872 Dr. Weir Mitchel labeled the cases of severe pathological pain following traumatic limb with nerve injury, as *Causalgia*. Sudeck also described a similar condition with a striking atrophy of the distal limb following limb injury, but without a nerve injury. Sudeck's description in 1930 of bone changes became known as Sudeck's atrophy, and then later called reflex sympathetic dystrophy, because it responded well to a sympathectomy. Then, over the ensuing

years when the extreme complexity and wide range of clinical pictures became apparent, Sudeck's atrophy was renamed to CRPS type-1 (CRPS-1).

There is nothing homogenous about this disease group called CRPS-1. As yet no single causative factor, no single mechanism, and no single diagnostic test has been discovered. The average time between initiating injury and proposal of a CRPS-1 diagnosis is thirty months[4].

Fibromyalgia is a related dysfunctional pain, to CRPS.

Fibromyalgia shares with CRPS the features of; (i) responsiveness to ketamine therapy, (ii) having a central nervous system disordered pain processing, and (iii) having a high incidence of associated psychological disorders and depression. Fibromyalgia however differs from CRPS in that it (i) lacks any association with any form of peripheral injury, (ii) lacks any peripheral evidence of sympathetic changes, and (iii) lacks any visual peripheral tissue changes (e.g. redness, paleness, atrophy, and temperature differences).

There are two types of Complex Regional Pain Syndrome (CRPS). ***CRPS type-1*** is the modern term for the older Reflux Sympathetic Disease (RSD). ***CRPS type-2*** is the modern term for the older disease called causalgia. CRPS-2 involves injury to macroscopic nerves. This discussion will be limited to discussion of CRPS-1. All further references to CRPS, in this text, can be inferred to mean CRPS type-1

In its very simplest, form Complex Regional Pain Syndrome (CRPS) type-1 has two core features;

(1) significant autonomic nervous system dysfunction. Skin, muscle and bone changes may follow that.

(2) classic neuropathic pain symptoms of intense burning pain, hyperalgesia and allodynia.

Note: A *burning* pain is characteristic by being constant, unlike pain from fresh somatic tissue injury that can abate during periods of stillness without moving the injured part.

Motor changes are likely only secondary changes resulting from disuse and are not immediate early features, and do not reflect injury to motor efferent nerve fibers. Motor weakness can be a profound late feature of CRPS patients. The diagnosis of CRPS-1 is commonly overlooked in the early phase of the disease as gross symptoms suggest multiple other explanations. Typically, it is only when the disease persists and develops subtly that a diagnosis of CRPS is even considered. Also, it is a very hard to treat disease. Patients suffer both more pain than usual, as well as psychological distress and functional impairment in their lives.

Research of CRPS in animals, has largely focused on CRPS type-2 using nerve ligation models. The results generally do not apply to CRPS-1. Animal models for CRPS-1 have only been developed in more recent years, and are not strongly affirmed as being good models or applicable to human CRPS-1 yet. Consequently, the ignorance about CRPS-1 is still very large.

Spontaneous onset, with no preceding injury, of CRPS is very rare, but described[5],[6]. Such rare cases must be strongly investigated to exclude inflammatory rheumatological disease. Also,

skeptical experts believe supposed spontaneous cases of CRPS do actually follow on an injury, but one the patient has forgotten about.

II. INCIDENCE[7,9]

Of all cases of diagnosed CRPS-1, 16.4% follow surgery, the others follow an injury. Orthopedic surgery is the single biggest surgical cause of CRPS. It is estimated 50 000 new cases are diagnosed annually in the USA. It is more common in mature woman (middle age upwards). After total knee arthroplasties one in 140 patients develop CRPS-1[8].

III. PATHOLOGY[9],[10],[11]

Coderre designed a rat model to simulate CRPS, to be used for research, that is based upon inducing microvascular pathology and inflammation[12]. It however cannot be totally assumed similar mechanisms underly all of human CRPS type-1 cases, but possibly some do. It is generally accepted that CRPS-1 is a likely *group diagnosis* covering many mechanisms that yield a *common clinical picture*. The common final pathology path, if it even exists, remains elusive. The autonomic system is centrally involved, as autonomic signs can be elicited bilateral in all patients using appropriate research tools, even when the gross clinical picture is only unilateral[13].

Although the diagnosis of CRPS-1 is excluded if a macroscopic nerve is injured matching the field of symptoms broadly, there is still a form of nerve micro-trauma that maybe initiates the cascade of events. Studies show skin biopsy signs of *29% reduced density of neural dendrites* of the sensory A-delta and C fiber types in the affected area of the CRPS. Hair-follicles and sweat glands also have abnormal innervation. Animal research suggest this neurite loss is secondary to the initiating injuries, but the possibility that it is rather secondary to the CRPS is not excluded in humans. Loss of dermal dendrites, with additional loss of mast-cell to dendrite association has been shown in human CRPS patients in affected limbs[14]. It is believed that these changes, are possibly from, or part of an early peripheral inflammatory process that precedes a full clinical picture of CRPS.

The early inflammation seen in some tissues may be a trigger auto-immune mechanism involving antibodies against peripheral adrenergic and cholinergic receptors. The auto-immune mechanism might not be a sustained one, and it may only be a temporary phenomenon that initiates the CRPS pathophysiology. This would explain the observation that steroid therapy is sometimes effective, but only if administered in the very early phases. Peripheral inflammation thus has an unclear role in CRPS. The propensity for an inflammatory process in the injured tissues to be the initiating even for some cases of CRPS, might be under genetic control with variable penetrance and thus varying ability to trigger CRPS, in different individuals. More research is needed.

Of special note, CRPS-1 does share two critical signs with neuropathic pain (CRPS-2), namely, *allodynia* and *hyperalgesia*, as well as sympathetically maintained pain. CRPS-1 however, critically

differs from neuropathic pain by having much evidence of involvement of inflammatory mechanisms and an autoimmune response, which CRPS-2 does not have. Therefore, the classification separation of neuropathic pain (CRPS-2) from CRPS-1 is justified[14].

There is also a functional coupling of *sympathetic* post-ganglionic neurons with afferent (sensory) neurons identified in bilateral dorsal root ganglionic neurons showing increased alpha-2-adrenoreceptor mRNA. That implies those affected sensory nerves are likely more responsive to standard catecholaminergic molecule stimulation.

ACE-Inhibitor therapy has been identified as a risk factor to develop CRPS-1. Angiotensin Converting Enzyme (ACE) metabolizes substance-P (SP) and bradykinin, neuropeptides. Use of ACE-I drugs thus increases SP and bradykinin which play a role in CRPS-1. Peripheral tissue sensitization at the site of trauma is mediated by release of substance-P and bradykinin into the peripheral injured tissue. This enhances nociceptor firing. No clear role of these manipulating (inhibiting or blocking) substances has yet been established in the development of CRPS-1. If their total effect were able to be inhibited pharmacologically, tissue healing would certainly be impaired as well. Therefore, prophylactic CRPS therapy aimed at SP and bradykinin at this site might be limited in value.

Sensitization of the central nervous system is key part of the CRPS-1 pathology. It is triggered by the initial *intense and sustained nerve signal inputs from the periphery*. A consequence is release into the spinal cord of Substance-P, bradykinin, and glutamate which all activate the NMDA receptors. The result is an exaggerated perception of pain from nociceptive stimuli (hyperalgesia). Also, normal non-painful stimuli get experienced as pain as well (allodynia). It seems this central sensitization then leads to later CRPS-1 developing that includes autonomic nervous system dysregulation.

A higher early pain score than that seen in average patients, is a strong predictor of the patient developing a later CRPS. In one study, the pain score patients had with forearm fractures at three and a half days after acute injury, was identical to the unusual persistent pain scores pain scores at five weeks after acute injury, in the subgroup that ultimately developed CRPS[15]. When the patients in each group were subjected to tests measuring skin temperature and blood flow, it was shown the acute group had normal sympathetic control, whereas the late CRPS group had severe impaired sympathetic control. Thus, it is believed, indicates that CRPS's prime mechanism does not involve exaggerated PERIPHERAL inflammation. Also, the *pain* experienced in each group, despite having similar scores, must have very different etiologies.

Nerve changes on microscopy affect only afferent nerve fibers (sensory), specifically being C-fibers[16]. Muscle changes show a decrease in type-I muscle fibers, as seen in muscle disuse.

CRPS-I is also seen in children, and is considered to have a better overall prognosis than that seen in adults[17]. It has also been seen that in children, that a very high fraction of them has severe psychological disease, many including sexual abuse experiences and suicidal thoughts.

Burns are associated with development of CRPS too[18].

One in every 140 patients, at the least, after a total knee replacement will develop CRPS[19].

CRPS of the foot has been reported after unusually long time in labor for child birth[20]. That likely reflects the fetal head causing a pressure injury to the pudendal nerve with its L4-4 and S1-4 nerve root origins. The sciatic nerve reflects matching nerve roots, L4-5 and S1-3, is clearly easily involved in CRPS at spinal cord level.

It has been shown in CRPS sufferers that there is often deep muscle hyperalgesia, measurable with pressure devices, in muscles far removed form the original injury site, as well as on the contralateral side[21]. Deep muscle hyperalgesia is the most prominent and most common sensory change seen in remote tissues of these CRPS-1 suffers. Furthermore, this deep muscle hyperalgesia correlates strongly with the patient also having dystonia. Dystonia is persistent intermittent muscle contractions. Dystonia is characterized by painful prolonged muscle contractions. Dystonia is however not specific to CRPS-1. Parkinson's disease is the most common cause of dystonia.

The sympathetic nervous system (SNS) has a biphasic clinical appearance in CRPS-1 patients. In the early phase SNS seem to be peripherally inhibited initially, giving the red warm limb of early CRPS-1. In the late phase CRPS-1 patients exhibit the opposite with cold bluish limbs. The cold-blue late phase may be due to impaired endothelial vasodilator responses as well as reduced levels of nitric oxide and endothelin-1. The warm early phase of CRPS-1 may be linked to increased adrenergic receptors on nociceptor fibers after the injury. Circulating catecholamines in blood draining the affected limb are reduced, likely reflecting reduced SNS activity releasing the catecholamines. The late cold-blue phase might thus be, in part, due to compensatory strong up-regulation of adrenergic receptors and a resulting over-responsiveness.

The brain of CRPS-1 patients also undergoes changes. The cortical somatotropic maps reduce in size corresponding with the affected limb reduction in mass. Those changed areas recover if the CRPS condition resolves. There is also loss of grey matter in certain other brain areas. Likely these gray matter changes are secondary to the condition of CRPS and not causative of the clinical picture.

No clear genetic factors for the development of CRPS-1 have yet been identified, but members of families with a high incidence of CRPS tend to acquire CRPS at younger ages.

Psychological events are strongly associated with CRPS. The extreme distress shown by some CRPS-individuals led to mistaken suggestions once, that CRPS-1 was entirely a pure psychosomatic disease. That is not currently believed. Certainly, there are some proven links between psychological factors and immune factors in general. Also, emotional distress can increase catecholaminergic activity. The links between psychological factors and CRPS-1 are still unclear, as to whether they are associated, secondary or causative, and also unclear as how large that link is. Finally, it seems pre-existing psychological factors do not alter the incidence or risk for CRPS-1. Pre-existing psychological illness is however, usually worsened by CRPS. Treating the psychological diseases as part of treating CRPS seems to contribute towards improvement or resolution of CRPS.

The disease is often bilateral, especially as subtly seen using sensitive tests[21]. Bilateralism is also occasionally overtly seen with severe symptoms.

Some doctors like to describe three phases in typical cases;

PHASE ONE; Lasts one to three months. Pain is severe and burning. Muscle spasms are common and hair growth can occur.
PHASE TWO; This last three to six months. Pain intensifies and swelling can occur.
PHASE THREE; the skin atrophy and bone changes are no longer reversible. Pain is unyielding and wide spread. Muscle loss is severe and limbs become contorted.

IV. CLINICAL PICTURE and DIAGNOSIS of CRPS.

In 10% of cases there is no identifiable injury and the CRPS is considered spontaneous. Some experts consider *spontaneous CRPS* to be very rare. Some experts disbelieve in spontaneous CRPS, and think that the patient has forgotten the original triggering injury. CRPS type-1 can have profound effects on bladder detrusor and sphincter function, and is most commonly seen after lower limb injuries[22],[23]. Some experts doubt that CRPS of major joints and the trunk exists. That belief however, does not serve the actual patients who do have truncal involvement and no alternative diagnosis than CRPS to guide their medical care.

This illness is complex and this resulted in it having many names in the past. Reflex sympathetic dystrophy was an early name. It is now called Complex Regional Pain Syndrome (CRPS) type-1. For the purposes both of *treating* CRPS type-1, as well as *evaluating* very many proposed therapies, tight CRPS type-1 diagnostic criteria were proposed by the IASP. There remain however many patients who may not fully comply with these diagnostic criteria, but who also have no alternative diagnosis. They can be considered part of spectrum of hyperalgesia conditions. These individuals may still be tentatively labeled as CRPS type-1 suffers by their treating physicians.

The value of making a correct or best diagnosis. CRPS is hard to diagnose with consistent accuracy. Over-diagnosing CRPS makes scientific studies unreliable. It also restricts the quest to understand the illness and find a cure. Under-diagnosing CRPS deprives some patients of potential alleviating therapy. Under-diagnosing CRPS may also create medico-legal situations where blame for a bad clinical outcome is levied onto innocent healthcare providers when incorrect alternate explanations get proposed suggesting liabilities exist for some party.

Whenever a symptom collection is given a label, or a diagnosis, the label implies a prognosis can be predicted, it suggests some specific therapies may be helpful, and finally it offers an explanation of what is going on. The explanation how the illness came about may suggest some medical negligence, or even may conversely explain no medical negligence is to blame. For the purposes of science, very tight diagnostic criteria offer some advantages, but not without a price. The price might be omission of subtypes thus preventing their recognition. For the purposes of patient care over-diagnosing is never a problem provided no therapy is applied that is unduly costly or risky or lacking in reasonable evidence of benefit.

It is with these thoughts that IASP now has a duel diagnosis system; one strict one for research and one more lax for treating patients. That system however is still imperfect and does not specifically include pain suffers with secondary autonomic dysfunction of bladder or rectum. This should be included in the future.

Having very strict diagnostic criteria for CRPS-1 may serve a research purpose for this very complex illness, but that concept cannot be used to deny medical care to patients whose signs and symptoms fit no other diagnosis. Those patients who fall outside the Budapest diagnostic criteria for CRPS, but who fit no other diagnosis, should be considered a possible CRPS subtype and deserve research as well, as rare as their group may be. Their existence cannot be denied.

There are no diagnostic laboratory tests. Research-grade tests for indicating deep muscle hyperalgesia and skin vascular changes support the diagnosis of CRPS, but are not obligatory for making a clinical diagnosis of CRPS.

Pain is the foremost feature. CRPS-1 is a pain syndrome. The pain tends to be experienced in the deep tissues. Muscle weakness is part of the syndrome but only develops after pain becomes a problem. The weakness might be secondary to the reflex inhibition of movements due to the pain.

Autonomic nervous system dysfunction is the second absolute diagnostic criterium. It is most commonly seen in a distal limb as edema, but all other vascular signs and symptoms can be present. Limb sympathetic changes may appear as warmth, redness and swelling, or as coolness, pallor, and tissue shrinkage. Less recognized are truncal autonomic dysfunction affecting the rectum and bladder[22].

There are no universal gold-standard diagnostic criteria for CRPS. The last formal IASP criteria of 1994 are very sensitive, but possibly over-diagnosed cases which challenges scientific research. A group of experts in 2003 drew up criteria now known as the Budapest Criteria, which were much stricter, but less sensitive. They are possibly more suitable for research, but not necessarily useful to patients with a chronic pain conditions struggling to find a diagnosis. It is now proposed that patients who fulfill Budapest criteria for CRPS, but not those of the IASP, be labeled as Complex Regional Pain Syndrome Not Otherwise Specified (CRPS-NOS). It is estimated 15% of patients diagnosed under Budapest criteria now will carry the CRPS-NOS diagnosis. In 2010 Harden et all,[24]proposed the IASP modify its criteria slightly to embrace the Budapest Criteria more. There are thus two sets of diagnostic criteria for CRPS. One is strict and for research use, and one is more lax and for clinical patient care.

The **diagnostic criteria** for the diagnosis of CRPS-1 <u>of the limbs</u> are;

Pre-requirements (Lax criteria for clinical patient care);

(1) A known *inciting event*: a noxious injury causing immobilization of the limb part,

(2) *Pain that is "regional*", that is, pain not fitting a neurotome or dermatome distribution. This thus excludes a specific nerve injury etiology, as in CRPS-type-2.

(3) The *pain is disproportionate* in duration and severity to that expected for the known deficit, injury or trauma.

(4) There are (usually) more *distal abnormal sensory, motor, sudomotor, vasomotor, autonomic changes*, and or visible trophic skin or tissue changes. Sometimes symptoms will be proximal on the body soma, although distal on the spinal cord

arrangements for supplying nerve origins. Example, a primary knee injury and secondary urinary bladder complaint can occur.

(5) The *illness must have variable time course over a time period greater* than that of a normal healing period.

Those above criteria, of which mostly should be met to earn consideration of the *final diagnostic criteria* as set out by the IASP for researchers, of which EACH one must be met are;

I. The pain is disproportionate to the event.

II. There is at least ***ONE* SYMPTOM,** currently or previously, in at least three of the four following categories:

- SENSORY; reports of hyperesthesia or allodynia.
- VASOMOTOR; reports of asymmetry between left and right sides for skin color or tissue temperature.
- SUDOMOTOR/EDEMA; reports of asymmetrical sweating and swelling
- MOTOR/TROPHIC; reports of decreased range of motion, and muscle weakness, dystonia, tremor. Reports of hair, skin or nail changes (thicker, thinner)

III. There is at least ***ONE* SIGN** in at least two of the following categories:

- SENSORY; observation hyperesthesia or allodynia.
- VASOMOTOR; observation of asymmetry between left and right sides for skin color or tissue temperature.
- SUDOMOTOR/EDEMA; observation of asymmetrical sweating and swelling
- MOTOR/TROPHIC; observation of decreased range of motion, and muscle weakness, dystonia, tremor. Observation of hair, skin or nail changes (thicker, thinner)

IV. *No differential diagnosis can be found* to explain the signs and symptoms.

The limitations of these diagnostic criteria, is that they did not include other symptoms of autonomic dysregulation that involve the urinary bladder. That can be modified at a future revision of the diagnostic criteria.

a) BILATERALISM OF COMPLEX REGIONAL PAIN SYNDROME

All patients with CRPS have evidence of bilateral changes in their limbs, and within their brains. That absolutely proves a central nervous system mechanism underlying the disease. Also, this bilateralism is unique to CRPS as a disease, and thus diagnostic of CRPS. Unfortunately, the tests to diagnose this bilateralism are experimental tests and not widely available as clinical diagnostic tests, nor are the tests positive at every stage of one individual's disease process.

Lenz using structural MRI imaging and controls showed a mix of bilateral disinhibition cortical changes and also other changes on the cortical side matching the original injury side[25]. They measured relative amounts of white and gray matter. They postulated that the pain experienced in chronic pain patients, as in patients with

established CRPS, is driven at the level of the brain (supra-spinal level), and there is no longer input of afferent signals from the periphery.

Lenz also tested somatosensory cortical disinhibition in CRPS sufferers[26]. When using healthy controls, significant reduction of paired-suppression was observed bilateral in the somatosensory cortex of CRPS suffering patients. The hypothesis is, this bilateralism of signs indicates impaired CENTRAL motor-sensory circuits when the patient has CRPS.

Van Rijn did a thorough literature review and retrospective study on 185 CRPS patients and strongly showed a large fraction of CRPS patients had developed bilateral limb complaints[27]. Her data showed that clinically noted symptoms and signs were confined to one limb in 52% of patients. In all the other 48% of patients, a second limb also acquired signs and symptoms of CRPS at some point in time, as well. Half of those *multi-limb CRPS* patients had a symmetrical bilateral distribution of disease, whilst the others' second limb was on the same side or a different (diagonal) limb on the opposite side. A typical delay from the onset of complaints on the first limb to the second (if symmetrical or bilateral) was 19 months, but it was simultaneous in 11% of patients. The study excluded patients who had second injuries, as the study was only interested in spontaneous (injury free) involvement of second limbs. There were a few patients with triple and four-limb involvements (1%).

A knee injury involving the femoral nerve tissue distribution (L2-4), and obturator nerve (L2-4) overlaps with the nerve roots of the sympathetic nerve supply of the bladder (T12 to L2). It is readily understood thus why knee injury triggering a CRPS type-1 illness would involve the urine bladder and impair bladder emptying.

b) BLADDER INVOLVEMENT in C.R.P.S. type-1

The incidence of bladder involvement as part of the autonomic nervous system is unknown. The fact that it occurs is however certain. Chancellor reviewed the scientific literature to that time, and reported on 20 patients that he had examined[28]. The pelvis and perineum have also been recognized now, as also being a potential prime target of injury initiation and syndrome development of CRPS-1 and CRPS-2[29]. Twenty consecutive patients with diagnoses of CRPS (Reflex Sympathetic Dystrophy) were referred for urological assessment due to having new onset urological complaints. None of the twenty patients studied had had prior urological symptoms preceding them acquiring CRPS. Urological symptoms spanned a range of complaints including urgency, incontinence, frequency, and inability to urinate. In all twenty patients, complete urological assessment could find no other explanation for the symptoms other than the CRPS and its associated autonomic nervous system defects. Anticholinergic drugs and intermittent catheterization seemed mostly successful in the long term. Some example anticholinergic drugs for the bladder are Oxybutynin (Ditropan^{R}), and Solifenacin (Vesicare^{R}) to diminish urgency of micturition. The CRPS had to be medically treated as well. The main differential diagnosis is *autonomic dysreflexia*, which characteristically also has facial sweating and flushing, hypertension, bradycardia attacks as well.

c) DIFFERENTIAL DIAGNOSIS OF C.R.P.S.-1

It is a diagnostic requirement for CRPS-1 that other possible diagnoses that could cause the same pain be excluded. The prime differential diagnosis is CRPS type-2 due to injured macroscopic nerve element, causing neuropathic pain.

The general differential diagnoses are;

1. Fibromyalgia.
2. Infection causing inflammation.
3. Non-infective causes of inflammation – e.g. rheumatoid arthritis.
4. Vascular occlusive disease, and tissue ischemia.
5. Malingering.
6. Factitious disorder. (serious mental disorder with faking of disease and willingness to undergo painful tests)
7. CRPS type-2 (identifiable large nerve injury)

d) RISK FACTORS FOR ACQUIRING C.R.P.S type-1

These are best summed up by Pons and Shipton[30]. Due to (i) the remarkable heterogeneity of the disease, (ii) the scarcity of the illness, and (iii) lack of a united world consensus on diagnostic criteria CRPS, research is handicapped. Accordingly, discussion of risk factors for acquiring ACRPS-1 is not dogmatic and comments are generalized. The following risk factors may be either *contributary-causative* or only *associative-predictive* of a forthcoming development of CRPS.

1. **Woman** are most at risk, but men and children also get CRPS, if not only much more rarely.
2. **Post-menopausal status** applies to most of the woman acquiring CRPS-1.
3. The most common causes of CRPS-1 are **wrist and ankle fractures**, especially if **crushing** was an element in the injury. Other **intra-articular fractures** are modest risk events to trigger CRPS. Overall **orthopedic patients** form by far the greatest subgroup of CRPS patients, but not exclusively so.
4. Great degrees of **immobilization** after the primary injury.
5. **Pain scores exceeding 2.5**, on a 10-point numerical scale pain scale over the first **three days** after initial trauma.

The following factors are often strongly associated with CRPS-1. This may reflect that CRPS-1 worsens them severely, if present. They however have no evidence of contributing to the incidence of CRPS. Furthermore, treating them in established CRPS patients, apart from the independent merits of that, might possibly increase the chance of recovery from CRPS-1. These questionable factors are; (a) prior pain, (b) pre-operative notable stress, (c) having had a diagnostic bone scan, and (d) prior depression and other psychiatric illnesses.

V. DIAGNOSTIC TESTS

Any test considered diagnostic of an alternative diagnosis should be strongly considered in order to exclude it. There is however, no single test that is diagnostic of CRPS. MRI imaging is

helpful in the early stages, if a limb is foremost involved[31]. Patchy, multifocal bone marrow edema in subcortical regions is considered relatively classic for CRPS. Also contrast-enhanced MRI may show many forms of tissue edema or thickening from skin to muscle in the presence of CRPS. Unfortunately, none of these signs are pathognomic for CRPS and other differential diagnoses capable of causing swelling or inflammation need to be excluded, such as rheumatoid arthritis, immobilization, diabetes mellitus, lymphatic edema and tunnel syndromes.

Tests to variously document skin blood flow changes between left and right limb sides or before and after therapies, are useful research tools, but not necessary for diagnostic purposes.

Three-phase bone scintigraphy measuring the extent of bone uptake of a tracer has been studied[32]. Uptake did diminish generally in serial tests, as therapy progressed across 18 months. The test is not useful to diagnose CRPS. The test was not found useful to monitor the progression of CRPS healing or deterioration. It was however seen that hyper-fixation of trace at the first test preceding general therapy strongly identified the individuals who would respond best to therapy.

VI. PROGNOSIS

In general, the most successful special therapies (e.g. Ketamine) or interventions (e.g. sympathectomy) occur when performed within the first 12 months of the illness[33]. Sympathectomies if performed within the early period of under 12 months illness duration *can* be 100% successful in relieving CRPS-1 symptoms for some individuals. However, the fraction of those individuals obtaining any degree of benefit is only about 60%. The reminder, despite early sympathectomy, show zero clinical improvement. However, if sympathectomy is performed later than 24 months after start of symptoms, the success rate of sympathectomy falls to 44%. CRPS is generally considered a poor prognosis illness.

It has been reported that after a diagnosis of CRPS is made, and treated variously, that 70% of the patients will have partial improvement in some signs and or symptoms[34]. Twenty-five percent will have no improvement. Only 5% of the patients will have zero complaints. A group of 25% will still fulfil all criteria for the diagnosis of CRPS. Patients with high anxiety levels and fear of pain experience the worst prognosis.

VII. TREATMENTS for C.R.P.S.-1

There is no cure for CRPS type-1 and therapy is *aimed at **relief*** of symptoms. Most current reviews agree that there is no one proven therapy of high efficacy for CRPS-1[35],[36],[37],[30]. As CRPS type-1 likely has multiple etiologies, and even differing mechanisms at different phases, some therapies are seen to work better in some patients and not in others. Also, some therapies work best if given early in the course of CRPS only. Other therapies only reveal any benefit in the late phases of the course of the disease. There are many sham therapies based on small observational studies each claiming uniquely successful results, and that are seldom replicated by other researchers. Birklein[15] emphatically recommended that invasive therapies, e.g. sympathectomies, should best only be administered in academic centers recognized nationally, for having an expertise in treating CRPS.

Continuous post-surgical regional anesthesia studies that sustained local anesthesia via infusions after surgery have therapeutic effect on CRPS[38]. Soldiers with injured limbs in battle have high propensity for develop CRPS and early use of regional anesthesia has multiple advantages,

including likely reducing the risk of later development of CRPS-I[39]. It is sometimes said that giving the painful tissues a "pain vacation" for long enough will greatly improve the pain, of CRPS patients. One patient was reported by Dr. Aram Shahinyan where a cervical epidural infusion was set up using a disposable set rate plastic infusion pump[40]. The patient was instructed to switch the pump on when pain was felt and off when relief was felt. The pump's reservoir could last 30 hours at full flow. The local anesthetic used, was bupivacaine 0.1%, as 0.05% produced zero analgesia. The patient stretched that duration to 18 days, by using the pump intermittently. The patient achieved total freedom from pain by day 18, when the infusion was removed. He was still pain free at the 6th month follow-up exam. This author has also placed one patient on a T3 thoracic epidural for CRPS syndrome on the sternum following a midline sternotomy for cardiac surgery. The patient had allodynia, deep seated continuous pain and was very frustrated as he was on large doses of multiple oral analgesics including oxycodone. The patient was admitted to hospital and the T3 level epidural commenced running 0.2% ropivacaine at 6ml per hour. Testing with ice showed a block range from C8 to T5. He had approximately a 90% pain reduction immediately. Then slowly and progressively from about the 12th-hour onwards, the grade of analgesia got less. It was thought that this was evidence of local anesthetic tolerance developing. Local anesthetic tolerance is well established phenomenon, but seldom recognized as the typical acute pain deminishes as the healing process of tissue progresses. This cases observation, linked to the report of Shahinyan above [40], strongly suggest that an INTERMITTANT PATTERN of local anesthetic administration will be more effect when dealing with dysfunctional pain. Much research is needed to verify that thought.

Ketamine was very favorably reviewed used as an analgesic supplement to general anesthesia in 2005 by Himmelseher[41]. Himmelseher highlighted using a dose of 0.5 mg/kg ketamine injected IV with induction and then 0.25mg/kg, as an hourly supplementary bolus throughout the anesthetic for large bone related surgery. A modest amount of midazolam or any benzodiazepine, given with induction eliminates the bad dreams. Ketamine has been suggested in a 2007 review to be more affective in early cases and less effective in advanced long-established cases[42]. Ketamine has been used in one case for 5 days at an anesthesia grade dose of 3 to 5 mg/kg/hour with dramatic results[43]. In that report of Kiefer, a lady had severe untreatable pain in an entire arm, with the full clinical picture of CRPS. When on the ketamine infusion the edema and arm discoloration improved on the second day of infusion. One the day after the infusion was stopped the patient's arm was 100% normal, with normal movement possible, and zero pain. The remission from pain was still complete at 8 years after treatment. The post-ketamine psychiatric symptoms needed an extra month of midazolam.

The foremost recent researcher into the benefits of ketamine for CRPS patients is Sigtermans. In a 2009 study he investigated sixty CRPS-patients, with half the patients forming a saline control group. It was a dose finding study and the mean dose at trial end was 22mg/hour (+-2) for 70 kg patients. That dose gave mostly acceptable tolerance of side effects with good analgesia. The drug therapy lasted 4.2 days. By the time of twelve weeks was reached, eleven weeks after the drugs, the ketamine group pain-scores had risen back to matching the pain-scores of the saline treated control group. Clearly ketamine was very effective against CRPS pain. The ketamine had long-lasting benefit beyond the period of therapy, but was unfortunately not curative with the doses used as all patients had relapsed by 12 weeks later. Sigtermans published a second ketamine study in 2010[44]. Ten CRPS patients were given seven 5-minute infusions at increasing doses. Responses to experimental heat pain was assessed. Each infusion was separated

from the preceding infusion by twenty minutes. The extent of heat-induced-pain improvement was dose related. That analgesic effect on heat-induced-pain however, ended immediately after termination of each infusion. The CRPS-pain conversely, was potently reduced by ketamine during infusion, at the effective doses. When CRPS-pain relief was produced, it extended to up the last observations at the five-hour conclusion of the trial. The maximum and actual duration of the CRPS-pain analgesia was not measured. It was then concluded, that ketamine's analgesic effect on CRPS-pain had a different mechanism to its analgesic effect on acute-heat-induced-pain. It was postulated that ketamine had a disease modulating role on CRPS pain possibly by desensitizing spinal cord NMDA receptor, or by enhancing brain inhibitory control of the spinal cord. Sigtermans in his 2011 study administered ketamine to another thirty CRPS-1 patients for 100 hours, whilst a matching control group of thirty CRPS-patients received saline placebo[45]. Ketamine and its metabolite which were studied, were shown by Sigtermans to rapidly disappear from the body after infusion termination. Sixty-seven percent of *ketamine* patients experienced analgesia, versus the 23% of *placebo* patients who experienced analgesia. In this study, Sigtermans' ketamine patients who did experience analgesia, had their CRPS-pain relief last a mean time of 50 days. It was thus concluded that the ketamine induced a cascade of benefits, including desensitization excitatory receptors in the central nervous system. Conceivably these ketamine benefits, could be extended and even heightened if other therapies are combined with the ketamine, such as physical therapy, gabapentin, NSAIDs etc. This is for analysis in future studies.

The improvement of CRPS with ketamine has been shown to correlate with functional MRI brain changes observed a month later[46]. Meta-analysis of ketamine studies by Zhao in 2018 does not give strong clarity about the benefits of ketamine[47]. One of the challenges in reviewing the literature is the diversity of doses used, and the diversity of patients studied. That may artificially camouflage the true benefits of ketamine, as well as its best manner of therapy and dosing, as well as best patient selection.

This author has also seen a personal case of proven central spontaneous pain respond dramatically to ketamine. The patient had repeat surgery for a chronic foot condition. Nerve blocks were used, with general anesthesia. Upon awakening from general anesthesia, the patient reported severe foot pain, despite the nerve block evidence of fully working, with the patient reporting zero sensation to touch and having zero motor ability. The nerve blocks were repeated at more distal sites. The severe pain was unaltered. Then, fifty mg of intravenous ketamine, with one mg of midazolam, was administered. The patient recovered verbal responsiveness 15 minutes later and had zero pain in the foot. The pain score remained zero until the nerve blocks wore off 12 hours later, and thereafter the pain was easily managed with the standard analgesia protocol. This was clearly spontaneous pain, from spinal cord signaling, even in the absence of any nerve signals from the periphery. The blockade of the spinal cord NMDA receptors with ketamine terminated that spontaneous pain and blocked hyperalgesia developing in the subsequent days.

This author's interpretation on the merits of intra-operative ketamine, is that the earlier in the disease's progression that ketamine it is used, the better the results can be. A small ketamine dose, (0.5 mg/kg) with a 50mg minimum, routinely given during bone surgery whilst under anesthesia or under sedation, may be significantly CRPS preventative. The least conclusion about a small single dose of perioperative ketamine, is that the ketamine will reverse existing opiate induced hyperalgesia for up to 30 hours, and reduce post-surgical opiate needs. If the incidence of CRPS is reduced as well, that is a bonus second effect. The reduced use of opiates, might

additionally and separately contribute to a lesser chance of CRPS-1 developing later. This is much potential for research in this field to add to the validation of theoretical beliefs and tentative research observations.

Spinal cord stimulation has been successful in treating CRPS type-1[48]. A strong call, however, has been made to avoid all invasive therapies in adolescents and children with CRPS-I, due to near zero evidence of benefit in Children[49].

Intravenous lidocaine and ketorolac under tourniquet, administered as in a Bier's block, has been reported to resolve CRPS[50].

Niaki used intravenous phentolamine block under tourniquet, as in a Bier's block, with strong suggestion of syndrome improvement in a sizable portion of patients[51].

Bisphosphonates, such as Fosamax[R] and Boniva[R], have had some enthusiastic support for having benefits with CRPS, but only if given when the pain zone is warm, involved bone fracture, and within the first three months [52],[53].

Use of topical anesthesia on the affected injury area, or even the adjacent tissues alone, both inhibit cortical areas as assessed by EEG monitoring[54].

Transcranial Magnetic Stimulation has also been suggested to have therapeutic potential but this is not yet proven[55].

Vitamin C administered for 50 days has been shown to be beneficial too[56].

Intravenous block using *guanethidine alone* to induce a local sympathectomy, as in a Biers block, has no benefits in CRPS, and may even worsen the condition despite the fact arterial vasodilation occurs[57]. One study of one group, without controls, added lidocaine to the guanethidine IV block, and observed a general improvement in patients[58].

Treatment for CRPS-1 can be categorized as follows;

(1) Physical therapy. The person must be encouraged as much as possible to pursue living a normal life, and use the affected body parts. "Challenge the pain".
(2) Psychological therapy.
(3) Sympathetic blocks.
(4) Medications.
(5) Surgical sympathectomy.
(6) Spinal cord stimulation[59].
(7) Intrathecal opioid pumps, are no longer recommended.
(8) Limb amputation[60],[61],[62],[63]. This is generally considered never a therapy to be offered. It should maybe, only be very rarely considered for intractable disease, if the patient strongly requests this. A long time must be taken before executing the patient's request. Patients who reach this point are seemed very happy with the surgery in the few cases reported. There about 250 reported cases.

VIII. FINALLY; The role of the anesthesia provider.

The anesthetist or anesthesiologist is never the one to specifically diagnose that a patient has CRPS type-1. The anesthetist or anesthesiologist is never the one to specifically treat a patient with CRPS type-1. The anesthesia provider is however, often in a convenient place to provide much *treatment* that may prevent CRPS type-from developing in a patient. The anesthesia provider is often in a position to provide care that could treat a CRPS type-1 that is already in an initiating phase.

The concept of *pre-emptive analgesia* was proposed by Crile in 1913[64]. In an editorial in 2003, PW Lui referenced Crile and proposed intra-venous Ketamine to be the best pre-emptive analgesia possible[65]. The best time to "pre-treat" a future CRPS is the peri-anesthetic period. No medical specialty is better equipped to manage that, than that of anesthesiology.

This kind of care as CRPS-preventive-therapy is speculative, unproven, but based on logic and some evidence. It will be near impossible to study the following suggestions in prospective, blinded and randomized fashion due to the paucity of cases on a day to day basis. Achieving a large enough study group in any single institution is impossible. Furthermore, omitting the specific care from a study control group would be unethical. Much of the care that is here recommended is basic care for other good reasons. The recommended care is likely to only be truly beneficial in (1) the totality of all the components, (2) the intensity or largeness of the recommended doses, and (3) the sustaining of the therapy for sufficient duration.

Based on (A) this author's experience as an anesthesiologist, a life time of trying to treat post-surgical pain optimally and a special interest in regional anesthesia, and (B) an understanding of the scientific literature reviewed on the preceding pages these recommendations are made;

Global plan:

i. **Avoid opiates maximally.** Use them only for break-through pain despite all other feasible optimal analgesia care. Try to restrict their day time use to three days maximum post-surgical usage. Thereafter try to restrict usage to nocturnal only with a final limit being the sixth to seventh night only. Also, minimize intraoperative use of opiates. Absolutely do not use opiates as pre-medication. Opioid free anesthesia has been proposed as way to prevent persistent post-surgical pain, and hyperalgesia, implicitly including CRPS[66],[67].
ii. **Utilize regional anesthesia as much** as is feasible and practical. Start nerve blocks prior to surgery, and try to maintain the nerve blocks for three days and through at least two post-surgical nights.
iii. **Administer ketamine** intraoperatively as a dose of 50mg at induction, then 25 to 50mg/hour at least for the first two hours of surgery, and avoiding administration in the last 30 minutes.
iv. **Maximize use of non-sedating analgesics.** The leading two are acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs).

The big question is, who should get this perioperative Comprehensive Pain Therapy Plan (CPTP)?

Based on the above understandings of CRPS type-1, the patient at most risk to develop CRPS type-1 has the following features;

(1) They have had a prior pain-causing injury, or surgery to the same limb about to be operated.
    - Also consider a patient with a large acute injury older than 48 hours that had an element of tissue crushing involved, and that has required a lot of opiates.
    - Any patient coming for limb bone surgery, who has been on oral opiates continuously for longer than a month pre-operative.

(2) They report a history of having experienced any degree of allodynia in the preceding year. They have had CRPS type-1 before in their lives.

(3) They are smokers of tobacco, and or marijuana, and or consumers of cocaine.

(4) This surgery is a re-operation of the same limb or bone.

(5) They are mature or older woman.

(6) They have emotional or psychological illness like, anxiety or depression and are on therapy. Be double concerned if they spontaneously express fear of pain.

The CRPS-1 prevent-treat plan in more detail;

- **Avoid opiates**:
    - Start by educating the patient beforehand.
        - *Lower their expectation for pain relief*. Tell them although zero pain is an ideal goal, your promised goal is keeping the pain at a low enough level that they can cope with it. State that you cannot guarantee zero pain, but that you will care for them as best you can. Patients comprehending this and having lowered analgesia expectations, do best on analgesia therapy.
        - *Also explain the problems with opiates.* Explain that opiates do not cure pain. Opiates make one sleepy, a bit happy, make one not care about the pain, and reduce the pain slightly. Opiates however stimulate the bodies mechanisms that amplify pain. That means opiates despite helping a bit for pain relief "now", simultaneously tend to extend the duration of time that one still needs pain killers. Explain thus opiates will just be used, *if really needed*, only early in the recovery period to round off the other more curative treatments. Explain the less the amounts of opiates they need and the shorter the duration they use them, the better they will be in the long term.
        - *Emphasize that you care for them and will do all you can for them.*
- **Use regional anesthesia** to deafferentate the spinal cord and brain from pain signals.
    - Nerve blocks need to be maintained for a long period after the surgery. Consider maintaining the block to the first morning after surgery as a minimum, to the *second*

morning as just starting to be CRPS preventative, and to the third morning as ideal. There probably is no benefit to maintaining it beyond 5 days after surgery.

- This means using specific major nerve blocks, or epidural anesthesia. In the distal lower leg, it can mean needing to block two nerves. If only one nerve block is maintained by perineural infusion it should cover at least 75% of the injured tissues nerve supply. The other nerve(s) supplying the remaining 25% of the injured tissues should at least be blocked for period by single shot injections expected to last a few hours, at least, beyond the end of surgery.
- *Encourage as much activity as possible* within the capabilities from that limb, within bed, if ambulation is not possible. Arrange for assisted physical therapy twice daily. Encourage the patient to be active by themselves, as much as possible. This will prevent bed and pressure sores, preserve muscle strength, reduce risks for venous-thrombosis, and will also foster tissue healing.

- **Administer ketamine**. It does not matter whether the patient is anesthetized or sedated. A small single dose of 50mg administered once at the start of anesthesia is very effective in reversing any existing opiate induced tolerance, or opiate induced hyperalgesia, with the benefit lasting 24 hours. The doses of ketamine that have been shown effective in treating CRPS are much larger and need 25 to 50 mg repeated dose throughout the surgery, with avoidance of a dose in the last 30 minutes of surgery. Alternatively, that hourly dose could simply be infused over the hour. It is unclear whether bolussing or infusing is superior.
  - Never administer ketamine without an accompanying amount of midazolam, or another benzodiazepine. This must be done even of the patient is under propofol sedation or volatile anesthesia. This will minimize the patient experiencing discomforting hallucinations after the ketamine therapy. Consider administering a dose like midazolam 1 to 5 mg per hour during the ketamine infusion.
  - Warn the patients that they may experience sleep dreams for six months after the therapy that are more vivid than usual. The phase will however always come to pass.
- **Use NSAID's**, if not contra-indicated. Short term course of NSAIDs, like for 5 days have been shown to not affect long term bone healing in humans. Very importantly, animal research into the side-effects of NASIDs on bone healing, show a definite immediate negative effect on bone healing. Of great note, In the animals that impaired-bone-healing is temporary. Bone healing normalizes immediately upon the final dose of NSAID after 5-7 days usage, followed by accelerated period of healing so that final bone repair is as firm as it would have been had a NSAID never been used. It is however important to stop the NSAIDs after 5 to 7 days of treatment, if bone cuts or fractures are involved in the surgery.
  - It is recommended that the NSAIDs be prescribed in fixed scheduled regular doses for the first 3 to 5 days. Only after that period, should prescribing revert to an "if needed for pain" type of optional usage by the patient.
  - These can be used indefinitely, only if no bone healing is needed.
- **Use acetaminophen**, if not otherwise contra-indicated. Prescribe maximum doses at fixed scheduled doses for the first 3 to 5 days after surgery. Only after that period, should prescribing revert to an "if needed for pain" type of optional usage by the patient. These can be used indefinitely.
- **Opiates**. Always use only as *rescue analgesia* and never as primary analgesia.
  - In the immediate post-anesthesia period opiates may be used as judged needed until the patient has recovered full consciousness.

- Opiates must initially only ever be administered with discretionary administration, by either the patient themselves via a PCA, or by a nurse injecting IV, SC, or IM. Injectable opiates can be made available for the first 36 hours, or so, after surgery.
- Thereafter revert to discretionary use of oral opiates until 3rd or 4th day.
- Thereafter limit oral opiates to night-time usage until the eighth to tenth night after surgery, with large bone cutting. For smaller surgeries limit opiates to 4- or 5-days usage after surgery.

- Other less efficacious therapies. These are therapeutic options that are believed by some to have small benefit, that is generally not grossly observable if used alone. These therapies however, can as group have additive effects that become modest. It can contribute to all the above therapies, in an extreme pain-challenged patient;
  - Gabapentin started pre-surgery.
  - Total opiate avoidance intra-operative, except to obtund intubation sympathetic effects.
  - Total volatile anesthetic avoidance (use propofol TIVA)
  - Full dose amitriptyline. Research suggest the drug could have anti-hyperalgesia effects in opiate-dependent subjects in full doses, although in very low doses the drug paradoxically worsens pain[68]. One trial using low dose amitriptyline did find suggestion of analgesia benefits in chronic pain[69]. A Cochrane analysis could not find evidence of benefit, but the authors still recommended it be used to treat neuropathic pains due to their years of perceived favorable clinical results suggesting benefits[70]. An animal study showed clear analgesic effects of amitriptyline for neuropathic pain, with a mechanism independent from noradrenergic, serotonergic and gabapentinoid mechanisms, but that also greatly analgesia therapies acting on those systems[71]. In children with CRPS gabapentin and amitriptyline are equally effective[72]. In 1995 intrathecal amitriptyline in animals showed profound analgesia effects, and the study suggested an NMDA receptor effect[73]. That explanation for that effect has not further validated in other research yet. Recommended dose is 25 mg three times per day in adults, for the duration of the first five post-surgical days.

IX. CONCLUSION.

- Most recommended scientific papers;
  - **KETAMINE**. Himmelseher S, et al. **Ketamine for perioperative pain management**. Anesthesiology. 2007;102(1):211-220.
  - **PATHOLOGY.** Gupta G, et al. **Complex Regional Pain syndromes**. Emedicine.medscape.com. Updated 2018-June 20
  - **DIAGNOSIS.** Bruel S. **An update on the pathophysiology of complex regional pain syndrome**. Anesthesiology 2010 Sep;113:713-25
  - **DIAGNOSIS** (50 pages). Harden RN, et al. **Complex regional pain syndrome: practical diagnostic and treatment guidelines,** 4th edition. Pain Medicine. 2013;14:180-228. (very long hard reading, but very authorative IASP document)

Note Bene: Although this is a referenced review, many statements within this text that are not specifically referenced in this document, will have their original references found in the following Reviews[34,30,1,9].

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