WHY NORMAL HORMONE SERUM LEVELS ARE ESSENTIAL FOR CHRONIC PAIN MANAGEMENT

CHAPTER 5
APRIL, 2013

BRINGING A NEW DIMENSION TO PAIN CARE

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TABLE OF CONTENTS

PRECIS: Modern laboratory testing and hormone replacement of pain-control hormones should be a fundamental of chronic pain management.

I. PURPOSE

This paper presents scientific background to support the contention that normal serum levels of some pain-control hormones are essential to chronic pain management. Over the past half-century an accumulation of clinical and scientific reports clearly point out this necessity and some of the material is reviewed here.[1-18]

II. LABORATORY ADVANCES

Laboratory advances now make hormone testing and replacement a reality. This statement could not have been made as recently as three years ago as many serum hormone assays were not readily available. It is important to keep this fact in mind, because the call to hormone test and replace hormones prior to the availability of today's testing technology could not be effectively done.

Historically it is interesting to note that serum blood testing for cortisol wasn't available until about 1960.[19,20] The most famous Addisonian of the last century, John F. Kennedy, had to be clinically managed without the benefit of cortisol serum levels. Progressively since Kennedy's day, serum hormone testing has developed to the point that rapid, accurate serum hormone levels of about all steroids made in the adrenals and gonads can now be easily obtained.

It is not just that refined laboratory instrumentation has emerged, but normal serum ranges have been identified. This is critical, because pain management needs to know the high and low of a given hormone such as cortisol, pregnenolone, or DHEA. (Table One) It does us little good to know that a level is "below 15 pg/ml" or that a range is "0 to 20 mcg/dl". Pain management patients, as opposed to most of those treated by an endocrinologist, have normal glands that are simply either over-or underworking. This author has witnessed, over the last 3 years, hormone tests with ranges for several pain-related hormones that were not previously available. For example, pregnenolone, progesterone, and adrenocorticotropin (ACTH) either couldn't be obtained or ranges went to zero. Even some of the hypothalamic releasing hormones such as corticotropin releasing hormone (CRH) are starting to be offered with a range for practical interpretation of central brain activity.

The upshot of the laboratory advances is that a non-endocrinologist can now easily and competently order the serum hormone tests that are critical to pain management.

III. THE PAIN CONTROL HORMONES

Some hormones directly and specifically help control pain. They may also enhance physiologic functions critical to pain control including energy, sleep, movement, mood, cognitive abilities, and tissue regeneration. Hormones known to be critical for chronic pain control are mainly

produced in the adrenals, gonads, and thyroid. (Table One)

Pain is a potent stressor similar to fright or terror.[2,4,6,11] Pain signals reach the brain from any injury in the peripheral nervous system and activate three separate releasing hormones in the hypothalamus. They are corticotropin releasing hormone (CRH), gonadal releasing hormone (GRH), and thyroid releasing hormone (TRH). These three hormones, in turn, cause the anterior pituitary to release into the serum these stimulating hormones: adrenal corticotropin hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH). The end organs for stimulation are the adrenals, gonads, and thyroid which release into the serum the key pain control hormones: cortisol, DHEA, pregnenolone, testosterone, progesterone, estrogen, triiodothyrinine (T_3), and thyroxine (T_4). (Table One) These hormones rise in the serum to protect and heal tissue and eliminate pain.[21-25] A chronic pain patient with elevated hormone serum levels is in need of enhanced pain treatment.[12]

If pain isn't eliminated within a short time period, tissue in the hypothalamus, pituitary, adrenals, gonads, or thyroid may not keep up hormone production and serum levels of some of the hormones will drop below normal levels. Based on clinical experience, to date, the most common end-organ hormones to diminish in the serum with prolonged severe pain are: pregnenolone, cortisol, DHEA and testosterone.[5,10,14] Once pain is controlled and/or are replaced, serum levels return to normal. It is important to note that only severe pain will stimulate the hormone-stress system to the point that the end-organs will produce enough hormones to raise serum levels. Mild or intermittent pain, such as found in common degenerative arthritis, or low grade rheumatoid arthritis will not cause enough pain to lower hormone serum levels.[7,21] Besides the hormones noted here, there are others that undoubtedly have a pain control function. Included in this group is melatonin, adrenalin, and parathyroid. These are not included due to inadequate information about their direct effect on pain. Oxytocin and human chorionic gonadotropin (HCG) clearly have a potent pain control role, but commercial serum assays are not available at this time.

TABLE ONE

MAJOR PAIN CONTROL HORMONES*

CORTISOL

PREGNENOLONE

PROGESTERONE

DEHYDROEPIANDROSTERONE (DHEA)

TESTOSTERONE

ESTROGEN

THYROID (T_3, T_4)

*OXYTOCIN

*HUMAN CHORIONIC GONADOTROPIN

***Cannot now be measured by commercial serum tests.**

THE STEROID CLASS

The pain control hormones produced in the adrenals and gonads are collectively called steroids.[1,26] The basic steroid structure contains the perhydrocyclopentanophenanthrene ring, and, for short, is often called sterane. (Figure One) For several years, the production of endogenous steroids was exclusively ascribed to the adrenals

and gonads but it is now well established that various other tissues such as the bowel, liver, prostate, and nervous system can synthesize or metabolize some steroids.[1] The chemical nature of steroids allows them to behave as lipophilic molecules, particularly when they are free or non-conjugated to sulfate radicals. Therefore, unconjugated steroids synthesized by peripheral glands may reach or act on several tissues in the body including the peripheral (PNS) and central nervous system (CNS) since free steroids are capable of crossing the blood-brain barrier.[22-26] Numerous studies indicate that steroid hormones exert a large array of biological effects including the control of sex behaviors, reproduction, development, stress, and the regulation of the activity of various important physiological systems such as the immune, cardiovascular, respiratory, and nervous systems.[1,27] Receptors of various steroid hormones are expressed in several neural structures allowing steroids to crucially control the development, growth, maturation, differentiation, and plasticity of the CNS and PNS.[24,25,27]

Because of their diverse effects on the CNS and PNS, steroids were early on suspected to be affected by pain and when activated control pain and healing. Cholesterol, which is the basic substrate from which steroids are derived, was given intravenously to rats in 1927 by Cashin and Macavek.[28] These curious researchers observed that pain was suppressed. Later, in 1942, Selge and Mason demonstrated that the steroids, progesterone and deoxycorticosterone, **w**ould induce sedation and anesthesia in the rat.[29] Together, these observations paved the way for the development of various synthetic analogues of cortisol which reduced pain through activation of gamma aminobutyric acid-A receptors ($GABA_a$) and suppression of inflammation. Nowadays, the therapeutic use of glucocorticoids and their analogs is generally considered the most effective strategy against inflammatory pain.

IV. GLUCOCORTICOSTEROIDS

A. DEFINITION AND DESCRIPTION

Glucocorticosteroids (GCS) usually include cortisol, cortisone, and corticosterone. They are referred to as "gluco" because they regulate glucose metabolism and do not carry out the functions of mineral corticosteroids.[31] The vast majority of GCS are produced in the adrenal cortex under stimulation of the pituitary hormone, ACTH. Lesser amounts of GCS are made in the gonads and other tissues. Glucocorticoids are the most profoundly activated and involved with pain control than all the other steroids. In a chronic pain patient, the serum concentrations may be high or low depending on pain severity and length of time the patient has been in uncontrolled pain.

TABLE TWO

CRITICAL FUNCTIONS OF GLUCOCORTICOSTEROIDS IN PAIN RELIEF

- Modulates blood-brain barrier, CNS receptors, and autonomic nervous system
- Activates the anti-inflammation system
- Regulates glucose metabolism
- Heals and protects Tissues

B. HISTORY

Cortisone was isolated from crystalline extracts of beef adrenal glands in 1935.[29] The word cortisone is a name introduced by Dr. E.C. Kendall of the Mayo Foundation to identify a compound which had previously been referred to as 17-hydroxy-11-dehydrocorticosterone or "Kendall's Compound E".[29] Once identified, investigators administered

it in many animal experiments and to humans with a variety of diseases.

Cortisone, now usually referred to as cortisol or hydrocortisone, is necessary to maintain life. Adrenolectomized animals die unless given cortisone. Between 1935 and 1950 clinical investigators found that its administration was of great benefit in rheumatoid arthritis, acute rheumatic fever, gout, systemic lupus erythematosus, periarteritis nodosa, cranial arteritis, asthma, allergies, and some neoplastic diseases.[29] The reporting investigators did not necessarily focus on the pain associated with these diseases, but all almost always acknowledged its betterment in their writings. Today, over a half century later glucocorticosteroids are still used in the diseases described prior to 1950 plus several other painful conditions that have an inflammatory component. GCS preparations and analogues have today become a standard, "backbone", treatment for amelioration of painful, inflammatory conditions. They are administered systemically, topically, orally, and injected into the intrathecal space, joints, and focal pain sites. The latter are often called "trigger points". Curiously, despite the daily, universal use of GCS in pain management, the necessity to maintain, serum cortisol levels has escaped general recognition.

C. ANTI-INFLAMMATORY PAIN RELIEF

GCS primarily control pain by suppressing inflammation. GCS induce anti-inflammatory actions on damaged peripheral and CNS tissue which activates nociceptive mechanisms and generate pain sensation.[31-40] Tissue regeneration effects of GCS, in part, result from their ability to inhibit the expression of collegenase (the key enzyme involved in tissue degeneration during inflammation) and pro-inflammatory cytokines or

to stimulate the synthesis of lipocortin which blocks the production of eicosanoids. Even in neuropathic pain which may not have a significant inflammatory component, GCS's may inhibit the initiation of neuropathic pain, or attenuate the pain. Most chronic pain states undoubtedly have some degree of inflammation and immune impairment, so it is incumbent on the pain practitioner to maintain cortisol serum levels for prevention of tissue destruction as well as regeneration.

D. MAINTENANCE OF NEUROLOGIC FUNCTIONS

Recent studies show GCS production in the adrenals have profound effects on neurologic functions that are essential for pain control.[22-26,31,35,37] GCS leave the adrenals and travel in the serum to target areas in the CNS and PNS. The blood brain barrier which allows passage of intrinsic biochemical and administered therapeutic agents is modulated by adrenal hormones.[30] Neuronal excitability and receptor binding requires adequate GCS availability. Specific

actions and functions are carried out by adrenal steroid receptors on neuronal membranes in the CNS and on lymphocytes in blood. Naturally receptors must have normal blood levels to receive its fuel for activation and function. GCS have also been found to play a role in cognitive function and memory. They have a profound effect on carbohydrate metabolism in the CNS. Either too high or too low serum cortisol levels may be clinically associated with severe mental impairment including depression, attention deficit, cognitive assimilation, and memory loss.

E. INTERFERENCE WITH OPIOIDS

While the healing and regenerative effects of GCS are well known it is poorly appreciated that too little or too much serum GCS can interfere with opioid treatment and effectiveness.[41]

GCS are required to modulate the blood brain barrier and opioid receptors.[24,26,38] A lack of cortisol over time may also over-sensitize the CNS to opioids. Over-sensitization of the CNS to morphine is well-documented in animal studies, and the author has observed many patients with opioid hyperalgesia who have low serum cortisol levels. This resolves when cortisol serum levels return to normal.

In long-term treatment of severe, chronic pain with opioids, a deficiency of serum GCS may occur as opioids occasionally suppress serum cortisol. It is for this reason that routine cortisol monitoring is recommended in chronic pain patients who must take opioid analgesics.

F. CRITICAL NEED TO DIAGNOSE HYPER AND HYPOCORTISOLEMIA

In modern day medical care, of all the pain-control hormones only low serum levels of cortisol may pose a life-threatening situation. While a deficiency of any pain control hormone noted here may cause complications, their low hormone levels are rarely associated with death. A very low cortisol serum level, however, is the exception. Dr. Addison described 11 cases of adrenal failure in 1855.[42] No serum cortisol levels were, of course, available and his cases were all patients who had a history of weight loss, muscle wasting, low blood pressure, fatigue, and exhibited a faded yellow hue to the skin with brown pigmentation. At autopsy adrenal glands were atrophic and fibrotic, and in some cases, hardly identifiable as they had shrunk so much. Two of Dr. Addison's cases gave histories of severe pain (one facial, the other extremity). It is the author's belief that many severe pain patients die quietly in bed due to unrecognized cortisol failure. Some of these patients may have been falsely accused of "overdose" or "medication misuse".

To help identify adrenal insufficiency and possible adrenal failure and impending death, Tables Three and Four list signs and symptoms of hyper and hypocortisolemia. A serum cortisol level below about 5.0 mcg/dl should suggest adrenal insufficiency and below 1.0 mcg/dl a life-threatening urgency. I cannot find any references to what the critical life-supporting level has to be, but I recommend it be about 1.0 mcg/dl. Any level below 5.0 mcg/dl warrants at least temporary support with hydrocortisone, and below 1.0 mcg/dl urgent administration of cortisone.

Although hypercortisolemia is not life-threatening in the short term, the long term complications are

TABLE THREE

CLINICAL FEATURES OF CUSHING'S SYNDROME

FEATURES	PROPORTION % PATIENTS
Obesity Or Weight Gain	95%
Facial Plethora	90%
Decreased Libido	90%
Rounded Face	90%
Thin Skin	85%
Menstrual Irregularity	80%
Hypertension	75%
Hirsutism	75%
Depression	70%
Easy Bruising	65%
Glucose Intolerance	60%
Weakness	60%
Osteopenia/Fracture Dental Erosion	50%
Nephrolithiasis	50%

Adopted from Newell-Price J, Bertango X, Grossman AS, Nieman L. Cushing Syndrome. Lancet 2006;362:1605-1617.[43]

profound. (See Table Three) Included are hypertension, hyperglycemia, truncal and facial obesity, cervical fat pad ("buffalo hump"), mental impairment, and muscle wasting. A most serious problem in pain patients is decalcification of bones, joints, and teeth causing osteopenia and osteoporosis. Sudden vertebral collapse, hip dysplasia, knee joint erosion, and renal stones are common complications in pain patients.

The complications of hyper and hypo-cortisolemia may occur if high or low serum levels are constant or if they are intermittent, over time. Opioids may occasionally suppress cortisol production. In summary, chronic pain patients who require daily opioid medication should be routinely screened for serum cortisol levels.

TABLE FOUR

COMMON FEATURES OF HYPOCORTISOLEMIA IN PAIN PATIENTS

WEAKNESS

WEIGHT LOSS

MUSCLE WASTING

ANOREXIA

HYPOTENSION

MENTAL APATHY

TACHYCARDIA

YELLOWISH HUE OF SKIN

PIGMENTATION AROUND SKIN CREASES OR SCARS

These symptoms were reported in Addison's original 1855 description of patients who died of adrenal failure.[42]

V. NEUROSTEROIDS

A. DEFINITION AND DESCRIPTION

Some interesting hormones have picked up the new title, neurosteroids.[1,44] The term neurosteroid designates bioactive steroids that are endogenously synthesized in neurons and/or glial cells in the central nervous system (CNS) and peripheral nervous system (PNS). The chemical structure of neurosteroids is identical to those produced in the adrenals and gonads, but the main criteria to be called a neurosteroid is that its production in the CNS or PNS is independent from the production in these glands and of the stimulatory activity of the hypothalamic releasing hormones and the stimulatory hormones of the pituitary, adrenocorticotropin (ACTH), follicle stimulating hormone (FSH), and luteinizing hormone (LH). There are three neurosteroids which are of critical importance to the control and even the permanent reduction of pain: pregnenolone, progesterone, and dehydroepiandrosterone (DHEA).[45-58] (Table One) A close relative of progesterone,

allopregnanolone, is synthesized in the CNS but apparently not in adrenal or gonadal tissue.[56] Estrogen may be synthesized in the spinal cord and may someday be recognized as a neurosteroid.[1]

B. PREGNENOLONE, PROGESTRONE, AND DHEA

Multiple animal studies are quite clear. All three neurosteroids provide neuroprotection and neurogenesis when there is experimental, injury to laboratory animals.[44-55,57] Neurosteroids modulate nervous system activity and pain control by acting through various membrane receptors including $GABA_a$, NMDA, and sigma.[46] In addition, the neurosteroids have anti-fatigue and memory enhancement properties. To date, a limited number of clinical studies show that neurosteroids may reduce pain and some troubling symptoms such as allodynia. This author has begun routine serum testing for these three neurosteroids and administering them in patients who have low serum levels. In my open-label trials, patients generally report clinical improvement in some symptoms such as less baseline pain, fewer flares, less allodynia, less fatigue, and better mental functions.[58] Opioid use is reduced in most patients. DHEA has been particularly useful in females who take opioids and have low testosterone levels. It is known to raise testosterone levels.

The proportional contribution of CNS, PNS, and adrenal-gonadal production to serum levels of pregnenolone, progesterone, and DHEA is unknown, but testing in my patients suggests that CNS and PNS production may contribute to the overall serum pool. This author has observed severe pain patients who have low serum levels of adrenocorticotropin (ACTH) and cortisol but have normal levels of pregnenolone and DHEA which shouldn't occur unless there is a serum contribution from other than the adrenals. I have observed the reverse which suggests there may be CNS and PNS suppression of neurosteroids in the face of normal adrenal production. Given the critical pain control functions of these three neurosteroids, it appears logical to maintain serum levels by simple, systemic administration.

VI. SEX OR GONADAL STEROIDS

A. PHYSIOLOGIC FUNCTION IN PAIN

Estrogen and testosterone are the major gonadal or sex steroids. Gonadal releasing hormone (GRH) is in the hypothalamus, and it is stimulated by pain and can be suppressed by opioids. These hormones are responsible for the difference in pain perception between males and females.[59-61] In general, women report more pain than men and exhibit higher risk for developing chronic pain.[61-63] Variations in sex steroid levels, receptor expression, and mechanisms of action in the nervous system have been correlated with the development of chronic pain. Indeed, androgens; particularly testosterone, which are higher in males exert analgesic effects in humans and experimental models while estrogens have both hyperalgesic and analgesic effects depending on

the experimental conditions. Testosterone and its synthetic derivatives, known as "anabolic steroids" are widely known to accentuate muscle and tissue growth. This single characteristic makes it a critical hormone in pain treatment because tissue regeneration is dependent on it.

B. POTENTIATION OF OPIOID DRUGS

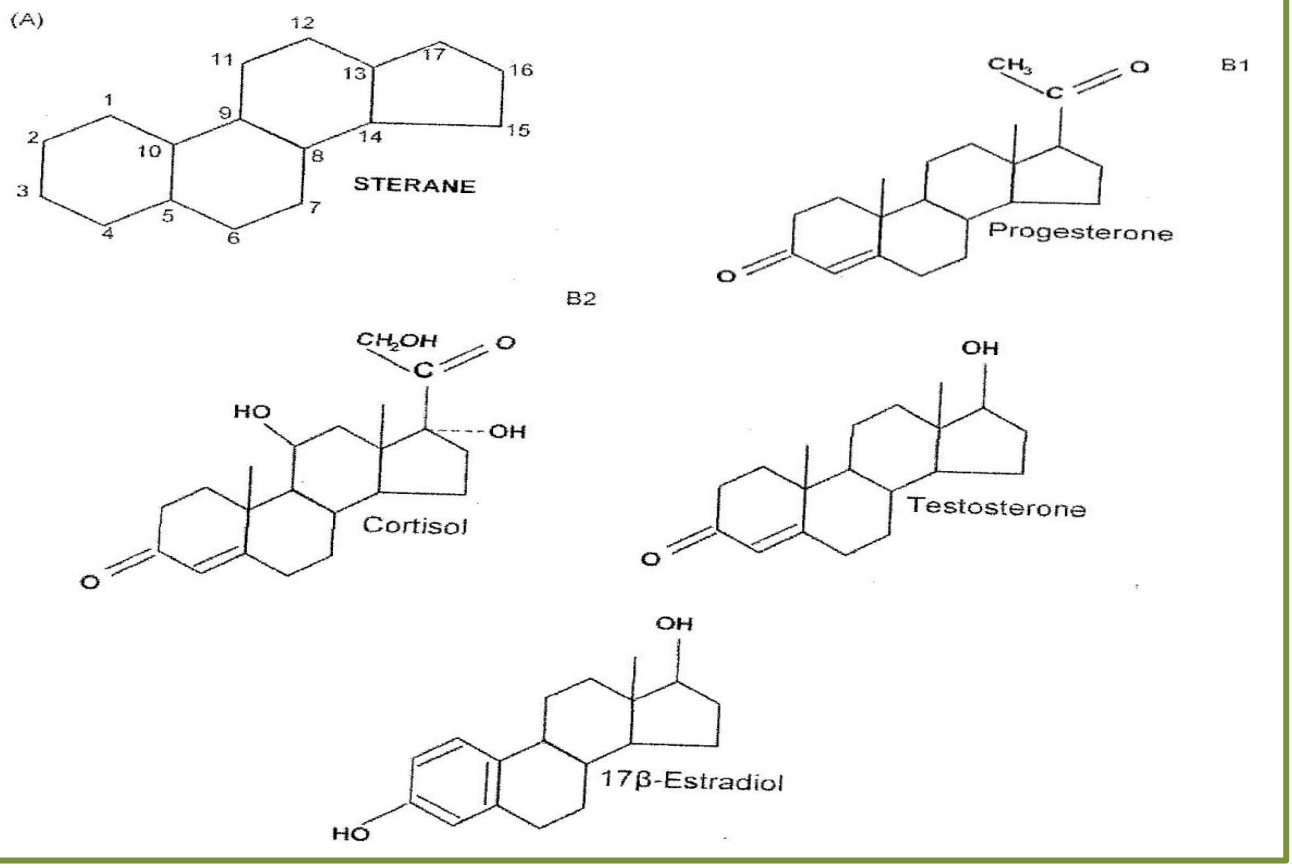
In addition to sex steroid-based dimorphism in pain sensation and in risk of developing pathologic pain syndromes, the relationship between opioids and sex steroids has also been investigated by different research groups. Studies focused on the rat spinal cord indicate that the sex steroids modulate anti-nociceptive responses to opioid drugs through the control of expression of opioid kappa and delta receptors in spinal sensory neurons.[64] Most important, investigations in humans and animals of the interactions between opioids and sex hormones in pain modulation suggest that chronic opioid administration without testosterone supplementation may contribute to the perpetuation of chronic pain and to continued administration of unnecessarily high doses of opioids.[65-68] To date, far less is known about estrogen than testosterone in chronic pain patients. In part this is due to a lack of serum testing in males and the great variations found between pre and post-menopausal females.

C. TESTOSTERONE

Some clinical effects related to deficient testosterone such as impaired tissue growth and regeneration are widely known. Others include

FIGURE ONE

STRUCTURE OF SOME KEY PAIN-CONTROL STEROIDS



decreased libido, poor sexual performance, depression, fatigue, adverse cardiac events, and prostatic hypertrophy. Less well known is the direct and significant impact that testosterone has on pain. It plays a protective role in pain perception[67-69]. After an injury it promotes rapid healing and prevents the development of chronic pain. Lower serum testosterone levels have been clinically reported to be associated with loss of opioid effectiveness and hyperalgesia, which is excessive pain perception.

D. ESTROGEN

Considerable evidence now suggests that estrogens modulate at least certain types of pain including migraine, temporomandibular joint disorders, and arthritis[1,70-72]. Because estrogens can modulate functions of the nervous, immune, skeletal, and cardiovascular systems, estrogenic modulation of pain is an exceedingly complex, multi-faceted phenomenon. Estrogens produce both pro-and antinociceptive effects that depend on the extent to which biologic system of the body is involved in a particular type of pain.[72-73]

It is clear that pain tolerance is generally lower in females than males. Moreover, a number of chronic pain conditions such as fibromyalgia, interstitial cystitis, and migraine are more common in women. Estrogens appear to decrease certain types of joint and musculoskeletal pain. For example, a subset of data from the Women's Health Initiative, including over 10,000 women who had hysterectomies and were randomly assigned to receive estrogens or placebo, showed that estrogen-treated women were significantly less likely than placebo-treated women to have undergone any type of joint replacement during the approximately 7 years they were followed.[74]

Given estrogen's diverse actions, it is not surprising that estrogen receptors are distributed to areas known to influence nociceptive transmission. Receptors are found in the brain stem, dorsal root ganglion cells, and several areas in the brain that mediate stress, anxiety, and pain including the hypothalamus, amygdala, periagueductal gray, and dorsal raphe nucleus.

At this time, I cannot identify any studies that have attempted to determine estrogen serum levels in pain patients. One of the difficulties is the current commercial laboratory practice to offer a variety of estrogen assays including total estrogens, estradiol, estrone, and estiol. It is unknown if, in the human, active pain patient, whether one assay is more relevant than another. Laboratories also like to help the gynecologic-oriented practitioner with non-pain problems by reporting estrogen serum levels that are pre-or post-menopausal and in the follicular or luteal phase of the menstrual cycle. In pain patients, opioids obviously suppress estrogen since amennorhea is very common. No attempt to systematically measure estrogen serum levels and provide replacement in pain patients is known to this author.

VII. THYROID

A. RELATIONSHIP TO PAIN

The thyroid produces 2 types of primary hormones, triiodothyronine (T_3), and thyroxine (T_4). Production is stimulated by thyroid-stimulating hormone (TSH) which is produced in the anterior pituitary. The hypothalamus contains thyrotropin releasing hormone (TRH) which activates TSH in the pituitary. Pain stimulates the release of thyroid hormones. Serum hormone levels increase with severe pain and may lower if severe pain exists, unabated, for a long time

period.[75] It is undoubtedly this mechanism which has caused a diagnosis of hyperthyroidism ("Grave's Disease") to be rendered in some pain patients. More common, however, is the association of low serum thyroid concentrations in some painful conditions.[76,77] Myxedema is a collection of fatty, mucin deposits in tissue particularly around the eyes and ankles that occurs if thyroid serum levels remain too low too long. Painful conditions reported to be caused by hypothyroidism include arthralgia, myalgia, tenosynovitis, and carpal tunnel syndrome[76,77].

Few cases of abnormal (high or low) serum thyroid levels (T_3 of T_4) have been reported with painful conditions. So few, in fact, that it is difficult to recommend routine thyroid screening in pain patients. Although TRH, TSH, and serum thyroid levels may be suppressed by opioids, this phenomenon has seldom been reported. In summary, it appears that the thyroid gland is quite resilient, has great storage of hormones, and seldom shows abnormal serum levels in chronic pain states. It does have pain control properties.[78-80]

B. THE CONTROVERSY

There is a bitter controversy involving hypothyroidism. At the heart of the controversy is that many respected clinicians believe there is a form of hypothyroidism that is not reflected by serum levels of TSH, T_4, and T_3. When the thyroid gland fails to produce enough thyroid to maintain normal serum levels of T_3 and T_4, it is called "Type I". It is diagnosed by the finding of low T_3 or T_4 and elevated TSH. Some clinicians believe there is a "Type II" hypothyroidism which occurs in the face of normal serum thyroid levels.[81] The problem is peripheral resistance to thyroid hormones at the cellular level. Consequently, they believe that hypothyroidism is markedly underdiagnosed and that practitioners should initiate thyroid treatment with desiccated ("bio-identical") thyroid based solely on specific signs and symptoms. These include pain, fatigue, dry skin, and hyporeflexia. (See Table Five)[75,76] Screening for thyroid serum levels is certainly

TABLE FIVE

HYPOTHYROIDISM SYMPTOMS AND SIGNS

SYMPTOMS

FATIGUE
LETHARGY
SLEEPINESS
MENTAL IMPAIRMENT
DEPRESSION
COLD INTOLERANCE
HOARSENESS
DRY SKIN
DECREASED APPETITE
WEIGHT GAIN
DECREASED PERSPIRATION
CONSTIPATION
MENTAL DISTURBANCES
PARESTHESIA

SIGNS

SLOW MOVEMENTS SLOW SPEECH HOARSENESS
BRADYCARDIA
DRY SKIN
NONPITTING EDEMA
HYPOREFLEXIA
DELAYED RELAXATION OF REFLEXES

Some clinicians believe that thyroid should be administered if a number of signs and symptoms are present despite normal serum levels of T_3 and T_4. This is the only pain-control hormone that carries this belief.

prudent, however, if a number of the signs and symptoms listed in the Table are present. In pain practice today, autoimmune inflammatory disease is quite prevalent and a autoimmune process commonly attacks the thyroid gland. The most common form of autoimmune disease which attacks the thyroid is known as "Hashimoto's Disease", and it is accompanied by abnormal serum antibodies which can be assayed to help make the diagnosis.

Naturally it will be up to each individual pain practitioner as to whether he should administer thyroid to a patient with normal serum levels of TSH, T_3, and T_4.

VIII. OPIOID SUPPRESSION OF HORMONE SERUM LEVELS

Opioids acutely increase growth hormone (GH), thyroid stimulating hormone (TSH), and prolactin (PR) but decrease LH, testosterone, estradiol and oxytocin.[82] The effect of opioids on ACTH and cortisol are variable. Chronic opioid administration,[83] however, is one of hormone suppression.[87] Opioids appear to preferentially suppress LH rather than FSH. The major opioid effects on the sex steroids are amennorhea and irregular menses due to low estrogen levels and hypogonadism with low testosterone levels in males. For example, one study of long-term intrathecal administration, showed that 14 of 21 premenopausal women developed amenorrhea, and the remaining seven developed irregular menstruation. As many as 86% of men receiving intrathecal opioids, demonstrate hypogonadism.[83-87] Hormones suppressed include not only testosterone by LH, FSH, and estradiol. In summary the main side-effects of opioids involve decreases in GRH, LH, FSH, testosterone, and estradiol. Available studies of long-term intrathecal opioid administration about 9.2% or opioid-treated patients had cortisol levels below 5 mcg/dl, suggesting adrenal insufficiency.[82] Other reports show that transdermal and oral opioids may lower cortisol levels to the point that replacement is required. Thyroid serum levels are essentially unaffected.

The pain practitioner who prescribes opioids must understand that hormonal suppression is the major long term complication of opioid therapy. Furthermore, hormone levels will have to be determined by serum testing. Deficient hormones will have to be replaced. If not done, the patient will suffer from inadequate pain control and other complications such as hyperalgesia. Replacement of suppressed serum levels of testosterone, cortisol, pregnenolone, and DHEA will enhance pain control and help minimize the need to raise opioid dosages or rotate opioids.

IX. THE PROBLEM OF HIGH SERUM HORMONE LEVELS

The name of this document makes one immediately think that the issue is only deficient serum hormone levels. While low levels are the focus here, it must be pointed out that high hormone serum levels are a special problem in pain management as noted in prior sections.

Foremost, high serum hormone levels indicate that pain is uncontrolled.[87] Pregnenolone, cortisol, DHEA, and testosterone may all rise above normal levels with uncontrolled pain. They do not all simultaneously raise because they do not have the same rates of production, reserve, and excretion form their producing gland. For example, pregnenolone may rise while the others remain normal or may even show a deficiency.

TABLE FIVE

HIGH HORMONE SERUM LEVELS

- Means That Pain Is Uncontrolled

PROBLEMS

- Interference with Analgesia
- Complications such as Osteoporosis and Hypertension

The other two major problems with high serum levels are; (1) Interference with analgesia and healing; (2) complications, particularly with cortisol. (Table Five)

X. SUMMARY

Uncontrolled pain and opioid administration may both depress hormone serum levels that call for hormone replacement. Advances in laboratory technology have now made it possible to determine the need for hormone replacement in chronic pain patients. Until recently, only select hormone testing was available, but today an entire profile of several hormones necessary for pain control can be obtained. Hormone testing and replacement should be a foundation in chronic pain management as certain hormones are essential for healing, nerve regeneration, mentation, and analgesic effectiveness.

References

1. Mensah-Nyagan A.G., Meyer L., Schaeffer V., et al. Evidence for a key role of steroids in the modulation of pain. Psychoneuroendocrinology, Volume 34, Issue SUPPL. 1, 2009, S169-S177.
2. Shenkin HA. Effect of pain on diurnal pattern of plasma corticoid levels. Neurol1964;14:1112-1115.
3. Glynn CJ, Lloyd JW. Biochemical changes associated with intractable pain. Br Med J 1978;1:280-281.
4. Mellor DJ, Stafford KJ, Todd SE, et al. A comparison of catecholamine and cortisol responses of young lambs and calves to painful husbandry procedures. Aust Vet J 2002;80:228-233.
5. Moore RA, Evans PJ, Smith RF, et al. Increased cortisol excretion in chronic pain. Anesthesia 1983; 38:788-791.
6. Nakagawa H, Hosokawa R. Study of the stress response to acute pain in the awake human. Pain Clinic 1994;7:317-324.
7. Khorami S, Muniyappa R, Nackers L, et al. Effect of chronic osteoarthritis pain on neuroendocrine function in men. Clin Endo Metab 2006;11:4313-4318.
8. Neeck G, Crofford LJ. Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome. Rheumatic Disease Clinics of North America 2000;26:989-1002.
9. Straub RH, Cutolo M. Involvement of the hypothalamic-pituitary-adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis: viewpoint based on a systemic pathogenetic role. Arthritis Rheum. 2001 Mar;44(3):493-507.
10. Strittamatter M, Bianchi O, Ostertag D, et al. Altered function of the hypothalamic-pituitary-adrenal axis in patients with acute, chronic and episodic pain. Schmerz (Berlin Germany) 2005;19(2):109-16.
11. Tennant F. Intractable pain is a severe stress state associated with hypercortisolemia and reduced adrenal reserve. Drug Alcohol Depend 2000;60(suppl 1):220-1.
12. Tennant F, Hermann L. Normalization of serum cortisol concentration with opioid treatment of severe chronic pain. Pain Med 2002;3: 132-134.
13. Tennant F, Shannon JA, Nork JG, et al. Abnormal adrenal gland metabolism in opioid addicts: implications for clinical treatment. J Psycho Drugs 1991;23:135-149.
14. Tennant F, Hermann L. Using biologic markers to identify the legitimate chronic pain patient. Amer Clin Lab 2002;(June) 8-17.
15. Atkinson Jr JH, Kremer EF, Ward HW, et al. Pre- and post-dexamethasone saliva cortisol determination in chronic pain patients. Biol Psychiatry 1984;19:1155-1159.
16. Russell U. Neurohormonal aspects of fibromyalgia syndrome. Rheum Dis Clin North Am 1989;15:149-168.
17. Park JY, Ahn RS. Hypothalamic-pituitary-adrenal axis function in patients with complex regional pain syndrome Type I. Psychoneuroend 2012;37:1557-1568.
18. Hyyppa MT, Alaranta H, Lahtala K. Prolactin and cortisol responses to the experience of low back pain. Pain 1985;23:231-242.
19. Tennant F. John F. Kennedy's Pain Story: from autoimmune disease to centralized pain. Prac Pain Manag 2012;9 :53-68.
20. Mattingly D. A simple fluorimetric method for the estimation of free 11-hydroxycorticoids in human plasma. J Clin Path 1962;15:374-379.
21. Neeck G, Federlin K, Graef V, et al. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J Rheumatol 1990;17:24-9.
22. Grossman A, Gaillard RC, McCartney P, et al. Opiate modulation of the pituitary-adrenal axis: effects of stress and circadian rhythm. Clin Endocrin 1982;17:279-286.
23. Jones KJ. Gonadal steroids and neuronal regeneration: a therapeutic role. Adv Neurol 1993;59:227-240.
24. McEwen BS, de Kloet ER, Rostene W. Adrenal steroid receptors and action in the central nervous system. Physio Rev 1986;66:1121-1188.

25. Svec F. Glucocorticoid receptor regulation. Life Sci 1985;36:2359-2366.
26. Holaday JW, Law PY, Loli HH, et al. Adrenal steroids indirectly modulate morphine and betaendorphin effects. J Pharmacol Exp Ther 1979;208:176-83.
27. Gibson A. The influence of endocrine hormones on the autoimmune nervous system. J Auton Pharmaco 1981;1:331-340.
28. Cashin M, Moravek V. The physiological action of cholesterol. Am J Physiol 1927;82:294-298.
29. Thorn GW, forsham PH, Frawley TF, et al. The clinical usefulness of ACTH and cortisone. New Eng J Med 1950;242:783-793, 824-834.
30. Long JB, Holaday JW, Blood -brain barrier: Endogenous modulation by adrenal-cortical function. Science 1985227: 1580-1583.
31. Stewart PM, Krone NP, Melmed: Williams Textbook of Endocrinology. In: The adrenal cortex. 12th ed. Phileadelphia, PA Saunders Company; 2011: chap 15.
32. Wiegers GJ, Reul .TMHM. Induction of cytokine receptors by glucocorticoids: functional and pathological significance. Trends Pharmacol Sci 1998;19:317-321.
33. Wilckens T. Glucocorticoids and immune function: physiological relevance and pathogenic potential of hormonal dysfunction. Trends Pharmacol Sci 1995;16:193-97.
34. Horner HC, Packan DR, Sapolsky RM. Glucocorticoids inhibit glucose transport in cultured hippocampal neurons and glia. Neuroendocrinology 1990;52:57-63.
35. Joels M, DeKloet E. Control of neuronal excitability by corticosteroid hormones. Trends Neurosci 1992; 15:25-30.
36. Sapolsky RM, Krey LC, McEwen BS. Prolonged glucocorticoids exposure reduces hippocampal neuron number: implications for aging. J Neruosci 1985;5:1222-1227.
37. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endoe Rev 1984;5:25-44.
38. Orchinik M, Murray TF, Moore FL. A corticosteroid receptor in neuronal membranes. Science 1991 ;252: 1848-1851.
39. Virgin C, Ha T, Packan D, et al. Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: implications for glucocorticoids neurotoxicity. J Neurochem 1991;57:1422- 1428.
40. Almawi WY, Beyhum HN, Rahme AA, et al. Regulation of cytokine and cytokine receptor expression by glucocorticoids. J Leukoc Bioi 1996;60:563-72.
41. McDonald RK, Evans ET, Weise VK, Patrick RW. Effect of morphine and nalorphine on plasma hydrocortisone levels in man. J Pharmacol Exp Ther 1959;125:241-7.
42. Addison T. On The Constitutional And Local Effects Of Disease Of The Supra-Renal Capsules. Samuel Highley, 32 Fleet St, London, 1855.
43. Newell-Price J, Bertango X, Grossman AB, et al. Cushing's Syndrome. Lancet 2006;367:1605-1617.
44. 2. Plassart-Schiess G, Baulieu F. Neurosteroids: Recent findings. Brain Research Reviews 2001;37:133-140.
45. Roglio I, Bianchi R, Gotti S, et al. Neuroprotective effects of dehydroprogesterone and progesterone in an experimental model of nerve crush injury. Neurosci 2008 Aug 26;155(3):673-685.
46. Shen W, Mennerick S, Covey DF, et al. Pregnenolone sulfate modulates inhibitory synaptic transmission by enhancing $GABA_a$ receptor desensitization. J Neuroscience 2000;20:3571-3579.
47. 6. Coronel MF, Labomlorda F, Roig P, et al. Progesterone prevents allodynia after experimental spinal cord injury. J of Pain 2011;12:71-83.
48. Morfin R, Young J, Corpechot C, et al. Neurosteroids: pregnenolone in human sciatic nerves. Proc Natl Acad Sci 1992;89:6790-6793.
49. Karishma KK, Herbert J. Dehydroepiandrosterone (DHRA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone induced suppression Eur J Neurosci 2002;16:445-453.
50. Bastianetto S, Ramassamy C, Poirier J, et al. Dehydroepiandrosterone (DHEA) protects hippocampal cells from oxidative stress-induced damage. Brain Res Mol Brain Res 1999;66:35-41.
51. Guth L, Zhang Z, Roberts E. Key role for pregnenolone in combination therapy that promotes recovery after spinal cord injury. Proc Natl Acad Sci 1994;91:12308-12312.
52. Lazardis J, Charalampopoulos I, Alexaki V, et al. Neurosteroid dehydroepiandrosterone interacts with nerve growth factor (NGF) receptors preventing neuronal apoptosis. Plos Biol 2001;9(4):e1001051.
53. Baulieu EE, Robel P. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as neuroactive neurosteroids. Proc Natl Acad Sci 1998;95:4089-4091.
54. Immamura M, Prausad C. Modulation of GABA-gated chloride ion influx in the brain by dehydroepiandrosterone and its metabolites. Biochem Biophys Res Commun 1998;24:243-(3):771-115.
55. Vallee M, Mayo W, Le Moal M. Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and memory in cognitive aging. Brain Res Brain Res Rev 2001;37(1-3):301-312.
56. Kilts JD, Tupler LA, Keefe FJ, et al. Neurosteroids and self-reported pain in veterans who served in the Military after September 11,2001. Pain Med 2010;10:1469-1476.
57. Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. Front Neuroendocrinol 2000;21:1-56.
58. Tennant F. Clinical trial of progesterone for intractable, central pain. Presented at Amer Acad Pain Med, Palm Springs, CA 2012.
59. Chesterton LS, Barlas P, Foster Ne, ET AL. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101:259-266.

60. Craft RM, Mogli JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. Eur J Pain 2004;8:397-411.
61. Berkley KJ. Sex differences in pain. Behav Brain Sci 1997;20:371-380.
62. Aloisi A.M., Affaitati G., Ceccarelli I., et al. Estradiol and testosterone differently affect visceral pain-related behavioural responses in male and female rats. European Journal of Pain, Volume 14, Issue 6, 2010, 602-607.
63. Aloisi A.M. Gonadal hormones and sex differences in pain reactivity. Clin J Pain 2003;19:168-174.
64. Dawson-Basoa M, Gintzler AR. Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms. Pain 1996;64:608-615.
65. Amini H, Ahmadiani A. Increase in testosterone metabolism in the rat central nervous system by formalin-induced toxic pain. Pharmacol Biochem Behav 2002;74:199-204.
66. Aloisi A.M., Bonifazi M. **S**ex hormones, central nervous system and pain. Hormones and Behavior, 50, issue 1, 2006, 1-7
67. Aloisi A.M. Gonadal hormones and sex differences in pain reactivity. Clin J Pain 2003;19:168-174.
68. Hau M, Dominguez OA, Evrard HC. Testosterone reduces responsiveness to nociceptive stimuli in a wild bird. Horm Behav 2004;46:165-170.
69. Harbuz MS, Perveen-Gill Z, Lightman SL, et al. A protective role for testosterone in adjuvant-induced arthritis. Br J Rheumatol1995;34:1117-1122.
70. Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. Obstet Gynecol 1998;92:982-988.
71. Jones KJ. Gonadal steroids and neuronal regeneration: a therapeutic role. Adv Neurol 1993;59:227-240.
72. Evrard HC, Balthazart J. Rapid regulation of pain by estrogens synthesized in spinal dorsal horn neurons. J Neurosci 2004;24:7225-7229.
73. Green PS, Bishop J, Simpkins JW. 17 alpha-estradiol exerts neuroprotective effects on SK-N-SH cells. J Neurosci 1997;17:511-515.
74. Cirillo DJ, Wallace RB, Wu L, et al. Effects of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. Arthritis Rheum 2006;54:3194-3204.
75. Dons RF, Shaki KMM. Changes in triidothyronine mark severe pain syndrome: a case report. Military Med 1994; 159:465-6.
76. Penza P, Lombardi R, Camozzi F, et al. Painful neuropathy in subclinical hypothyroidism: clinical and neuropathological recovery after hormone replacement therapy. Neurol Sci 2009;30:149-151.
77. Sonkin L. Therapeutic trials with thyroid hormones in chemically normal thyroid patients with myofascial pain and complaints suggesting mild thyroid insufficiency. J Back and Musculoskeletal Rehab 1997;85-90.
78. Wiess SC, Trudeau VL. Thyroid hormone and gamma-amino-butyric acid (GABA) interactions in neuroendocrine systems. Comp Biochem physiol 2006;144:332-344.
79. Wartofsy L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "Euthyroid Sick Syndrome". Endocrin Rev 1982;3:164-216.
80. McIver B, Gorman CA. Euthyroid sick syndrome. An overview. Thyroid 1997;7:125-132.
81. Starr M. The energy factors within our cells in Hypothyroidism Type II: The Epidemic Columbia, MO. Mark Starr Trust, 2011,pp55-61.
82. Vuong C, Stan HM, Vum V, et al. The effects of opioid analogs on animal and human endocrine systems. Endocr Rev 2010;31:989-132.
83. Abs R, Verhelst J, Maeysaert J, et al. Endocrine consequences of long term intrathecal administration of opioids. J Clin Endocrinol Metab 2000;85(6):2215-2222.
84. Elliott JA, Horton E, Fibuch EE. The endocrine effects of long-term oral opioid therapy: a case report and review of the literature. J Opioid Manag 2011;7:145-154.
85. Finch PM, Roberts LJ, Price L, et al. Hypogonadism in patients treated with intrathecal morphine. Clin J Pain 2000; 16:251-254.
86. Roberts LJ, Finch PM, Pullan PT, et al. Sex hormone suppression by intrathecal opioids: a prospective study. Clin J Pain 2002;18:144-148.
87. Rubinstein AL, Carpenter DM, Minkoff J. Hypogonadism in man using daily opioid therapy for non-cancer pain is associated with duration of action of opioid. Presented at Amer Acad Pain Med Palm Springs, Feb 2012.
88. Tennant F. Hormone testing and replacement in pain patients made simple. Pract Pain Manag 2012;12:54-62.