THE INTRACTABLE PAIN SYNDROME

A CALL FOR RECOGNITION AND PREVENTION

By

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FOUNDING DOCUMENT

This paper has been drafted to summarize the current status of this syndrome and provide the rationale for the initiation of our Research and Education Project.

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1. PROLOGUE

Astute observers have long recognized that a sub-group of persons with chronic pain develop constant pain accompanied by such severe impairment of physiologic and psychosocial functions that the person is incapacitated and may suffer an early death. There have even been calls to label this occurrence a "disease." Over the past 5 decades this subgroup of chronic pain patients has often been labeled "persistent" or "intractable." This recognition has had enough merit that the latest International Classification of Disease (ICD-10) now lists intractable pain as a separate condition with its own identification number. Based on recent research it is most appropriate and accurate to diagnose certain individuals as having the Intractable Pain Syndrome (IPS). This syndrome is not a symptom or disease, but a complication of an underlying, painful disease or injury that produces excess electrical impulses that travel into the brain and spinal cord (central nervous system or CNS) and create pockets of tissue-destructive inflammation. Loss of CNS tissue in this process may include the neurotransmitter-receptor systems that control pain and regulate the cardiovascular, endocrine, and immunologic systems. With this loss of tissue, the afflicted persons develop constant pain and measurable evidence of cardiovascular, endocrine, and immunologic abnormalities. Hence, the systemic signs and symptoms indicate a specific syndrome of multiple body-wide manifestations termed Intractable Pain Syndrome. There is, however, some promising news for those afflicted with IPS. Clinicians have achieved good results in treating some patients by following a medication protocol designed to treat the underlying disease and to provide pain relief, while simultaneously correcting detected physiological abnormalities. The result, in some cases, has been the reversal or reduction of the magnitude of the impairments that the patients had developed. In other words, some patients with severe long-standing pain and significant impairments can, with a regimen tailored to their needs, achieve effective pain relief, and regain lost capabilities and function. To date this new understanding is not well known outside research circles. Therefore, the Tennant Foundation has initiated a Research and Education Project to bring information on this syndrome to patients, families, and medical practitioners. This paper presents the background, history, and basics of the Intractable Pain Syndrome as well as the rationale to treat it and initiate research and education on it. The overall goal of this new project is to bring recognition and treatment of the syndrome to pain care and to foster its prevention, since it is often a devastating, catastrophic medical condition.

2. INTRODUCTION

It has long been known that a sub-group of persons with chronic pain develops constant excruciating pain, hypertension, tachycardia, and the inability to carry out physiologic and mental functions.[1-4] This condition has long been known to cause immense suffering and an early death.[5] This sub-group of chronic pain patients has often been referred to as having "intractable" pain, but there has not been, until recently, a rational explanation for this occurrence.[4]

Research in recent years has now determined that these unfortunate individuals have transformed from a simple chronic pain state into a physiological and pathologic state that

should properly be called “Intractable Pain Syndrome” (IPS). It should be called a syndrome, because it involves specific physical signs, symptoms, and physiologic abnormalities that occur together in a recognizable complex. In addition to a causative, painful disease or injury, the syndrome is underpinned by pockets of inflammation in the brain and spinal cord (hereafter CNS) which damage or even destroy the mechanisms that control pain and some critical physiologic functions necessary for daily living. These areas of damage and tissue loss in the CNS can now be imaged and documented with high-technology brain scans.[6-10] Loss of CNS tissue may cause profound dysfunction of the cardiovascular, endocrine, and immunologic systems, which leads to disability, immense suffering, and a premature death.[11-16] The physiologic abnormalities in IPS can be objectively assessed, and their presence identifies the unfortunate person who has the syndrome. (Tables One-Three) This report pulls together some basic information that is known about IPS and serves as a “primer” for research and education.

3. THE CONCEPT THAT CHRONIC PAIN IS A DISEASE

Many astute observers of persons who have severe chronic pain have written and advocated that severe, chronic pain be labeled a disease.[18-24] Their basis for the claim has been that the persons they observed had many symptoms and disabilities in addition to their pain. They even recognized that death came early and quickly to many of these patients.[5] These writings and observations have, in general, focused on the subjective psychological, emotional, and disabling ramifications in the patients, as they had little in the way of objective tests or evaluation tools to study and objectively identify chronic pain patients whose pain had transformed into a disease state affecting many body systems causing immense suffering and inability to function. The calls to label chronic pain a disease, however, have essentially “fallen on deaf ears.” Although the exact reasons why chronic pain has not been generally accepted as a disease are uncertain, we believe the answer is twofold:

1. All chronic pain patients were lumped together in the writings that called for chronic pain to be labeled as a disease. In other words, anyone who had pain lasting over 90 days whether a bunion or arachnoiditis, would have the disease label. For example, the most common cause of chronic pain is arthritis of joints, and this is almost universal in everyone over about age 65. A disease label that would essentially include every elderly person is not a viable proposition.

2. The writings to call chronic pain a disease are absent any objective criteria to separate simple chronic pain patients from those who have the serious, debilitating clinical profile of IPS.

While we believe the advocacy writings to label chronic pain a disease have clearly brought enlightenment and recognition of the terrible plight of some persons with chronic pain, only those persons whose condition transforms simple chronic pain to IPS can be labeled as having pain as a disease.

4. HISTORY OF INTRACTABLE PAIN

The first association of the word "intractable" to "pain" that we can identify was in 1933.[24] In that year the Shorter Oxford English Dictionary on Historical Principals defined intractable as "not easily treated or dealt with."[25] It also acknowledges a 1607 reference which states intractable is "resisting treatment or effort." British physicians Hunt and Linnett, in 1960, wrote a seminal article simply entitled, "Intractable Pain."[1] In this article they praised the value of anti-inflammatory agents for the treatment of simple chronic pain conditions but stated that some chronic pain patients were "intractable "and required narcotic (opioid) drugs for treatment. Shortly after this article, British and Irish physicians formed an "Intractable Pain Society" to enhance diagnosis and treatment of the condition.[2] The first use of the term to describe physiologic complications of intractable pain was in 1978 when 2 Canadian physicians (Glynn and Lloyd) used the term "intractable" in a paper entitled, "Biochemical Changes Associated with Intractable Pain."[3] As reported in the British Medical Journal they found that these patients had elevated carbon dioxide levels due to impairment of breathing caused by the presence of intractable pain. A Philadelphia neurologist by the name of Shenkin, shortly after a blood test for cortisol was developed, found, in 1964, that cortisol levels were pathologically altered in some chronic pain patients.[26] These studies were the forerunners of a longer list of studies that have demonstrated that persons with intractable pain have objective physiologic abnormalities that separate them from the simple chronic pain patient. Beginning in the 1990s, some state legislatures began passing intractable pain laws. These laws fundamentally defined intractable pain as "incurable by any known means."[4] The intent of these laws was to permit physicians to prescribe opioids without retribution or discipline by their state medical boards. These laws were helpful for over two decades in that they enabled opioid prescribing for persons suffering from intractable pain.

These laws, however, have had a tragic outcome. In recent years, the states and the federal government have essentially ignored these laws by prosecuting physicians who prescribed opioids and restricting the availability of opioids even when prescribed. Basically, these actions have been taken due to the belief that opioids, even when prescribed to legitimate pain patients, are now overly associated with abuse, addiction, and overdoses to allow medical use even as a last resort treatment.

The term "intractable" has not been embraced by any professional organization. Early in the 21st century, there was a movement to replace the term "intractable" with "high-impact" or "persistent. These terms have not found any widespread acceptance either, as these labels are more ill-defined than the term intractable.[15,19,26] These terms also trivialize those persons with IPS who should be viewed as having a catastrophic illness. Interestingly, the new International Classification of Diseases (ICD-10), has classified "intractable pain" as a disease and assigned it a code for billing and data collection purposes (code R-52).

In summary, the term "intractable" has emerged in that it both signifies an incurable state and implies that a subgroup of severe chronic pain patients exists among the population of chronic pain patients. The terms "persistent" or "high-impact" pain and the concept of chronic pain as

a disease has not found general acceptance, and all persons who have a painful condition that lasts over about 90 days have continued to be labeled as having "chronic pain." Recent research has clarified the issue so that understanding and diagnostic testing can now identify chronic pain patients who started with "simple" chronic pain but have developed a complex of physiologic abnormalities for which the most appropriate name is the "Intractable Pain Syndrome." Since opioids are now highly limited and restricted by government fiat, it is essential that research and clinical investigation find alternatives to them, and this necessity is one of several reasons for formation of our Research and Education Project.

5. DEFINITION

IPS is a complication of an underlying painful injury or disease that causes inflammation and tissue destruction inside the CNS which results in constant pain and the physiologic and pathologic dysfunction of the neurologic, cardiovascular, endocrine, and immunologic systems.

It is important to point out that the underlying painful condition or injury produces inflammation (often called neuroinflammation) and tissue loss by sending excess electricity (often called "signals" or "impulses") into the CNS. "Hot spots" or pockets of tissue loss are caused by an immunologic cell in the CNS called a microglia, which brain scans have clearly documented as the cause behind loss of CNS tissue.[27-36] The presence of the resulting cardiovascular, endocrine, and immunologic abnormalities can now be assessed and documented by objective physical findings and laboratory tests. In other words, IPS can be objectively recognized and those persons who have it can be easily differentiated from persons with simple chronic pain. (Tables One to Three)

6. BRAIN SCANS CONFIRM IPS

The basic and fundamental reason that IPS has not been recognized or labeled until now is that there was no single cause or rationale to tie together the various ramifications of IPS. In other words, there has been no concrete or rational explanation that joins these seemingly disparate parts such as constant pain, hypertension, and hypoglycemia into one entity. This issue has now been clearly resolved thanks to brain scan technology.

This technology has developed to the point that brain scans can identify pockets of tissue loss in the CNS that are caused by inflammation.[6,9,13,26-31] Unfortunately, a loss of tissue on a brain scan means that some critical neurotransmitters and receptor systems have been damaged or destroyed. The loss of normal CNS tissue is responsible for IPS as the loss of tissue prevents the CNS from exerting its normal control over pain and regulation of the cardiovascular, endocrine, and immune systems. A few years ago, the knowledge that a painful injury or disease could produce enough electrical impulses to produce CNS inflammation that damages or destroys vital physiologic functions would have been a preposterous belief. We now know this is the underpinning of a catastrophic syndrome thanks to brain scans and research on electricity generated by injury or disease.

7. GLIA CELL ACTIVATION AND INFLAMMATION

The electricity (i.e. impulses or signals) generated by a painful injury or disease travels along nerves into the CNS. These electrical charges activate immune cells in the CNS called glia that form pockets of inflammation and damage. The process of developing glial cell activation and inflammation is now called "central sensitization."[34] This term has been selected by physicians to describe the glia cell-inflammatory process, because the entire CNS is over-reacting to pain and produces such symptoms as anxiety, headaches, appetite change, depression, insomnia, loss of attention span, mental focus and fatigue.

8. LOSS OF NEUROTRANSMITTER-RECEPTOR SYSTEMS

Many functions of the brain and spinal cord are carried out by what are called neurotransmitter-receptor systems (NTRS). Neurotransmitters are chemicals that cause a signal to various nerve cells directing them how to function by attaching to a microscopic bit of tissue called a receptor, because it receives the neurotransmitter. Receptors are the action points or "spark plugs" of the brain cells in the CNS that initiate the functions of memory, motivation, energy, analytic thought, pleasure, pain control, and such physiologic actions as breathing, blood pressure, immune function, and temperature control. Some receptors control enzymatic processes that include cleaning up harmful, metabolic waste produced by the signaling actions of the NTRS on cells. The NTRS are much like the battery in your car. The NTRS stimulate the production of electrical signals to the cells. Simply put, the chemical reactions produce electricity.

Unfortunately, the inflammation produced by electricity generated by a disease or injury causes loss of tissue that contains NTRS.[8,10,37,38] It is the loss or damage to at least six NTRS that contribute to IPS (Table Five). The loss of enzymatic receptors that clear the cellular waste debris as a result of the NTRS signaling process will cause harmful waste products to build up in the cells, causing a negative cellular function cascade, and an increase of neuroinflammation and autoimmunity as the immune system targets these products for removal. Some receptors that are activated by hormones are lost with tissue destruction, and this will also cause an increase of neuroinflammation and impaired healing. This understanding is new, and it is the most poorly understood aspect of pain, suffering, and impairment. There is no bigger need for education than this point, and this need is a major impetus for this Research and Education Project.

Six neurotransmitter levels and/or receptors appear to be potentially lost or damaged by pain-generated neuroinflammation: (1) endorphin; (2) dopamine-noradrenalin; (3) gamma aminobutyric acid (GABA); (4) N-methyl-d-aspartate receptor; (5) serotonin; and (6) endocannabinoids. Endorphins attach to the opioid receptor and this receptor is involved in pain control, immune regulation, and pleasure. The adrenaline surrogates in the CNS, dopamine-noradrenergic, have a receptor of their own that is involved in pain control, energy, motivation, attention span, and cardiovascular function. GABA is involved in pain control,

sleep, and regulation of all electrical nerve conduction in the body. The N-methyl-d-aspartate receptor is involved in pain control and a variety of mental functions. Several neurotransmitters attach to it. Serotonin regulates sleep patterns, energy, and pain. The endocannabinoids have their own receptor and help regulate pain and appetite.

Every one of the six NTRS are critical for pain control, and unfortunately any or all NTRS that are damaged or deficient may have to be medically treated by substitution with surrogates of the natural neurotransmitters or receptor stimulators. For example, opioids will have to substitute for endorphin, adrenalin surrogates such as dextroamphetamine or methylphenidate for dopamine, and gabapentin or diazepam for GABA, and ketamine as a receptor stimulator. Now that we realize there is the NTRS loss of tissue that produces neurotransmitters and that deficiency is present, it is the administration of neurotransmitter surrogates which forms the foundation for treatment for IPS. Opioids have been the traditional treatment for intractable pain since 1960.[1] Opioids are surrogates for the endorphin class of neurotransmitters. Endorphins are involved in multiple systems which partially explains their well-known ability to relieve pain. Some IPS patients need little except opioids to function and attain relief. Hopefully, patients will continue to have access to them since opioids may be the only effective pain-reliever in some IPS patients. For most patients with IPS, opioids are only one component of several that are needed. In medical science the surrogates of neurotransmitters are called by a technical pharmacologic name such as psychotropic, analgesic, neuropathic, or analogue. In this project the term “surrogate” will be used to label any drug given to make up for a deficiency of a neurotransmitter. A major reason for initiation of our IPS Research and Education Project is that hormone and neurotransmitter laboratory testing has begun, and patients, families, and physicians need to be educated on the benefits of these tests.

9. UNDERLYING CAUSES OF IPS

Over the past decade, it has been possible to identify and catalogue the conditions that produce simple chronic pain and those that cause IPS. The most common cause of simple chronic pain is osteoarthritis of joints and the spinal column. Essentially all persons over age 65 have some osteoarthritis. Other common simple pain conditions include neuropathies, muscle sprains and strains, fibromyalgia, headaches, and bunions (Table One). IPS is caused by a relatively small number of conditions that are not well known to the public, or most medical practitioners. Five basic conditions make up about 70-80% of these cases: (1) arachnoiditis; (2) genetic connective tissue/collagen disorders of the Ehlers-Danlos Syndrome (EDS) type; (3) reflex sympathetic dystrophy (RSD) also known as complex regional pain syndrome (CRPS; (4) brain injury caused by strokes or head trauma; and (5) serious end-stage osteoarthritis of the spine, hips, knees, or feet. (Table Two) The remaining causes include porphyria, sickle cell disease, Lyme, interstitial cystitis, and rare genetic disorders. It is the relative rarity of the conditions that cause IPS that has been a huge barrier to the understanding of IPS. It is further important to point out that these relatively rare conditions are of such severity that they have generated effort to specifically treat the condition as well as the IPS. The two categories of chronic pain, those with simple chronic pain versus intractable pain syndrome are quite distinct in appearance, physiology, and function. (Table Three)

10. CARDIOVASCULAR AND VASO-MOTOR HYPERACTIVITY

Besides constant pain, sympathetic hyperactivity, or hyperarousal "overdrive," with surges, is a cardinal or universal characteristic of IPS.[13,14] A major and serious adverse consequence is hypertension and tachycardia. The sympathetic nervous system is the stimulant or "up" part of the autonomic or involuntary nervous system. It is both operated and modified by adrenaline and its more potent analogues, nor-adrenaline, and dopamine. It counters or opposes a "down" system known scientifically as the GABAergic system, because the neurotransmitter gamma aminobutyric acid (GABA) is the sedating or tranquilizing agent. The GABA system keeps the sympathetic system in check; otherwise it will produce hypertension, tachycardia, constriction of small blood vessels , elevated temperature, overactive reflexes, sweating, diarrhea, severe anxiety, and what is now called Attention Deficit Hyperactivity Disorder (ADHD). Sympathetic "overdrive" also causes extreme fatigue, depression, insomnia, and loss of appetite (anorexia) which may then result in varying degrees of malnutrition and wasting of tissues.

The hyperactive sympathetic nervous system due to IPS is not only constantly present, it also produces sympathetic surges or waves. These surges are troubling at the least, and debilitating at worst, for the IPS patient. The surges raise blood pressure and pulse rate and may produce any or all of these symptoms: anxiety, headache, cold hands and feet, sweating, and diarrhea. Physical signs in addition to elevated blood pressure and pulse rate can include dilated pupils, overactive reflexes, increased breath rate, and cold hands and feet. Pain often flares during a sympathetic surge. The most dangerous aspect of the sympathetic surge is stress on the heart. It may cause coronary vasoconstriction and a myocardial infarction "heart attack" or an arrythmia. Death may occur suddenly during a surge even if the patient is asleep. Persons who already have a cardiac disorder such as arteriosclerosis are particularly prone to sudden death. Many IPS patients have died from a sympathetic surge only to have an unknowledgeable coroner say it was a "drug overdose."

11. ENDOCRINE AND METABOLIC ABNORMALITIES

IPS causes profound alterations in the hormonal (endocrine) system.[39,40] Once glial cells activate and neuroinflammation develops in the CNS, the body attempts to combat and cure the inflammatory process with its natural hormones. Hormones that the body uses for healing include cortisol, estradiol, dehydroepiandrosterone (DHEA), pregnenolone, progesterone, and testosterone.

The pain and inflammatory process in the CNS plus the sympathetic hyperactivity of IPS cause the body's endocrine stress system to also go into overdrive. The stress system is naturally designed to protect the body against sympathetic surges and promote healing both inside and outside of the CNS. The first step in the stress response is the release of hormones by the pituitary gland in the brain called adrenal corticotropin hormone (ACTH) and luteinizing hormone (LH). ACTH activates the adrenal gland to release and activate pregnenolone and cortisol. LH causes the sex glands (ovaries and testicles) to produce estradiol, progesterone, and

testosterone. The hormones all rise in the serum to combat pain, inflammation, and to promote tissue healing. As part of this process, the adrenal hormones also act on the pancreas causing glucose release. This information is critical to the diagnosis of IPS because all the hormones noted here, as well as glucose, initially go up in the serum and can be measured. Unfortunately, the endocrine system cannot keep up its overdrive state indefinitely. If pain and the inflammatory process in the CNS are not adequately controlled, these essential hormones can become depleted, with their levels dropping below normal in the blood. Once this hormone depletion occurs, multiple complications involving the immune, gastrointestinal, and sex systems ensue as they depend on various hormones for normal function. A critical scientific point has been realized about severe chronic pain and the endocrine system. A person who develops IPS will show multiple hormone abnormalities, therefore an IPS patient can be objectively identified by the finding of abnormal hormone levels in the blood. In other words, a legitimate uncontrolled and undertreated IPS patient will show one or more hormonal abnormalities.

IPS alters glucose metabolism since it, like cortisol and adrenaline, becomes elevated when the body is under stress. Most stressful situations are well known and intermittent, and stress may be caused by an adverse emotional or physical event. The problem with constant pain is that it does not stop. In fact, the argument can be made that constant pain is the most vicious, malignant stress because the endocrine system never gets to "shut off," rest, and recover. Even during sleep, which usually needs to be induced by sedating medication in IPS, the endocrine system cannot fully recover. Consequently, the endocrine system cannot keep up with the constant pain and stress, so multiple glandular hormone levels decline. This may include adrenaline and its surrogates nor-adrenaline and dopamine, insulin, the adrenal hormone cortisol and pregnenolone, and the gonadal hormones testosterone and estradiol.

Due to the demands of constant pain on cortisol and insulin, glucose metabolism is altered. Blood testing may show a diabetic pattern or a hypoglycemic pattern. Chronic hypoglycemia in the person with IPS may cause an internal craving for carbohydrates (sugars and starches) to the exclusion of protein and other necessary nutrients. Loss of a normal, regular (3 meals a day) appetite occurs and various other forms of malnutrition are present in an undertreated IPS patient. Unfortunately, a person with IPS is at risk for severe hypoglycemia and death from it.

12. IMMUNOLOGIC DEFICIENCIES

IPS has a major impact on the immunologic system.[16,41-44] Clinicians have observed that persons with IPS are quite susceptible to infection. Cancer incidence seems remarkably high in persons with IPS. No data, however, exists relating to infection and cancer rates in IPS. New studies are showing that IPS patients often have elevated inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, various cytokines, tumor necrosis factor, and white blood cell count.

There are 2 mechanisms by which IPS may cause autoimmune manifestations such as fibromyalgia, thyroiditis, and carpal tunnel syndrome. One is the entry of brain tissue particles

from CNS neuroinflammation sites into the general blood-lymph systems.[45] It is now known that CNS tissue is antigenic to the body if it gets outside the CNS. The second mechanism involves impaired lymphocyte function. Multiple hormones including cortisol, endorphins and testosterone that are critical to healing and immune functions are often suppressed in IPS.[39,40] Lymphocytes necessary for immune functions have receptors for multiple hormones. In simple terms some hormones supply the "gasoline" and "energy" for proper lymphocyte function.

13. DIAGNOSIS OF INTRACTABLE PAIN SYNDROME

Thanks to recent research on chronic pain patients, enough is known to objectively identify and separate the IPS patient from those with simple chronic pain. The major causes, symptoms, physical findings, and laboratory abnormalities of IPS patients have now been identified and described. The major symptom of IPS is constant pain. It is perceived as always present unless the afflicted person is asleep. This contrasts with the chronic pain patient who will describe their pain as intermittent (e.g. "comes and goes" "good days and bad"). Insomnia is almost universal and normally requires a medicinal sleep aid. Severe fatigue is also almost universal due to multiple factors including noradrenaline deficiency in the CNS and hormone deficiencies in the blood. A lack of attention span, memory, and ability to concentrate is quite common. Many patients can no longer read or take on tasks that require complex mental abilities. A change of appetite may occur due to inflammatory destruction or impairment of various NTRS.[46-49] For example, some IPS patients lose their appetites while others have cravings for high fat and carbohydrate foods. Table Five outlines criteria needed to make a diagnosis of IPS and is attached.

Since IPS is a serious catastrophic condition, we recommend that the diagnosis only be given under the following circumstances: (1) patient has an underlying disease or injury that produces pain; (2) pain is constant and debilitating; (3) hyperarousal of the cardiovascular system is present with elevated blood pressure, pulse rate, and other vasomotor dysfunction evidence such as cold hands or feet, hyperactive reflexes, or mydriasis (dilated pupil); and (4) laboratory presence of abnormal hormone, glucose, or inflammatory tests. (Table 5)

Like other serious catastrophic syndromes and diseases, some forms of IPS are less severe and in early stages. At this time there are no criteria for determining to which classification a patient may belong. Our Research and Education Project intends to develop such criteria to help manage cases and prevent progression from mild or moderate to severe or catastrophic stages.

14. EARLY DEATH IN IPS

Unless treated and controlled, IPS brings a premature death. There are no exceptions, because the human body can only endure sympathetic hyperarousal and hormone deficiencies for a limited period. The result of untreated IPS is immobility, starvation, cachexia, and terminus. Many IPS patients will commit suicide rather than endure the final physiologic end.

IPS patients who are undertreated die prematurely due to cardiac arrythmia, myocardial infarction "heart attack," hypoglycemia, adrenal failure, or an overwhelming infection due to their compromised immune system. (Table Five)

15. TREATMENT OF IPS

In contrast to persons with simple, chronic pain, IPS requires a systematic protocol and not just treatment with symptomatic analgesic drugs. The treatment protocol for IPS is one that requires multiple components. (Table Seven) First, treatment is directed at the underlying injury or disease as well as CNS inflammation. There will likely have to be some replacement of neurotransmitters by use of precursors or surrogates. Treatment may also have to ameliorate cardiovascular, endocrine, and immunologic abnormalities. Many IPS patients suffer severe insomnia, fatigue, poor attention span, and nutritional deficiencies which must also be addressed.[46-49]

A major lack of treatment for IPS patients is for what is known as "descending" pain. Most pain is "ascending" which means that electrical impulses from the injury or disease travel "up" or "ascends" into the CNS. The CNS also has a mechanism by which it sends electrical impulses down or descending into the site of injury or disease to control pain.[50-52] This system is regulated by the adrenaline derivative, noradrenaline. The NTRS that makes and regulates noradrenaline may be damaged in IPS. Specific drugs such as clonidine, duloxetine, amitriptyline, tizanidine, or adrenaline surrogates such as methylphenidate, may be required to control descending pain in IPS.

A major reason that IPS needs to be recognized as a specific clinical entity is because laboratory testing is on the threshold of providing specific information to help develop personal treatment for individuals.[53,54] Hormone and neurotransmitter testing panels have recently been developed which pinpoint specific deficiencies that must be corrected to obtain optimal pain relief. It cannot be overemphasized that the new era for IPS treatment can and must be based on scientific laboratory testing to improve care beyond simple symptomatic drugs such as opioids. Our Research and Education Project is being formed at this time to help educate on laboratory testing and the interpretation of laboratory test results to enhance treatment.

16. TREATMENT OF UNDERLYING CAUSES OF IPS

The optimal treatment is to control the underlying cause of IPS. Considerable progress has been made in recent years in this pursuit. For example, anti-autoimmune drugs known as "biologics" have been extremely successful in almost removing rheumatoid arthritis and psoriatic arthritis from the list of underlying causes of IPS. Radiation and chemotherapy have almost eliminated metastatic cancer as a cause of IPS. New migraine and headache drugs control these conditions well enough that they no longer cause IPS except in rare cases. Protocols for adhesive arachnoiditis have recently been developed. Use of anabolic measures to regenerate tissue have been initiated in genetic connective tissue (EDS type) disorders. Ketamine infusions are helping many RSD/CRPS victims. Electromagnetic therapies appear to

have some ameliorative effects on some IPS conditions. A major goal of this report is to foster treatments for the underlying causes of IPS. The use of opioid medication to symptomatically control IPS can best be reduced by treating the underlying cause of IPS. Special treatment approaches for arachnoiditis, genetic connective tissue diseases, RSD/CRPS, and central pain syndromes have all been initiated in recent years. These "first generation" approaches are demonstrating slow but steady progress in improving lives and controlling the complications of IPS.

17. A PROGRESSIVE SYNDROME

IPS is a "progressive" syndrome if left untreated. For example, the known cardiovascular complications of hypertension and tachycardia leading to the development of heart failure, sudden cardiac arrest, and renal disease can occur in IPS. The stress of constant pain on the hormonal system can initially cause cortisol and glucose levels to elevate. However, if pain is left uncontrolled, cortisol and glucose can fall to deficient levels due to the inability of the adrenal glands to keep up with demand. Hypoglycemia may result and even be a cause of sudden death.

Although documentation is in its early stage, it is believed that the locations of inflammatory damage in the CNS will continue to expand unless treated. Loss of CNS tissue due to inflammation causes multiple mental and intellectual impairments.

18. SELF-HELP AND FAMILY NECESSITY

Many persons with IPS will require some assistance with at least some activities of living. The loss of CNS tissue plus the cardiovascular and endocrine complications may render a person unable to do the physical, mental, logistical, and financial requirements of daily living. Those persons who have had IPS and been undertreated may have even developed some loss of mental capacities. Fortunately, some patients with severe long-standing pain and significant impairments have, with family support and a treatment regimen that addresses their specific needs, been able to achieve effective pain relief and regain lost function and mental capacities. Some patients with severe IPS have even recovered sufficiently to return to the workforce after a long absence.

Unfortunately, competent, compassionate, and willing medical care by professional medical practitioners is sorely lacking. At this time persons with IPS are probably more rejected than accepted by today's "big medicine" system of health plans, hospital networks, universities, and VA hospitals. One could make a good argument that deceit is rampant as patients are being told that good treatment is assured with a single expensive intervention, psychologic therapy, or drug when treatment of IPS requires a multi-component protocol or regimen to achieve relief of pain and suffering. There is much that patients and families can do for themselves: "self-help." A major focus of the Research and Education Project will be to teach "self-help" and "family-help" to complement whatever community resources may be available.

19. NEED FOR EARLY DETECTION AND PREVENTION

Since IPS is a catastrophic condition, this report calls for early detection and prevention of IPS. Every person with a simple chronic pain condition needs to be aware of IPS. For example, if a person with chronic back pain or EDS suddenly realizes that their pain is shifting from intermittent to constant, they need to be screened for IPS. It is clear IPS is best treated early and aggressively to prevent its serious complications and sequelae. A major goal of this paper is to foster not only awareness that IPS is a serious disorder, but to develop screening and prevention measures.

A self-screen questionnaire has been developed by our Research and Education Project and it is attached. Now that IPS can be identified and characterized, every person with chronic pain needs to know if they have developed IPS. All medical practitioners need to be aware of IPS, since IPS causes immense suffering, has multiple complications, and brings a premature death. It must be prevented and, if present, detected early and aggressively treated.

To date, preventive measures have been elusive as essentially no party has even considered prevention of IPS as a need. For example, if a person with chronic pain feels they are worsening or changing, what type of exercise, dietary supplements, or other measures should they do to prevent IPS? It is clear to us that there needs to be a major effort to identify measures to prevent IPS.

20. VALIDATION AND "NAME-CALLING": CESSATION OF STIGMA

A major reason for this report is to request that all parties involved clearly identify persons with IPS. Every person who has this syndrome must be fully aware of it and they along with their family and medical practitioners must develop a program to stabilize the condition and prevent it from progressing. Afflicted persons and their families and medical practitioners need to acknowledge the presence of IPS in each individual and develop a care program within the resources that are available.

Until now persons with IPS have been misunderstood and labeled with a plethora of pejorative terms. This situation can now cease as we have the scientific rationale for the development of IPS and the knowledge and measures to objectively determine its presence.

The key symptom and "tip-off" that IPS is present is the presence of constant pain and a disease or injury that is known to cause pain. When these 2 factors are present the individual needs a symptom review, physical examination, and laboratory tests to determine if IPS is present and what severity it may be. Terms such as "drug seeker" "pseudo-addict" "chronic opioid user" "pain behavior for secondary gain" "catastrophizer" "hypochondriac" "attention-seeking histrionic" "psychologic" or as having an "opioid use disorder" shouldn't be used to label a patient who hasn't had the benefit of the simple inflammatory, hematologic, and endocrine screens that are now available in every clinical laboratory. In summary, all parties need to recognize the presence of IPS, and a treatment program to achieve physiologic

functions and prevent progression of the condition within available resources needs to be pursued. Any fear that bona fide addicts who are simply seeking drugs will masquerade as someone with IPS is unfounded. Persons with IPS have distinct physical findings of cardiovascular hyperarousal and multiple laboratory abnormalities that are not present in addicts or drug-seekers.[40,53,54,55]

21. REDUCTION OF OPIOID USE

The use of symptomatic opioids to treat intractable pain has been the mainstay of treatment since the seminal report of Hunt and Linnett in 1960. Indeed, until now they have been about the only thing that has helped many persons with intractable pain. In addition, these persons have been helped without causing significant side-effects, abuse, or overdose issues. These patients are often persons who have been ill with IPS for many years, whose IPS has evolved to the catastrophic level of severity before finding treatment, and who have been stable on their opioid dosage. These persons should continue opioids and not be forced to discontinue. Why endanger a person due to opioid bias when they are clearly effective?

The understanding and discovery of IPS, however, has the potential to bring about the end of opioid use as we have come to know it. Why? A review of the IPS protocol in Table Seven explains this claim. There are several points in the protocol and measures where non-opioid treatments can intervene and eliminate or reduce the need for opioids. Persons with IPS who currently take opioids may be able to reduce their dosage by using any of the measures in the protocol. For example, opioids can be reduced by treating the underlying cause, suppressing neuroinflammation, administering neurotransmitter precursors or surrogates, replenishing deficient hormones, and controlling descending pain.

The use of opioid prescribing, going forward from the date of this report, will, we believe, be progressively reduced. The need to prescribe potent opioids will continue, but at a far reduced level. It is emphasized that current patients with IPS should be left on any successful opioid dosage or regimen. Astute medical practitioners should attempt to reduce opioid use by trying steps in the protocol that have not already been attempted and failed. The recent demand to stop opioids by fiat has led to deaths due to cardiac arrest, adrenal failure, and overdoses as patients have desperately scrambled to suppress pain and withdrawal by using unsafe pain-relieving substitutes. Going forward there should be no discussion about opioid dosages or use without a clear inclusion of what IPS means and how it should be recognized and treated.

22. SEVERITY AND TREATMENT

Like any catastrophic disease or injury, IPS can and should be categorized as to severity. To date, however, we have not established criteria for categories of severity, and this is a task we desire to complete. It is our view that many existing persons who have IPS have no awareness that they have it and were likely essentially untreated until they were in a severe or catastrophic stage so their only recourse was opioids, surgery, implants or other last resort, high risk measures. This project calls for recognition and early treatment of IPS. For example, a

person who has a painful condition with chronic, intermittent pain who begins to develop constant pain but has normal blood pressure, pulse rate, and blood hormone levels can and should be treated without the use of opioids or hormonal replacement.

Almost every "old time physician" will express the opinion that the most effective treatment is only possible when the precise diagnosis is known. The recognition of IPS is not only common sense but the recognition that it is present and acknowledged is the key to better, cheaper, safer treatment. Why? Treatment can be administered at any of several steps in the "Process of Development," (See attached Schematic) or as stated in the protocol (Table Six). One published, well done, and controlled study shows that lost brain tissue actually recovered following treatment of back pain.[30] Also, in some cases, clinicians have reported that patients with severe long-standing pain and significant impairments have, with the right regimen, not only achieved effective pain relief, but also regained lost capabilities; some have been able to return to work after years of being unable to work. Recovery to the extent of being able to re-enter the workforce is a tremendous achievement for these patients and brings financial stability to them and their families, as well as reducing the long-term financial burden on the healthcare system. This document and the creation of a "Research and Education Project" on IPS calls for recognition and prevention simply because both are possible and needed.

23. SUMMARY

IPS is a complication of an underlying painful condition and the development of inflammation and loss of tissue and neurotransmitter-receptor systems in the CNS. It is characterized by unremitting, constant pain and measurable pathologic and physiologic abnormalities in the cardiovascular, endocrine, and immunologic systems. If IPS is not adequately treated and controlled, inflammation in the CNS will continue, causing ever-worsening complications and generating pain and physiologic dysfunctions so severe that it will lead to a bed-bound state and early death. Persons with IPS can easily be identified and distinguished from those persons with simple chronic pain and persons who are drug seekers. This document is a call to recognize and prevent IPS. It is a catastrophic condition that must be acknowledged by all concerned parties. To assist with the critical needs of recognition, prevention, and treatment of those with IPS, this report has been developed to help launch a "Research and Education Project" to accomplish these goals.

ACKNOWLEDGEMENTS

1. The Intractable Pain Syndrome Research and Education Project would like to formally acknowledge the hard work in recent years of the members of the Alliance for the Treatment of Intractable Pain (ATIP), founded by Dr. Richard Lawhern. Dr. Lawhern and the ATIP members have tirelessly worked to make visible the issue of Intractable Pain, and the multiple issues facing doctors and patients in the new era of pain care. Their advocacy work, along with many other committed patient advocacy groups, individuals, patients, families, reporters, and physicians who are calling for more humane and skilled treatment for persons with intractable pain have served as an inspiration for this timely project.

2. The following individuals have provided on-going clinical information and data on IPS patients: Lloyd Costello, MD; Martin J. Porcelli, DO; Adam Hy, DO; Scott Guess, PharmD; and Donna Corley.

TABLE ONE
COMMON CAUSES OF CHRONIC PAIN CONDITIONS

Muscle sprains/strains
Osteoarthritis
Fibromyalgia
Headaches
Temporal mandibular joint
Carpal tunnel
Bunions
Plantar fasciitis
Irritable bowel
Bursitis
Herniation of intervertebral discs
Osteoporosis
Neuropathies of lumbar nerves, extremities, face

This is not a complete list of simple, chronic pain conditions.

TABLE TWO
MAJOR CAUSES OF IPS

Arachnoiditis - Lumbar-Sacral and Cervical
Genetic Connective Tissue/Collagen Disorders (e.g. Ehlers-Danlos)
Reflex Sympathetic Dystrophy (RSD)/Complex Regional Pain Syndrome (CRPS)
Brain Injury – from Stroke or Trauma
Osteoarthritis

These are the major causes of about 80-85% of IPS cases. This is not a complete list of all possible causes. Uncommon conditions include porphyria, Lyme disease, post-viral neuropathy, autoimmune disorders, Sickle cell disease, and interstitial cystitis.

Note: Osteoarthritis is probably the most common painful condition since essentially all persons over age 65 will have some degenerated joints. Pain can range from mild and intermittent to a severe form of IPS.

TABLE THREE
CHARACTERISTICS OF SIMPLE CHRONIC AND INTRACTABLE PAIN SYNDROME

	IPS	CP
Pain is Constant (24/7)	Yes	No
Treatment is Daily (Around the Clock)	Yes	No
Elevated Blood Pressure and Pulse Rate	Yes	Seldom
Elevated Temperature and Breathing Rate	Yes	No
Anorexia/Malnutrition	Yes	No
Insomnia	Yes	No
Depression, Hopelessness	Yes	No
Endocrine Abnormalities	Yes	No
Elevated Inflammatory Markers	Often	Seldom
Restriction of certain life activities (e.g. mobility)	Yes	Sometimes
Decreased capability for Requirements of Daily Living	Yes	No

TABLE FOUR

NEUROTRANSMITTER-RECEPTOR SYSTEMS THAT CONTROL PAIN

Endorphin – Enkephalin
Dopamine – Noradrenaline
Gamma Aminobutyric Acid (GABA)
Serotonin
Endocannabinoid
N-methyl-d-aspartate (receptor only)

IPS occurs after one or more of these neurotransmitter-receptor systems become impaired or dysfunctional.

TABLE FIVE

CRITERIA FOR DIAGNOSIS OF INTRACTABLE PAIN SYNDROME

I. PRESENCE OF CONSTANT PAIN

II. AN IDENTIFIABLE INJURY OR DISEASE THAT GENERATES PAINFUL ELECTRICAL IMPULSES

III. COMMON SYMPTOMS
- a. Insomnia
- b. Change in appetite
- c. Fatigue
- d. Decreased ability to concentrate
- e. Immobility

IV. PHYSICAL FINDINGS IN CARDIOVASCULAR SYSTEM
- a. Cardiovascular
  - i. Hypertension
  - ii. Tachycardia
- b. Vasomotor Hyperarousal
  - i. Hyperreflexia
  - ii. Mydriasis (dilated pupils)
  - iii. Elevated temperature/sweating
  - iv. Gooseflesh
  - v. Vasoconstriction (cold hands/feet)
  - vi. Skin color changes/and skin color asymmetry

V. ENDOCRINE/ INFLAMMATORY ABNORMALITIES
- a. Pituitary-adrenal-gonadal hormones
- b. Glucose blood levels
- c. Elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, cytokines)
- d. Lowered white blood cell count

A diagnosis of Intractable Pain Syndrome requires the presence of at least one finding in all 5 categories.

TABLE SIX
CAUSES OF DEATH IN IPS

Suicide
Cardiac Arrythmia
Myocardial Infarction (heart attack)
Adrenal Failure
Malnutrition
Sepsis/Infection
Hypoglycemia

TABLE SEVEN
TREATMENT PROTOCOL AND MEASURES FOR INTRACTABLE PAIN SYNDROME (IPS)

I. CONTROL OR SUPPRESSION OF UNDERLYING INJURY OR DISEASE

II. REDUCTION OF ELECTRICAL IMPULSES FROM THE INJURY OR DISEASE

III. REDUCTION OF GLIAL CELL ACTIVATION AND NEUROINFLAMMATION

IV. REPLACEMENT OR STIMULATION OF DEFICIENT NEUROTRANSMITTER-RECEPTOR SYSTEMS (NTRS)
   a. Endorphin
   b. Dopamine-Noradrenaline
   c. Gamma amino butyric acid (GABA)
   d. N-methyl-d-aspartate receptor
   e. Endocannabinoids
   f. Serotonin

V. CONTROL OF DESCENDING PAIN BY NON-OPIOID AGENTS

VI. CONTROL OF MAJOR COMPLICATIONS
   a. Insomnia
   b. Hormone deficiencies
   c. Hypertension/tachycardia
   d. Glucose/lipid control
   e. Appetite changes

VII. TISSUE REBUILDING ("ANABOLIC") MEASURES
   a. Hormone stimulation
   b. High protein diet
   c. Collagen/vitamin supplements

*Replacement or stimulation of the major transmitters-receptor systems is generally known as "symptomatic" care as it involves the administration of neurotransmitter surrogates for the key neurotransmitters that control pain. These surrogates have pharmacologic names including opioids, cannabinoids, neuropathic, antidepressant, and adrenergic, among others. The N-methyl-d-aspartate receptor is stimulated by ketamine and some other agents. Low dose naltrexone may stimulate endorphin receptors. Not all NTRS may need to be replaced or stimulated to achieve pain control.

TABLE EIGHT

SCREENING QUESTIONNAIRE FOR THE INTRACTABLE PAIN SYNDROME

Name_____ Today's Date_____

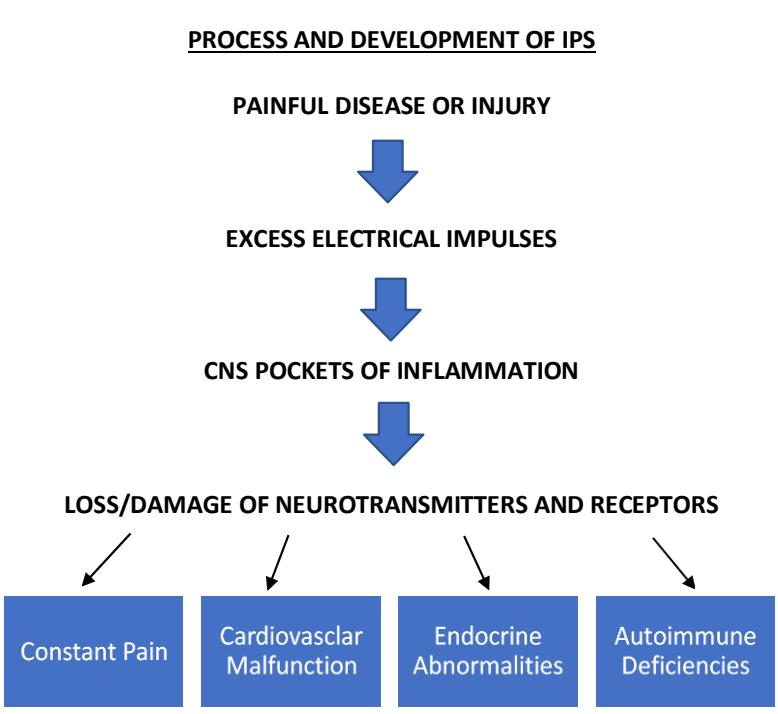
Last *First*

		YES	NO
1	Is your pain constant, meaning always present?		
2	Was your pain formerly intermittent, episodic, or skipped days before becoming constant?		
3	Does your pain keep you from falling asleep?		
4	Have you lost most of your appetite?		
5	Do you crave sugar and starches?		
6	Do you get episodes of heat, sweating, and elevated temperature?		
7	Are your hands and feet cold much of the time?		
8	Is your blood pressure elevated much of the time?		
9	Does your pulse rate elevate much of the time?		
10	Do you oftentimes have difficulty focusing or paying attention to conversations or when reading?		
11	Are you often too fatigued to leave home?		
12	Do you have periodic anxiety attacks with sweating, headache, and racing heart rate?		

If you have constant pain and answered "yes" to over half of the questions, you need to inform your physicians and family of this and be evaluated for the presence of 'Intractable Pain Syndrome".

SCHEMATIC ONE

PROCESS AND DEVELOPMENT OF IPS



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NOTE: Bibliographies to support and explain IPS can be found on the project's website; www.intractablepainsyndrome.com.