Traumatic Brain Injury:

A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.

Chapter 4: Neuroendocrinology

Clinical Signs and Symptoms of Hypopituitarism

Pituitary Dysfunction after Traumatic Brain Injury. Sorin G. Beca, Brent Masel, and Randall J. Urban. 2008

Clinical Signs and Symptoms	Associated Hormone(s)
Increased body fat.	GH, LH, FSH, ▲Insulin
Weakness, fatigue, decreased exercise tolerance	ACTH, GH, LH, FSH, TSH
Decreased muscle mass.	GH, LH, FSH
Loss of libido, erectile dysfunction, infertility, oligo-/amenorrhea.	LH, FSH
Ischemic heart disease (IHD).	GH and (DHEA-s)
Shortened life span .	GH
Weight loss, weight gain .	ACTH, TSH
Cognition, psychomotor speed .	GH, TSH
Attention, learning deficits.	GH, TSH
Memory loss or difficulty.	GH, TSH, LH, FSH

Hypothalamopituitary Dysfunction following Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage: A Systematic Review

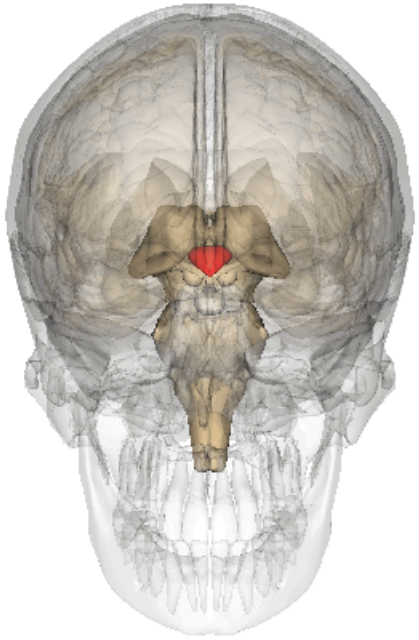
JAMA. 2007;298(12):1429-1438.

Table 4. Frequencies of Anterior Hypopituitarism in Adults in the Chronic Phase After Traumatic Brain Injury (TBI) or Subarachnoid Hemorrhage (SAH)[a]

Source	No. of Adults	No. (%) [95% CI]					
		Growth Hormone	LH/FSH	Adrenocorticotropic Hormone	TSH	Hypopituitarism	Multiple Deficiencies
TBI							
Bondanelli et al,[12] 2004	50	4 (8.0) [0.5-15.5]	7 (14.0) [4.4-23.6]	0	5 (10.0) [1.7-18.3]	14 (28.0) [15.6-40.5]	6 (12.0) [3.0-21.0]
Aimaretti et al,[14] 2005	70	14 (20.0) [10.6-29.4]	8 (11.4) [4.0-18.9]	5 (5.7) [0.3-11.2]	4 (7.1) [1.1-13.2]	16 (22.9) [13.0-32.7]	7 (10.0) [3.0-17.0]
Agha et al,[15,16] 2004	102	11 (10.8) [4.8-16.8]	12 (11.8) [5.5-18.0]	13 (12.7) [6.3-19.2]	1 (1.0) [0-2.9]	29 (28.4) [19.7-37.2]	6 (5.9) [1.3-10.5]
Popovic et al,[17] 2004	67	10 (14.9) [6.4-23.5]	6 (9.0) [2.1-15.8]	5 (7.5) [1.2-13.8]	3 (4.5) [0-9.4]	23 (34.3) [23.0-45.7]	7 (10.4) [3.1-17.8]
Leal-Cerro et al,[18] 2005	170	10 (5.9) [2.3-9.3]	29 (17.1) [11.4-22.7]	11 (6.5) [2.8-10.2]	10 (5.9) [2.4-9.4]	42 (24.7) [18.2-31.2]	15 (8.8) [4.6-13.1]
Agha et al,[19,20] 2005	48	5 (10.4) [1.8-19.1]	6 (12.5) [3.1-21.9]	9 (18.8) [7.7-29.8]	1 (2.1) [0-6.1]	Not reported	Not reported
Schneider et al,[21] 2006	70	7 (10.0) [3.0-17.0]	14 (20.0) [10.6-29.4]	6 (8.6) [2.0-15.1]	2 (2.9) [0-6.8]	25 (35.7) [24.5-46.9]	3 (4.3) [0-9.0]
Tanriverdi et al,[22] 2006	52	17 (32.7) [19.9-45.4]	4 (7.7) [0.5-14.9]	10 (19.2) [8.5-29.9]	3 (5.8) [0 12.1]	26 (50.0) [36.4-63.6]	5 (9.6) [1.6-17.6]
Herrmann et al,[23] 2006	76	6 (7.9) [1.8-14.0]	13 (17.1) [8.6-25.6]	2 (2.6) [0-6.2]	2 (2.6) [0-6.2]	18 (23.7) [14.1-33.2]	5 (6.6) [1.0-12.2]
Klose et al,[29] 2007	104	16 (15.4) [8.5-22.3]	2 (1.9) [0-4.6]	5 (4.8) [0.7-8.9]	2 (1.9) [0-4.6]	16 (15.4) [8.5-22.3]	6 (5.8) [1.3-10.3]
SAH							
Aimaretti et al,[14] 2005	32	7 (21.9) [7.6-36.2]	2 (6.3) [0-14.6]	2 (6.3) [0-14.6]	3 (9.4) [0-19.5]	12 (37.5) [20.7-54.3]	2 (6.3) [0-14.6]
Kreitschmann-Andermahr et al,[27] 2004	40	8 (20.0) [7.6-32.4]	0	16 (40.0) [24.8-55.2]	1 (2.5) [0-7.3]	22 (55.0) [39.6-70.4]	3 (7.5) [0-15.7]
Dimopoulou et al,[28] 2004	30	11 (36.7) [19.4-53.9]	4 (13.3) [1.2-25.5]	3 (10.0) [0-20.7]	2 (6.7) [0-15.6]	14 (46.7) [28.8-64.5]	4 (13.3) [1.2-25.5]
Total							
TBI and SAH	911	126 (13.8) [11.7-16.2]	107 (11.7) [9.7-13.8]	87 (9.6) [7.8-11.6]	39 (4.3) [3.2-5.8]	257 (29.8) [25.3-31.1]	69 (8.0) [5.9-9.3]
TBI alone	809	100 (12.4) [10.2-14.8]	101 (12.5) [10.2-14.8]	66 (8.2) [6.5-10.3]	33 (4.1) [2.9-5.7]	209 (27.5) [22.8-28.9]	60 (7.7) [5.6-9.2]
SAH alone	102	26 (25.4) [17.0-34.0][b]	6 (5.9) [1.3-10.5]	21 (20.5) [12.7-28.4][b]	6 (5.9) [1.3-10.5]	48 (47.0) [37.4-56.8][b]	9 (8.8) [3.3-14.3]

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.
[a] Defined as at least 5 mo.
[b] Significant compared with TBI.

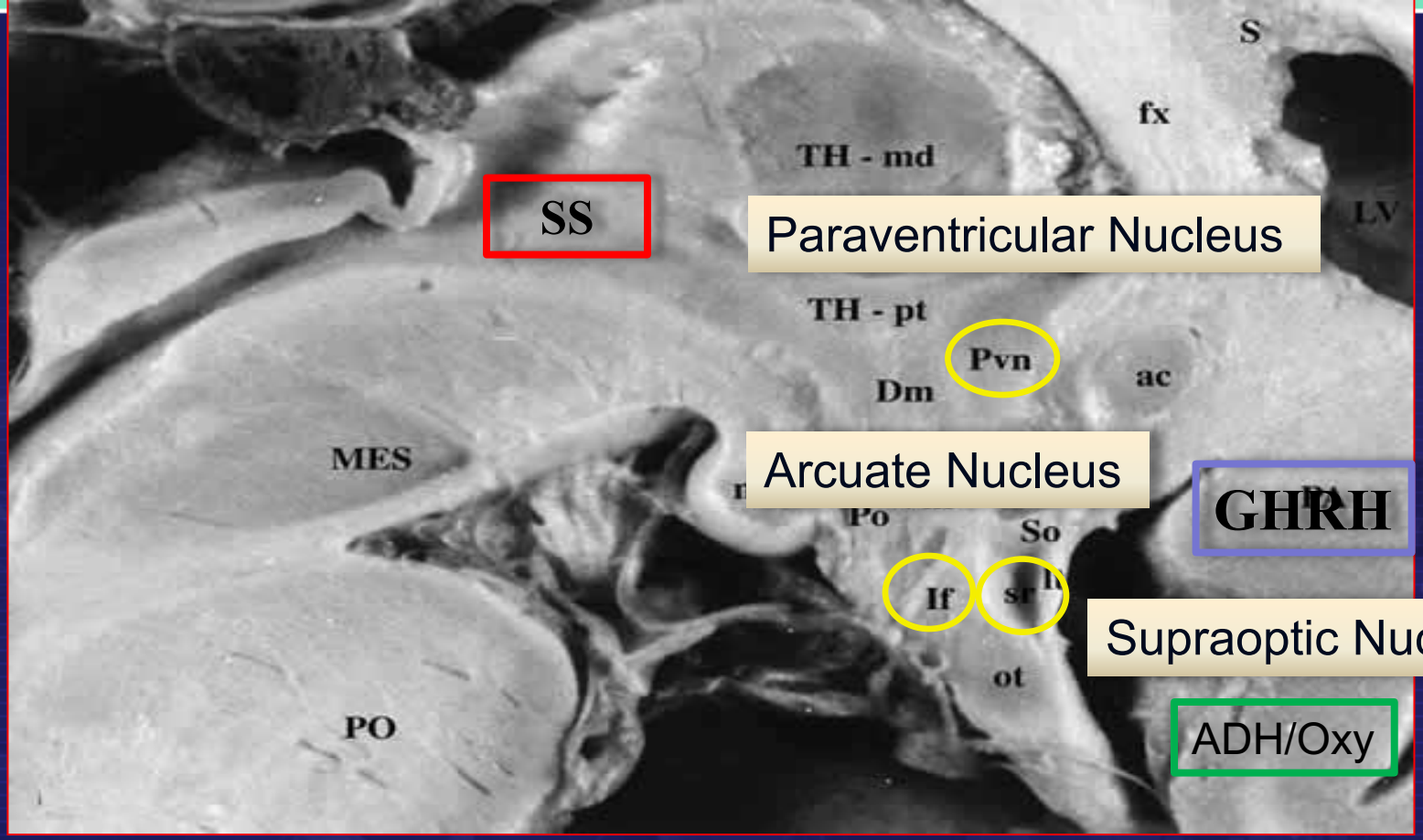
The Hypothalamus



Fundamentals

Functions of the Hypothalamus

- The hypothalamus is a very small, but extremely important part of the diencephalon that is involved in the mediation of endocrine, autonomic and behavioral functions. (4 gm)
- Recently found to participate in the immune system via Somatostatin.
- **The Hypothalamus**: (1) controls the release of 8 major hormones by the hypophysis, and is involved in (2) **temperature regulation**, (3) **control of food and water intake**, (4) **sexual behavior** and reproduction, (5) control of **daily cycles in physiological state and behavior**, and (6) mediation of **emotional responses.**



Many of the major cell groups are located near the midline. These include the preoptic nucleus (Pop), **paraventricular nucleus (Pvn)**, **arcuate nucleus (If)**, **supraoptic nucleus (Sr)**, dorsomedial nucleus (Dm), ventromedial nucleus (Vm), posterior hypothalamic nucleus (Po), and medial mammillary nucleus (mm). Ac = anterior commissure, fx = fornix, lt= lamina terminalis, ot = optic tract and chiasm, Lv = lateral ventricle, MB = midbrain, PN = pons, Sr = supraoptic recess, T = thalamus.

Nuclei of the Hypothalamus

Hypothalamic Nuclei	Function
Medial Pre-optic Nucleus	Regulates the release of GnRH from the adenohypophysis. Contains the sexual dimorphic nucleus which releases GnRH, differential development between sexes is based upon in utero testosterone levels.
Supraoptic Nucleus	Oxytocin and Vasopressin release.
Paraventricular Nucleus	TRH, CRH, Oxytocin, and Vasopressin release.
Anterior Hypothalamic Nucleus	Thermoregulation, panting, sweating, and Thyrotropin inhibition.
Suprachiasmatic Nucleus	Vasopressin release and Circadian rhythm.
Lateral Nucleus	Thirst and hunger (Leptin).
Dorsomedial Hypothalamic Nucleus	Blood pressure, heart rate, and GI stimulation
Ventromedial Nucleus	Satiety and neuroendocrine control.
Arcuate Nucleus	Growth hormone releasing hormone, feeding and dopamine regulation.

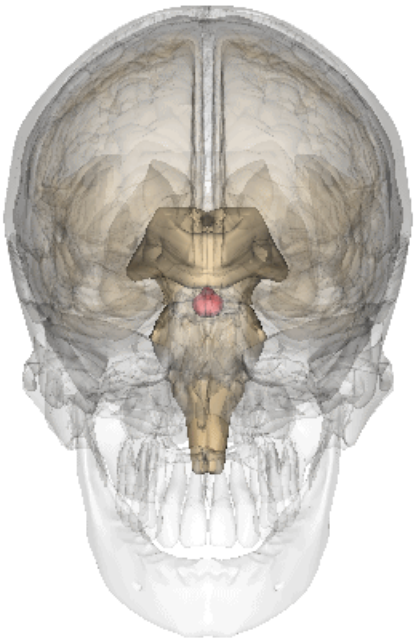
Table 4.1: Hypothalamic nuclei responsible for integration of hormonal homeostasis and the nervous system.

Hypothalamic Releasing Hormones

Secreted Hormone	Abrev.	Produced by	Effect
Thyrotropin releasing hormone (prolactin releasing hormone)	TRH (PRH)	Parvocellular Neurosecretory cells	Stimulates TSH and Prolactin release from AP.
Dopamine (Prolactin Inhibiting Factor)	DA or PIF	Neurons of the Arcuate Nucleus	Inhibits Prolactin release from AP
Growth hormone releasing hormone	GHRH	Neurons of the Arcuate Nucleus	Stimulates GH release from AP
Somatostatin (Somatotropin Release Inhibiting factor)	SSS or SRIF	Neurons of the Periventricular nucleus	Inhibits GH and TSH release from AP
Gonadotropin Releasing hormone	GnRH	Neurons of the Preoptic Area	Stimulates FSH and LH release from AP.
Cortotropin Releasing Hormone	CRH	Parvocellular Neurosecretory Cells	Stimulates ACTH release from the AP, and inhibits LH, GH, LH and FSH release.
Oxytocin		Magnocellular Neurons	Stimulates uterine contractions and lactation.
Vasopressin (ADH)	ADH	Magnocellular Neurons	Increases water reabsorption and decreases water loss from kidneys.

Table 4.2: Hypothalamic hormones.

The Pituitary Gland

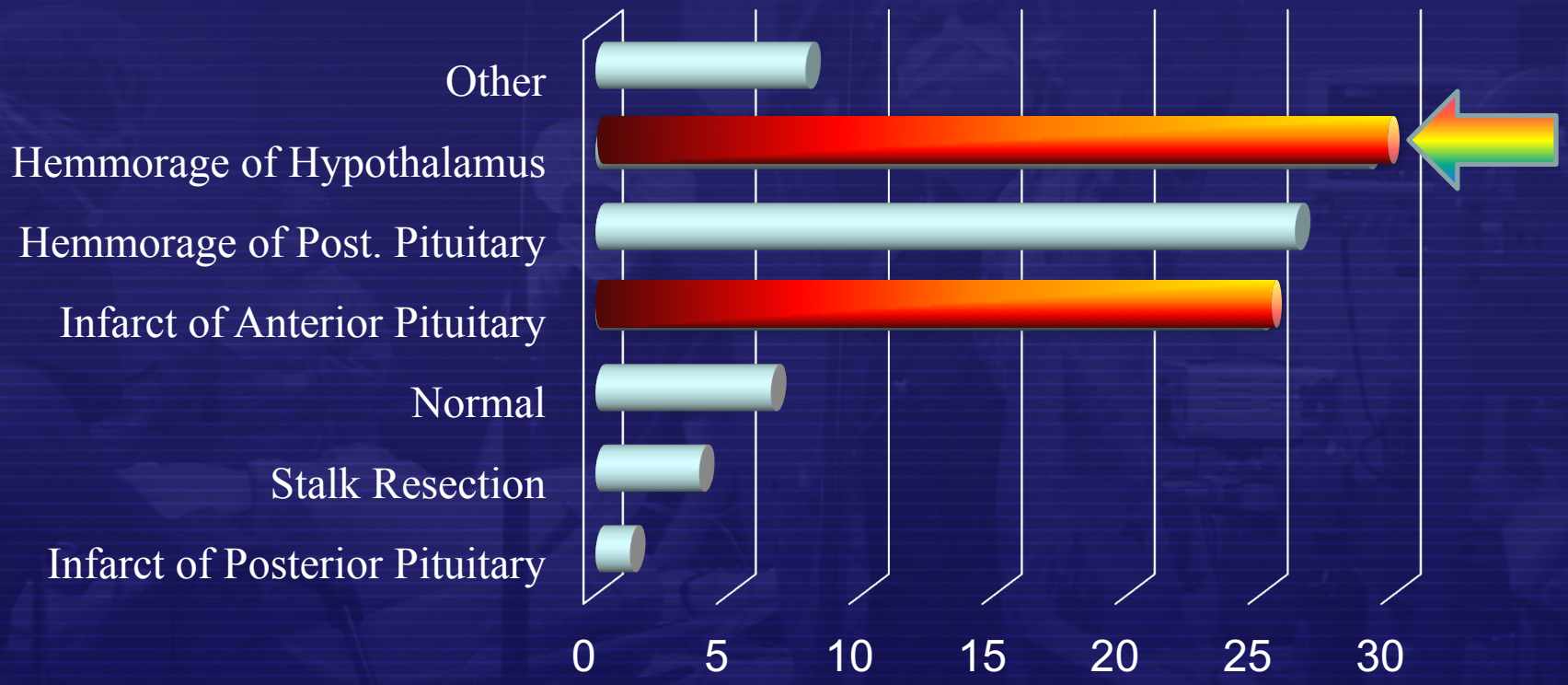


Anatomy of the Pituitary Gland

- The pituitary gland, typically weighing 0.5grams and measuring approximately 8 mm by 10 mm, is located within the sella turcica in the skull base.
- The adenohypophysis and neurohypophysis receive their blood supply primarily from the internal carotid arteries.
- The long hypophyseal portal vessels arise from branches of the internal carotid artery and anterior Circle of Willis above the diaphragma sella, travel down the infundibulum and provide the anterior pituitary gland with 70–90% of its blood supply.

Anterior Pituitary

Hypopituitarism Secondary to Head Trauma. J. Clinical Endocrinology and Metabolism 85:1353-1361. Benvenga S, et al. 2000.

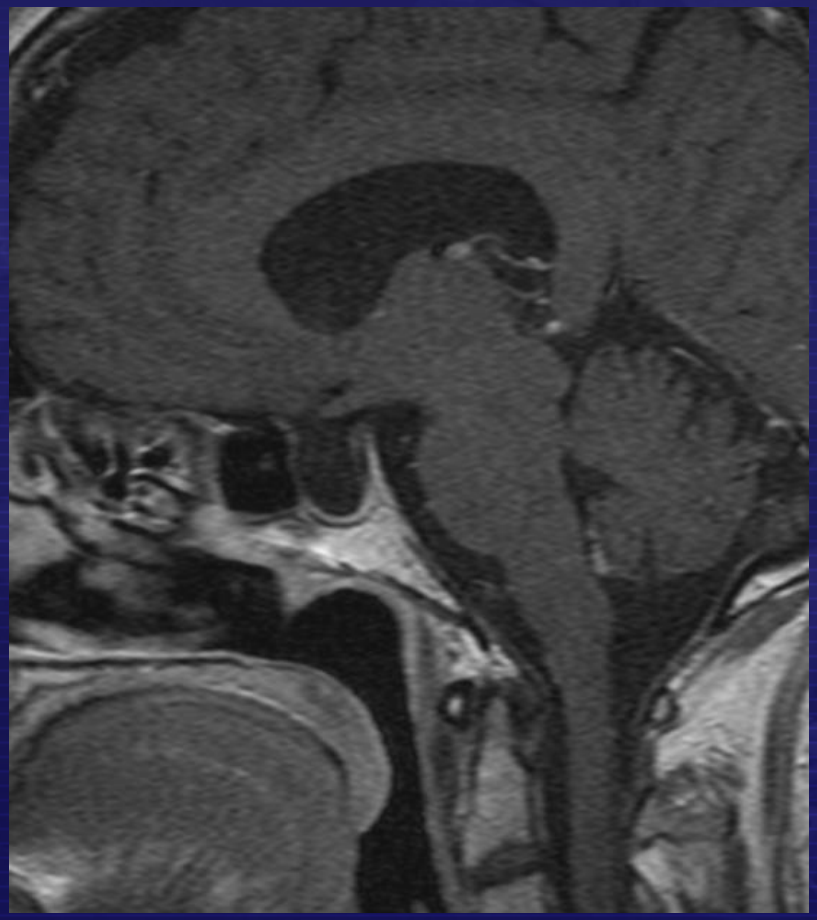


Hormones of the AP and their functions

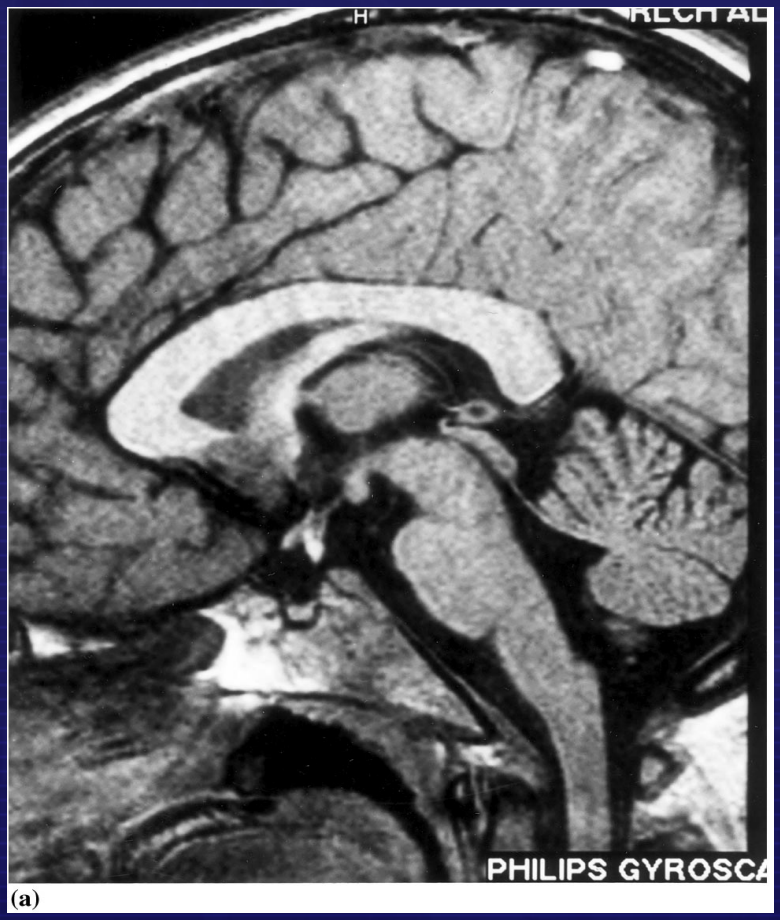
Secreted	ID	From	Effect
Growth Hormone (Somatotropin)	GH	Somatotrophs	Stimulates growth and cell reproduction. Stimulates Insulin-like growth factor 1 release from liver
Thyroid-Stimulating Hormone (Thyrotropin)	TSH	Thyrotrophs	Stimulates thyroxine (T4) and triiodothyronine (T3) synthesis and release from thyroid gland. Stimulates iodine absorption by thyroid gland
Adrenocorticotropic hormone (Corticotropin)	ACTH	Corticotrophs	Stimulates corticosteroid (glucocorticoid and mineralcorticoid) and androgen synthesis and release from adrenocortical cells .
Follicle-stimulating hormone	FSH	Gonadotrophs	In females: Stimulates maturation of ovarian follicles in ovary In males: Stimulates maturation of seminiferous tubules, spermatogenesis, production of androgen-binding protein from Sertoli cells of the testes.
Luteinizing hormone	LH	Gonadotrophs	In females: Stimulates ovulation and formation of corpus luteum In males: Stimulates testosterone synthesis from Leydig cells.
Prolactin	PRL	Lactotrophs	Stimulates milk synthesis and release from mammary glands Mediates sexual gratification

Table 4.3: Anterior Pituitary Hormones and their effects in humans.

Empty Sella Syndrome
Pituitary Atresia



Pituitary Stalk Syndrome
Traumatic Transection



(a)

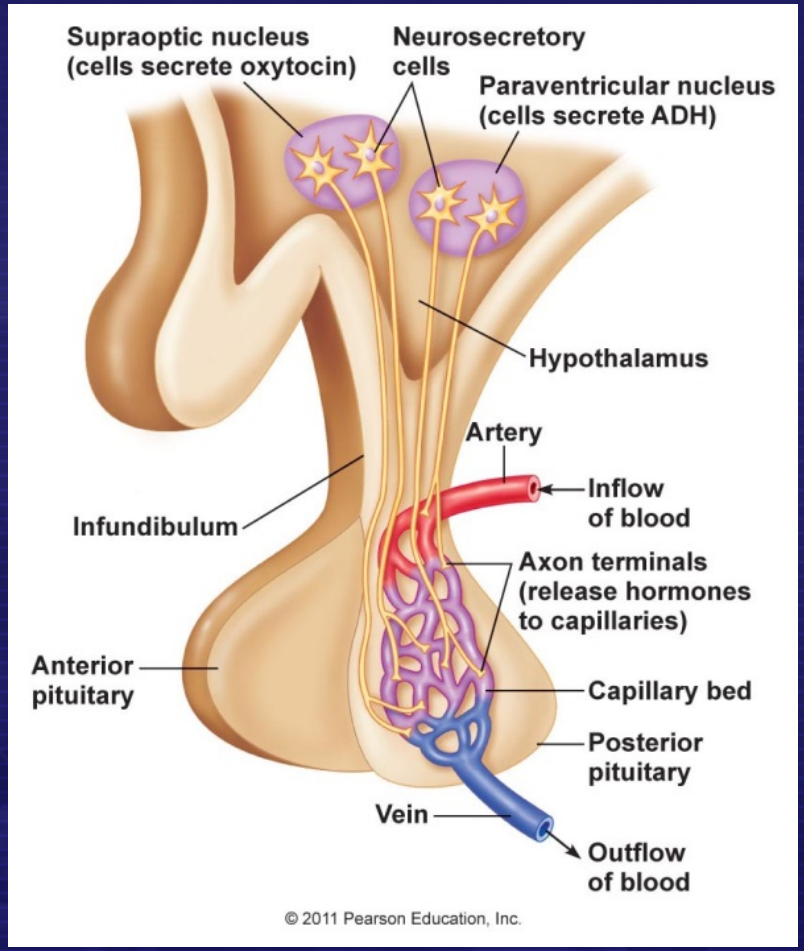
Posterior Pituitary

(neurohypophysis)

Secreted	ID	From	Effect
Oxytocin		Magnocellular Neurosecretory Cells	Uterine contraction, Lactation (letdown reflex), bonding reflex, intensification of orgasms in both females and males.
Vasopressin (Antidiuretic Hormone)	ADH	Parvocellular Neurosecretory Neurons	Increases water permeability in the distal convoluted tubule and collecting duct of nephrons, thus promoting water reabsorption and increasing blood volume.

Posterior Pituitary more protected.

- The long axons from the hypothalamus release their hormones ; Oxytocin and ADH directly into the capillaries of the posterior pituitary.
- This is in contrast to the trophic cells of the anterior pituitary producing hormones locally to be taken up by the hypophyseal



Missing Concept

(1) Adenoma. (2) Hypothalamic damage
-Micro-macro -Arcuate Nucleus

Prolactin Luteinizing Hormone Testosterone

Hypopituitarism following Traumatic Brain Injury and aneurysmal subarachnoid hemorrhage: a preliminary report. Daniel F. Kelly, M.D., Ronald Swerdloff, M.D., et al., Divisions of Neurosurgery and Endocrinology, UCLA; and Divisions of Neurosurgery and Endocrinology and Dept of Pediatrics, Harbor–UCLA Medical Center and Research and Education Institute, LA, California

- In this review of TBI cases, sixty-two percent (**62%**) of the patients had **increased serum Prolactin levels**!

- Tx: #1 Cabergoline.

Hypothalamo-pituitary Dysfunction following Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage: A Systematic Review

JAMA. 2007;298(12):1429-1438. doi:10.1001/jama.298.12.1429

Table 1. Clinical Consequences of Pituitary Hormone Deficiencies

Hormone Deficiency	Symptoms	Clinical Findings
Growth hormone	Anergia, poor quality of life	Osteoporosis, visceral obesity, reduced lean body mass, dyslipidemia
LH/FSH (sex steroids)	Oligomenorrhea or amenorrhea, sexual dysfunction, mood disorders, reduced vigor	Loss of secondary hair, reduced muscle mass and exercise tolerance (men), osteoporosis, infertility (men and women)
Corticosteroids	Life-threatening adrenal crisis (weakness, nausea, fever, shock), poor energy, weight loss	Hypotension, hypoglycemia, hyponatremia, myopathy, anemia, eosinophilia
Thyroid hormones	Poor energy, neuropsychiatric problems, weight gain	Bradycardia, hypotension, myopathy, neuropathy, skin, hair, and voice changes

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Neuroendocrine disorders after traumatic brain injury

J Neurology Neurosurgery & Psychiatry **2008**;79:753-759 A Agha L A Behan, J Phillips, C J Thompson, Academic Department of Endocrinology, Academic Department of Neurosurgery, Beaumont Hospital and RCSI Medical School, Dublin, Ireland.

- Marked changes of the hypothalamo-pituitary axis in the Acute Phase of TBI, with 80% of patients showing evidence of Gonadotropin deficiency, 18% with GH deficiency, 16% Corticotrophin deficiency, and 40% with Vasopressin abnormalities.
- There remains a high frequency of hypothalamic-pituitary hormone deficiencies among long-term survivors of TBI, with approximately 25% patients showing persistence of 1 or 2 pituitary hormone deficiencies.

A Point in summation

- The HAP axis is clearly involved in the regulation of NeuroActive Steroids; those hormones that are produced in the peripheral glands and enter the brain.
- On a secondary level, hypothalamic releasing hormones travel to the AP via the hypophyseal blood supply to generate pituitary trophic hormones that all have a central regulatory effect on the brains production of NeuroSteroids.
- Damage to either of these systems will cause failure in the homeostatic mechanisms for both NS and NAS. And there is the problem waiting to be resolved.

NeuroSteroids(NS) and NeuroActiveSteroids(NAS) in the Central Nervous System.

NS and NAS

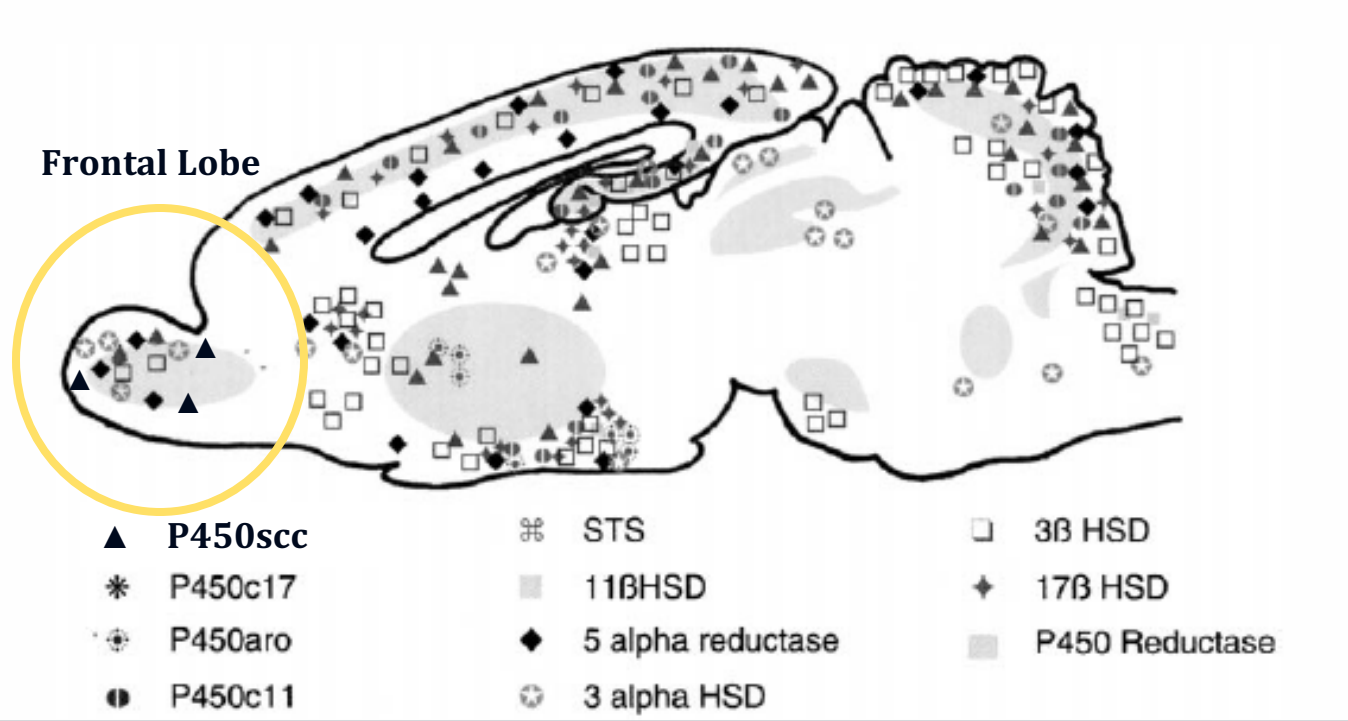
- NeuroActive Steroids (NAS) are the body's hormones that are produced in the periphery and pass through the BBB into the brain.
- Neurosteroids (NS) are those that are produced de nova in the brain by the glial cells like astrocytes, oligodendrocytes and microglia.
- Enzymes responsible for the production of NS have been identified within neurons too.

Biosynthesis of NeuroSteroids and regulation of their synthesis.

International Review of Neurobiology. Vol 46, 2001, Pages 33–60, Synthia H Mellon. Dept of Obstetrics, Gynecology, and Reproductive Sciences, The Metabolic Research Unit University of California-San Francisco. 94143-0556 USA. Hubert Vaudry European Institute for Peptide Research Laboratory of Cellular and Molecular Neuroendocrinology INSERM U-413, UA CNRS, University of Rouen 76821 Mont Saint-Aignan, France.

- The brain, like the gonads, adrenal glands, and placenta, is a steroidogenic organ.
- The steroids synthesized by the brain and by the nervous system have a wide variety of diverse functions.
- Neurosteroids mediate their actions not through classic steroid hormone nuclear receptors but through ion-gated neurotransmitter receptors. Therefore, the results are in real-time.

NS Regional Production



Schematic representation of an adult brain showing regional expression of enzymes involved in neurosteroidogenesis. P450scc uses the ER-stores of cholesterol to produce pregnenolone in the inner membrane of the mitochondria.

Luteinizing hormone receptor mediates neuronal Pregnenolone production via up-regulation of steroidogenic acute regulatory protein expression

. Journal of Neurochemistry, 2007, 100, 1329–1339 Tianbing Liu, et al, Dept of Pathology and Laboratory Medicine, University of Wisconsin, Madison, Wisconsin, Dept of Obstetrics and Gynecology, Graduate School of Medicine, University of Tennessee, Knoxville, Tennessee, Voyager Pharmaceutical Corporation, Raleigh, NC, Case Western Reserve University, Cleveland, Ohio, USA ¶Dept of Medicine, University of Wisconsin and the Geriatrics Research, Education and Clinical Center, VA Hospital, Madison, Wisconsin, USA

- As LH can cross the blood–brain barrier, present in cerebrospinal fluid and is expressed by neuronal cells, we tested whether LH might also modulate steroid synthesis in the brain.
- Treatment with LH caused a twofold increase in Pregnenolone secretion suggesting an increase in P450scc-mediated cleavage of cholesterol to Pregnenolone and its secretion from neurons.

NS Regulation of Production

Enzyme	Substrate	Product
P450scc (CYP11A1)	Cholesterol	Pregnenolone
3β HSD	Pregnenolone	Progesterone
P450c11β (CYP11B1)	11 Deoxycortisol	Cortisol
P450c11AS	18-OH-Corticosterone	Aldosterone
3α HSD	Pregnenolone or Progesterone	Allopregnenolone Alloprogesterone
P450c17 (CYP17A1)	Pregnenolone or Progesterone	DHEA
3β HSD	DHEA-s	Testosterone
P450aro	Testosterone	Estradiol

3α- and 3β-*Hydroxysteroid dehydrogenase*

The 3β-HSD complex is responsible for the conversion of:

- Pregnenolone to progesterone
- 17α-Hydroxypregnenolone to 17α-hydroxyprogesterone
- DHEA to androstenedione
- Androstenediol to testosterone
- Androstadienol to androstadienone

The 3α-HSD complex is responsible for the conversion of:

- Progesterone to allopregnanolone (ALLOP)
- Tetrahydrodeoxycorticsterone (THDOC)
- 3α-androstanediol to dihydrotestosterone (DHT)

Neurosteroids: Expression of Steroidogenic Enzymes and Regulation of Steroid Biosynthesis in the Central Nervous System

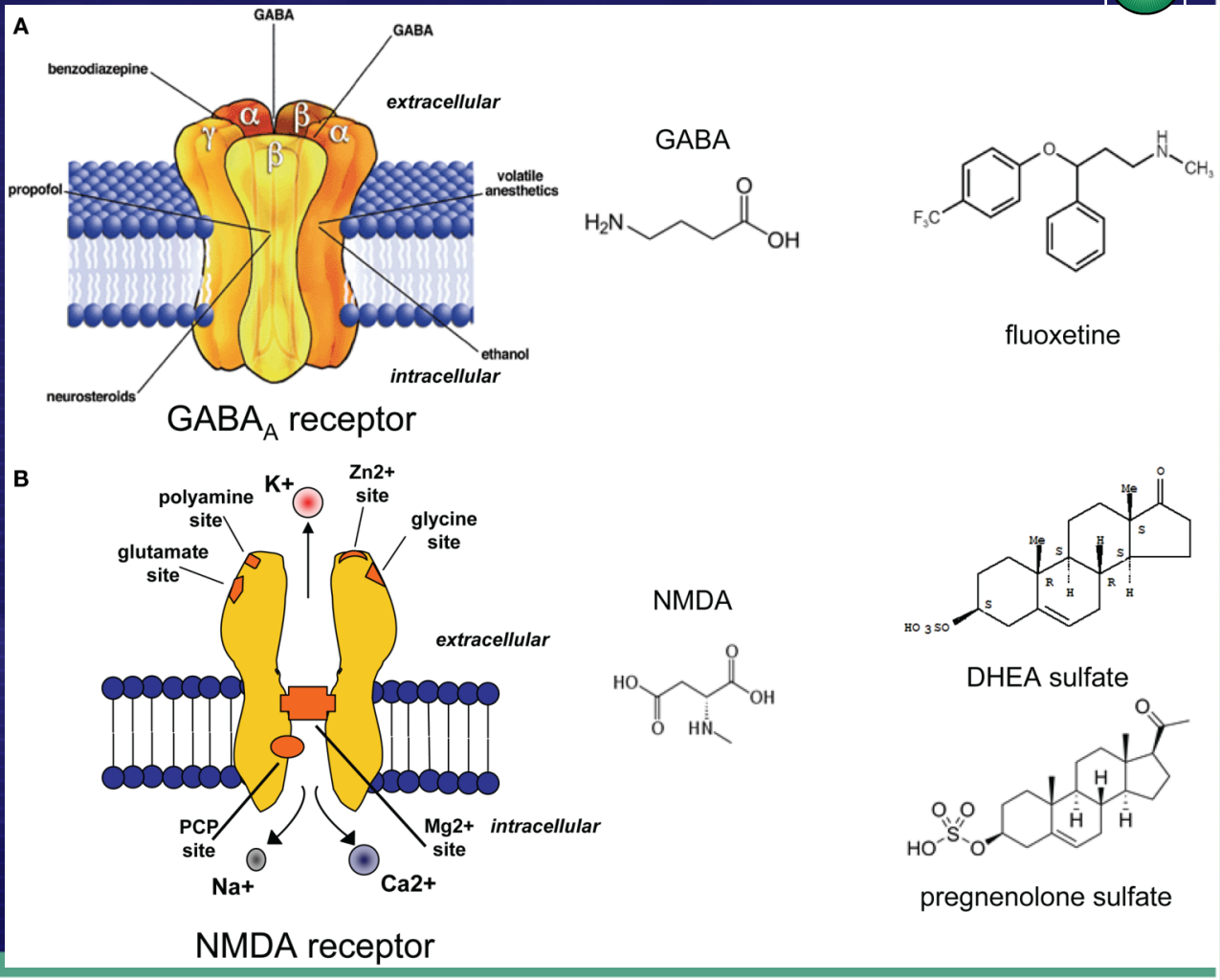
Pharmacological Reviews. Vol. 51, No. 1. (1999). Ayikoe G. Mensah-nyagan, Hubert Vaudry. Et al Institut Fédératif de Recherches Multidisciplinaires sur Les Peptides No. 23, Laboratoire de Neuroendocrinologie Cellulaire et Moléculaire, Institut National de la Sante et de la Recherche Medicale , UA Centre National de la Recherche Scientifique, Université de Rouen, Mont-Saint-Aignan, France; and Centre de Recherches en Endocrinologie Moléculaire, Le Centre Hospitalier de l'Université Laval, Quebec, Canada

- Neurosteroids, which are involved in the regulation of stress responses, anxiety, sleep, neurodegenerative processes, aggressive behavior, and cognitive activities,
- are now considered as key modulating factors of chemical neurotransmission.

Neurosteroids as neuromodulators in the treatment of anxiety disorders.

Front. Endocrinol., 2011 Patrizia Longone, et al., Rupprecht Molecular Neurobiology Unit, Experimental Neurology, Fondazione Santa Lucia, Rome, Italy. Child Neurology and Psychiatry, Dept of Neuroscience, University of Rome "Tor Vergata,", Rome, Italy. Deptt of Neuroscience, U. of Rome "Tor Vergata,", Rome, Italy. Dept of Psychiatry and Psychotherapy, U. Regensburg, Regensburg, Germany – Slide #3

- The **$GABA_A$ receptor** is an ionotropic receptor and ligand-gated ion channel. Its endogenous ligand is GABA, the major inhibitory neurotransmitter in the central nervous system.
- Upon activation, the $GABA_A$ receptor selectively conducts Cl^- through its pore, resulting in hyperpolarization of the neuron.
- This causes an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurring.



A Presynaptic Action of the Neurosteroid Pregnenolone Sulfate on GABAergic Synaptic Transmission. *Mol Pharmacol* 64:857–864, 2003

Zakaria MTCHEDLISHVILI and Jaideep Kapur Department of Neurology, University of Virginia Health Sciences Center, Charlottesville, Virginia

- A comparison of the pre- and postsynaptic effects of PS demonstrated that it was 100-fold more potent in inhibiting presynaptic GABAergic synaptic mechanisms than $GABA_A$ receptors.
- The net effect is a reduction in neurotransmission with potential clinical impact on anxiety, panic attacks, agitation, aggression, and insomnia.

Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis. PNAS. Sept 2006. vol. 103 no. 39. Roberto C. Agıs-Balboa, Graziano Pinna, Adrian Zhubi, Ekrem Maloku, Marin Veldic, Erminio Costa, and Alessandro Guidotti. Department of Psychiatry, Psychiatric Institute, University of Illinois, 1601 Taylor Street, Chicago, IL 60612

- The neurosteroids allopregnanolone (ALLO) and tetrahydrodeoxycorticosterone (THDOC) are potent positive allosteric modulators of GABA action at $GABA_A$ receptors.
- A decrease of brain neurosteroid availability has been associated with psychiatric conditions, including anxiety, aggression, pre- menstrual dysphoria, and cognitive and mood disorders.
- Anti-depressants (‘‘SSRIs’’) and antipsychotics may exert their beneficial effects, at least in part, by increasing the brain levels of Neurosteroids.

Looking at Neurosteroids

Considered by the Millennium-TBI as the missing component in the treatment of a number of CNS conditions and therefore, the reason for failed recovery.

Impaired neurosteroid synthesis in Multiple Sclerosis. Brain **2011**: 134; 2703–2721.

Farshid Noorbakhsh, Kristofor K. Ellestad,Ferdinand Maingat, Kenneth G. Warren, May H. Han, Lawrence Steinman, Glen B. Baker and Christopher Power. Dept of Medicine (Neurology), University of Alberta, Edmonton, Canada, Dept of Immunology, Tehran University Medical Sciences, Tehran, Iran, Depts of Neurology and Neurological Sciences, Stanford University, Stanford, CA , Dept of Psychiatry, University of Alberta, Edmonton, Canada, Dept of Medical Microbiology and Immunology, University of Alberta, Edmonton, Canada

- These studies are the first report of perturbed neurosteroidogenesis in multiple sclerosis and the related model, which also showed improved outcomes in terms of neurobehavioral deficits, neuropathology and neuromolecular changes with neurosteroid (allopregnanolone) replacement.
- The inflammation associated with demyelination in MS disrupts the glial production of neurosteroids furthering the loss of these neuropermissive hormones.

Progesterone Receptors: Form and Function in Brain.

Front Neuroendocrinol. 2008 May ; 29(2): 313–339Roberta Diaz Brinton, Richard F. Thompson, Michael R. Foy, Michel Baudry, Jun Ming Wang, Caleb E Finch, Todd E. Morgan, Frank Z. Stanczyk, Christian J. Pike, and Jon Nilsen. Dept of Pharmacology and Pharmaceutical Sciences, University of Southern California, Los Angeles, California, 90033 and, Loyola Marymount College, Los Angeles, CA, 90045-8405

- Progesterone and its neuroactive metabolites can promote the viability of neurons and function of glial cells within both the central and peripheral nervous system.
- Women have a greater risk of developing multiple sclerosis frequently with the onset of menopause.

Steroid hormones and neurosteroids in normal and pathological aging of the nervous system.

M. Schumacher, S. Weill-Engerer,, E.E. Baulieu et al, Inserm, 80 rue du Général Leclerc, Kremlin-Bicˆetre, France. Dept of Clinical and Veterinary Medicine, U. of Cambridge, Madingley Road, Cambridge, Instituto Cajal, 37 Avenida Doctor Arce, Madrid, Spain. Dept of Pharmacology, U. of Dundee. Inserm, Domaine de Carreire, Bordeaux, France. Dept of Endocrinology, Center of Excellence on Neurodegenerative Diseases, U. of Milan, Italy. Biological Research Center , Hungary. Institute of Cell Biology, ETH Hönggerberg, Zürich CH-8093, Switzerland.

- In Alzheimer's patients, there was a general trend toward lower levels of neurosteroids in different brain regions, and neurosteroid which were negatively correlated with phosphorylated Tau Protein and the β-amyloid peptides.
- The greatest loss of pregnenolone-s, progesterone-s, allopregnanolone-s, and DHEA-s occured in the Frontal Lobes.

The Neurosteroid Allopregnanolone Is Reduced in Prefrontal Cortex in Alzheimer's Disease

. Biological Psychiatry. Volume 60, Issue 12. Dec **2006**. Christine E. Marxx Christine E. Marx. Department of Psychiatry and Behavioral Sciences, Durham, North Carolina

- Neurosteroid levels (allopregnanolone, pregnenolone, dehydroepiandrosterone) were determined in postmortem prefrontal cortex (PFC) in subjects with AD and 15 cognitively intact male control subjects.
- Subjects with AD demonstrate significant reductions in PFC allopregnanolone levels, a finding that is relevant to neuropathological disease stage severity.

A new strategy in treatment of neurodegenerative diseases: Neurosteroids.

Ankara Üniv Vet Fak Derg, 60, 79-83, 2013. Gül Fatma YARIM Ondokuz. Ondokuz Mayıs Üniversitesi, Veteriner Fakültesi, Biyokimya Anabilim Dalı, Samsun.

- A large number of studies support the neurosteroids have neuroprotective, myelinating, anti-apoptotic and anti-inflammatory effects.
- Combined administration of 17β-estradiol and progesterone have been demonstrated to protect the brain from demyelination and stimulate remyelination.

17b-Estradiol protects against NMDA-induced excitotoxicity by direct inhibition of NMDA receptors. Brain Research 761 1997 338–341 Ž. Charles E. Weaver Jr., Mijeong Park-Chung, Terrell T. Gibbs, David H. Farb. Lab of Molecular Neurobiology, Dept of Pharmacology and Experimental Therapeutics, BU School of Medicine, Boston, MA 02118-2394, USA

- In a non-neuropermissive environment disruption of the regulation of glutamate, glycine (or serine), magnesium, sodium, calcium and potassium can lead to excitotoxicity and the loss of neuronal integrity.
- Physiologic levels of 17β Estradiol, during traumatic events, can protect the vulnerability of these Glutamate sub-receptors – the NMDAR, from developing a state of excitotoxicity associated with neuronal death.

ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury. Annals of Emergency Medicine, **2006**.07.932.Wright DW et al.

- Mortality was decreased by 50% in the Progesterone treated group although by 30 days the neurological outcome was the same as in the placebo group.
- On the Glasgow Outcome Score-Extended scale, 55.6% of patients who received progesterone and who had moderate initial brain injury had moderate to good scores at 30 days, compared with none of the placebo patients.

A Clinical Trial of Progesterone for Severe Traumatic Brain Injury. N Engl J Med 2014; 371:2467-2476, December 25, 2014 Brett E. Skolnick, Ph.D., Andrew I. Maas, M.D., Ph.D., Raj K. Narayan, M.D., Roland Gerritsen van der Hoop, M.D., Ph.D., Thomas MacAllister, Ph.D., John D. Ward, M.D., Neta R. Nelson, M.P.H., and Nino Stocchetti, M.D., for the SYNAPSE Trial Investigators. ProTECT III

- Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI.
- These data stand in contrast to the robust preclinical data and results of early single-center trials that provided the impetus to initiate phase 3 trials.

Suboptimal dosing parameters as possible factors in the negative Phase III clinical trials of progesterone for TBI.

Randy B. Howard1, Iqbal Sayeed, Donald G. Stein.
Randy B. Howard, Ph.D., Pharmacology Consultant, Drug Discovery and Development. Former Head of Pharmacology, Emory Institute for Drug Development, Emory University, Atlanta, Georgia.

- Although the Neurosteroid progesterone showed considerable preclinical efficacy as a neuroprotective agent in the treatment of TBI, and despite two moderately encouraging Phase 2 clinical reports, two similarly designed Phase 3 TBI clinical trials recently resulted in negative outcomes.
- Authors of this study believes that the dose used was insufficient to impact the outcome and therefore, the "failure".

Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury

. Brain Research 1049 (2005) 112 – 119. Edward H. Pettus, David W. Wright, Donald G. Steina, Stuart W. Hoffmana, Dept of Emergency Medicine, Emory University, Evans Building, Room 255, 1648 Pierce Dr NE, Atlanta, GA 30322, USA. Dept of Cell Biology, Emory University, Atlanta, GA 30322, USA

- The initial biomechanical force in TBI causes ionic imbalances, oxidative damage, microglial activation, immune cell invasion, and cytokine release.
- Activation of immune cells, triggers the production of free radicals and pro-inflammatory compounds such as cytokines, prostaglandins, proteases, complement factors, adhesion molecules, and inducible nitric oxide synthase.
- Research has shown that progesterone treatment given after TBI can reduce edema, necrosis, apoptosis, blood–brain barrier compromise, and the mediators of inflammation.

Anti-Pituitary Antibodies after traumatic brain injury: is head trauma-induced pituitary dysfunction associated with autoimmunity? European Journal of Endocrinology (2008) 159 7–13. Fatih Tanriverdi, et al. Dept of Endocrinology, Erciyes University Medical School, Kayseri, Turkey, Second University of Naples, Via S. Pansini, Naples, Italy, Dept of Neurosurgery, Erciyes University Medical School, Kayseri, Turkey and Dept of Medicine School of Medicine and Complejo Hospitalario Universitario de Santiago, Santiago de Compostela University, Santiago de Compostela, Spain.

- This is an initial study that shows the presence of the Anti-Pituitary Ab (APA) in TBI patients 3 years after head trauma.
- This investigation indicates that APA may be associated with the development of TBI-induced pituitary dysfunction.

Anti-Hypothalamus and Anti-Pituitary antibodies may contribute to perpetuate the hypopituitarism in patients with Sheehan's Syndrome.

European Journal of Endocrinology (2008) 158 147–152. Annamaria De Bellis, et al. Chair of Endocrinology, Dept of Clinical and Experimental Medicine and Surgery 'F. Magrassi, A. Lanzara', Second University of Naples, via Pansini N. 5, 80131 Napoli, Italy, Dept of Endocrinology and Metabolism, Erciyes University Medical School, Kayseri, Turkey, Chair of Surgery and Chair of Immunology, Dept of Clinical and Experimental Medicine and Surgery 'F. Magrassi, A. Lanzara', Second University of Naples, Naples, Italy

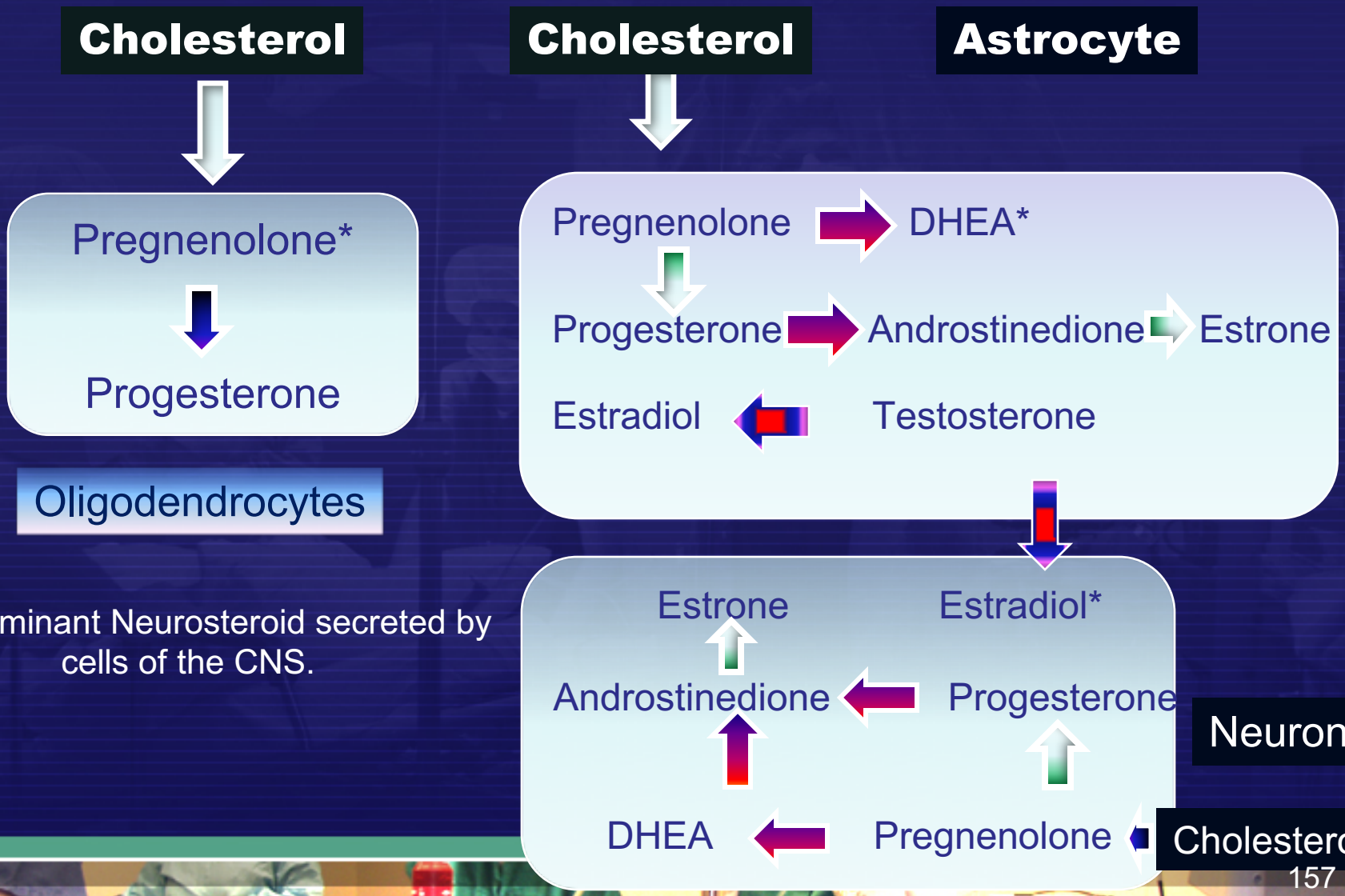
- Hypopituitarism caused by pituitary necrosis can be precipitated by severe hypotension secondary to massive bleeding with arrest of blood flow to the anterior pituitary gland due to vasospasm, thrombosis, or vascular compression.
- Subsequently, some SS patients were found to have both APA and AHA.

Astrocytes and Neurosteroids: Metabolism of Pregnenolone and Dehydroepiandrosterone. Regulation by Cell Density The Journal of Cell Biology, Volume 121, Number 1, April 1993 135-143 Yvette Akwa, Nicole Sanan~s, Monique Gou6zou, Paul Robel, Etienne-Emile Baulieu, and Claude Le Goascogne. INSERM U33, Lab Hormones, 94276 Bicetre Cedlex, France

- It was reported that Pregnenolone can be converted to Progesterone in glial cells, but mostly in oligodendrocytes.
- Thereafter, progesterone converts to allopregnanolone with neuroprotective and neuroregenerative effects.
- Astrocytes, which participate in the regulation of the CNS function, appear to also be involved in the metabolism of neurosteroids.
- It appears that the regional loss of Glia is proportionate to the loss of NeuroSteroids.

Neurosteroidogenesis in Oligodendrocytes, Astrocytes, and Neurons of cerebral cortex of rat brain.

Endocrinology 1999. Aug;140(8):3843-52.
Zwain IH, Yen SS.



* Predominant Neurosteroid secreted by cells of the CNS.

Summary

- Replenishment of the Neuro-Active Steroids will provide a gross benefit to the patient's suffering from the sequelae of Traumatic Brain Injury while;
- application of Neuro-Steroids will help to fine-tune the patient's recovery from many of the neuropsychological aberrations that occur secondary to altered neuronal transmissions and connectivity.

Therefore, we need to:

- **"Fill all the tires…. not just the ones in front."**

Primary Topics

- Laboratory Science
- The Paradigm in Result Interpretations (with cases)
  - Anterior Pituitary Hormones (trophic hormones) and their target hormones.
  - Posterior Pituitary Hormones

LC/MS/MS/MS

- HP – High Performance
- LC - Liquid Chromatography
- MS - Mass Spectroscopy (Parent)
- MS - Mass Spectroscopy (1st sub)
- MS - Mass Spectroscopy (2nd sub)

LC-MS/MS in the Clinical Laboratory – Where to From Here?

Clin Biochem Rev Vol 32 February 2011. **Stefan KG Grebe1, and Ravinder J Singh** Depts of Laboratory Medicine & Pathology and Medicine, Mayo Clinic Rochester, Minnesota 55905, USA

- Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has seen enormous growth in clinical laboratories during the last 10–15 years.
- It offers analytical specificity superior to that of immunoassays or conventional high performance/pressure liquid chromatography (HPLC) for low molecular weight analytes and has higher throughput than gas chromatography-mass spectrometry (GC-MS).
- In USA reference/referral laboratories, most steroids and biogenic amines are now assayed by LC-MS/MS, and the technology has started to penetrate into smaller laboratories.

Our TBI Panel 3426

Panel	Hormones	Abbreviation
✓	Growth Hormone	GH
✓	Insulin-like growth factor-1	IGF-1
✓	Insulin-like growth factor binding protein – 3	IGFBP-3
✓	Dehydroepiandrosterone-sulfate	DHEA-s
✓	Total Testosterone	T(T)
✓	Free Testosterone	F(T)
✓	Dihydrotestosterone	DHT
✓	Sex Hormone Binding Globulin	SHBG
✓	Estradiol	E2
✓	Estrone	E1
✓	Progesterone	PROG
✓	Pregnenolone	PREG
✓	Follicle Stimulating Hormone	FSH
✓	Luteinizing Hormone	LH
✓	Thyrotrophic Stimulating Hormone	TSH
✓	Tetraiodothyronine – Free	fT4
✓	Triiodothyronine – Free	fT3
✓	Reverse Triiodothyronine	rT3
✓	Triiodothyronine/ Reverse Triiodothyronine Ratio	T3/rT3 Ratio
✓	Cortisol	COR
✓	Adrenocorticotropic Hormone	ACTH
✓	Prolactin	Pro
✓	Vitamin D	Vit D
✓	Insulin	INS

Table 6.2: This is the panel that is being used by the Millennium Health Centers to assess both neurosteroids and neuroactive steroids.

Some theory of reference values. I. Stratified (categorized) normal ranges and a method for following an individual's clinical laboratory values. Clinical Chemistry, Vol. 21, No. 10, **1975**

- "The conventional population-based normal range has recently been shown to be a generally defective reference criterion for assessing individual laboratory test results".
- "The appropriateness of the population-based normal range as a reference for interpreting an individual measurement depends on the ratio of intra- to inter-individual variation in the constituent measured."

Optimal results from Median

Median – Low range plus the high range divided by 2.

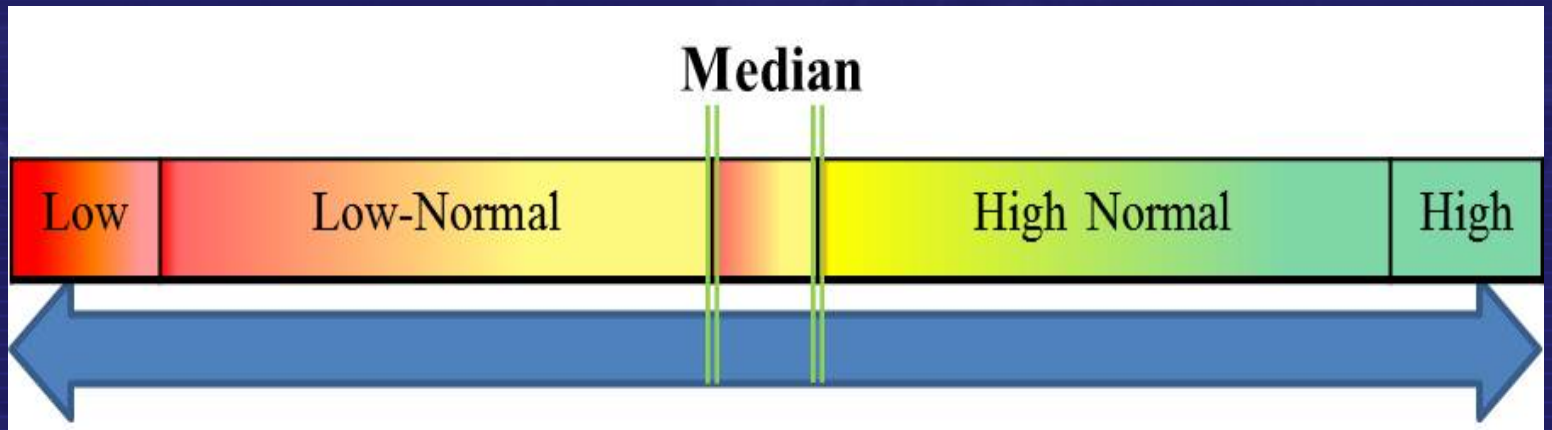


Figure 6.1 Optimal results with optimal treatment. Using treatment protocols to achieve a homeostatic balance so that each hormone hovers around its median range. Although this might be viewed as arbitrary, the concept of Homeostasis, a dynamic process, would place each hormone with points of its median if the net affect of both positive and negative feedback signaling was equal.

The Paradigm Shift

- Re-thinking how we have used laboratory results.
- Treat the numbers or the patient?
- What are the **Standards of Care**? Conform or re-establish the philosophy behind changing how to interpret the lab results.
- Are we treating or being just palliative?

Millennium-TBI Median Ranges

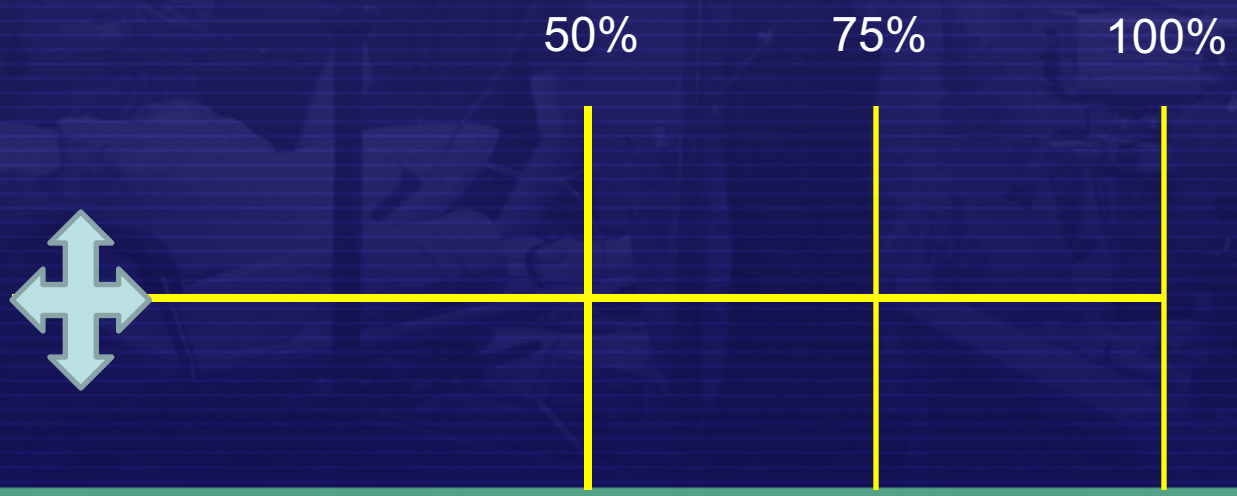
Hormone	Median M	Median F	Hormone	Median M	Median F
DHEA-s	200 ug/dL	277 ug/dL	Growth Hormone	5.0 ng/ml	5.0 ng/ml
T-Testosterone	690 ng/ml	44 ng/ml	IGF-1	>200 ng/ml	>200 ng/ml
F-Testosterone	14 pg/ml	2-4 pg/ml	IGFBP-3	4000 ng/ml	4000 ng/ml
DHT	< 52 ng/dl	< 30 ng/ml	TSH	2.5 mcu/ml	2.5 mcu/ml
SHBG	45 pg/ml	<75 ng/dl	fT4	1.5 ng/ml	1.5 ng/ml
Estrone	< 60 pg/ml	< 200 pg/ml	fT3	250 ng/dL	250ng/dL
Estradiol	<25 pg/ml	90 pg/ml	rT3	165 ng/dL	165 ng/dL
Progesterone	0.8 ng/ml	5-7 ng/ml	fT3/rT3 Ratio	> 1.06	> 1.06
Pregnenolone	210 ng/dl	210 ng/dl	TPO	< 35 IU/ml	< 35 IU/ml
Vitamin D3	> 60 ng/dl	> 60 ng/dl	ACTH (am)	< 35 pg/ml	< 35 pg/ml
LH	5.1 mIU/ml	22 mIU/ml	Cortisol (am)	< 15 ug/dl	< 15 ug/dl
FSH	7.0 mIU/ml	8.6 mIU/ml	Cortisol (pm)	7.3 Ug/dl	7.3 Ug/dl
Prolactin	11.25 ng/ml	13.75 ng/ml	Insulin	< 25 IU/L	< 25 IU/L

Table 6.1: These are the median "normal" blood result from Access Medical Laboratories of Florida that we use to guide our interpretations. Please note that female hormone results need to be correlated to the on-set of their menses if still cycling. Otherwise, the numbers used here are for peri- and post-menopausal women.

For certain hormone results below the median is optimal, i.e., estrogen in males and DHT levels in females.

Improved patient outcome

- Using the patients baseline results as a starting point we raise the levels of the insufficient hormones to between the 50th and 75th percentile of the range.
- It is an imperative that we always maintain physiological levels of all hormones.

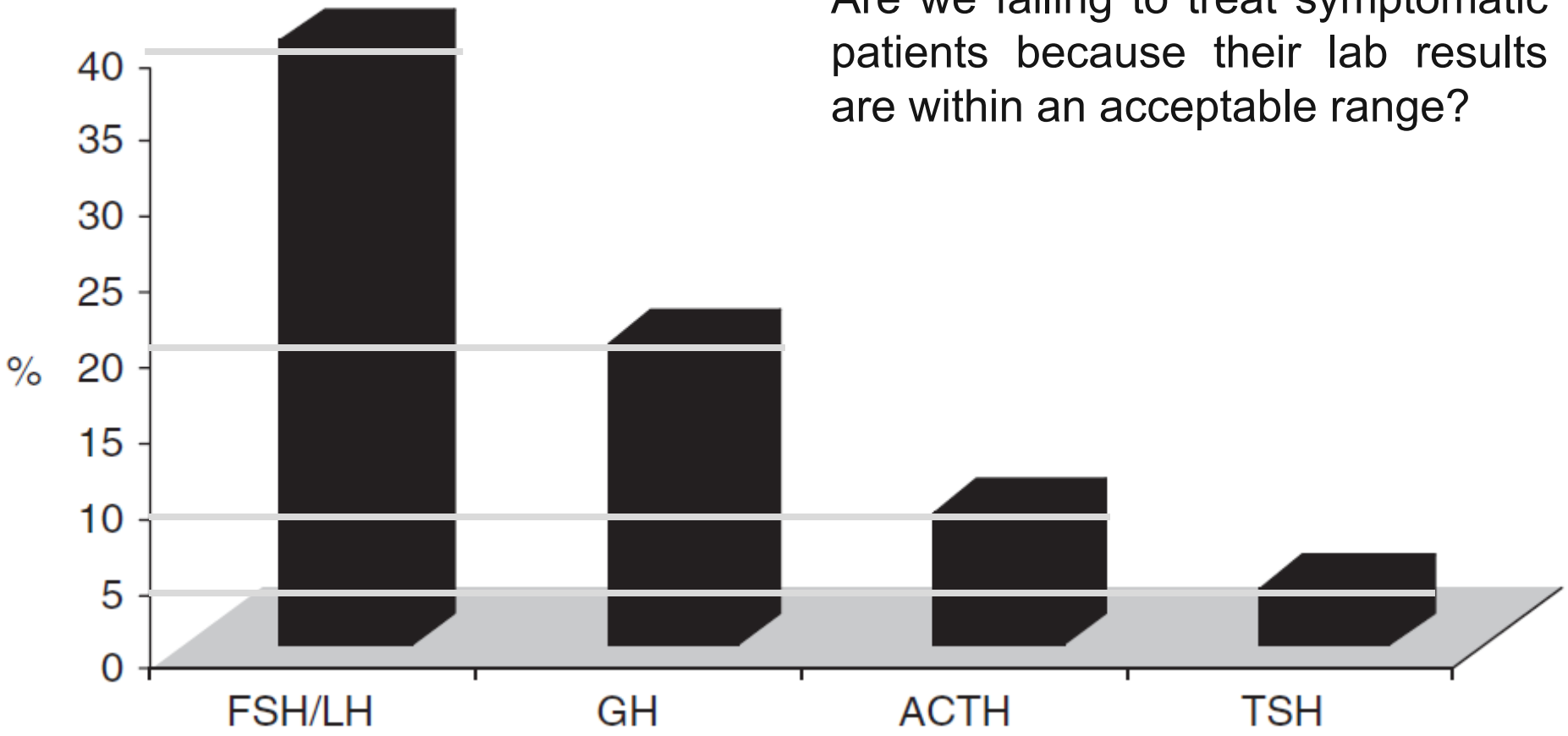


Pituitary functions in the acute phase of traumatic brain injury: Are they related to severity of the injury or mortality?

Brain Injury, April 2007; 21(4): 433–439

Faith Tanriverdi, Halil Ulutabanca, Kursad Unluhizarci, Ahmet Selcuklu, Felipe F. Casanueva, Fahrettin Kelestimur, Depts of Endocrinology, Neurosurgery, Erciyes University Medical School, Kayseri, Turkey, and Dept of Medicine. School of Medicine and Complejo Hospitalario Universitario de Santiago, Santiago de Compostela University, Santiago de Compostela, Spain

Are we failing to treat symptomatic patients because their lab results are within an acceptable range?



Growth Hormone

- The bulk of GH is produced between 8pm and 4am making it a difficult single sample to determine a patients production status.
- In the morning, the level of GH is usually on the low end of normal due to the rapid decay of the hormone (20min t1/2 free and 30min bound to GH-BP)
- Therefore, a 24hr urine sample is the better means of testing production levels.

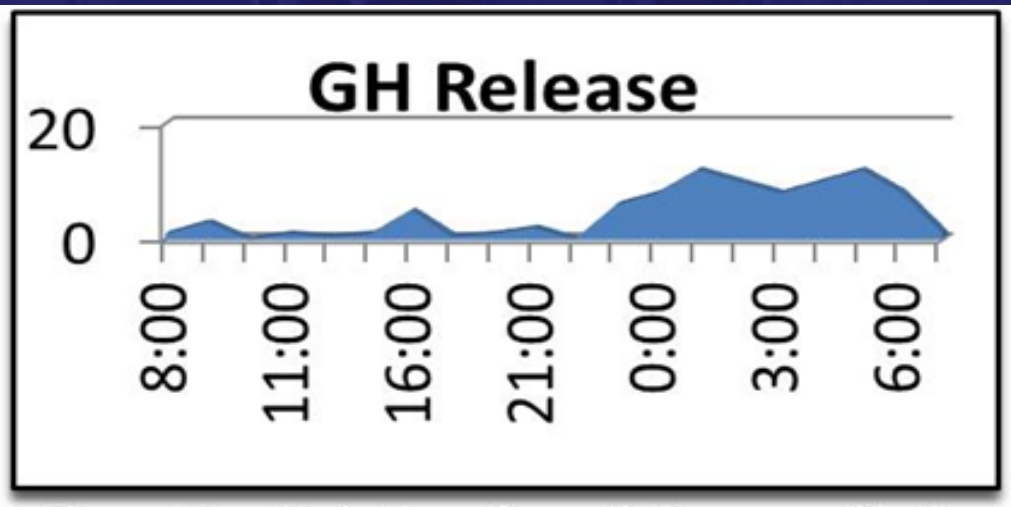
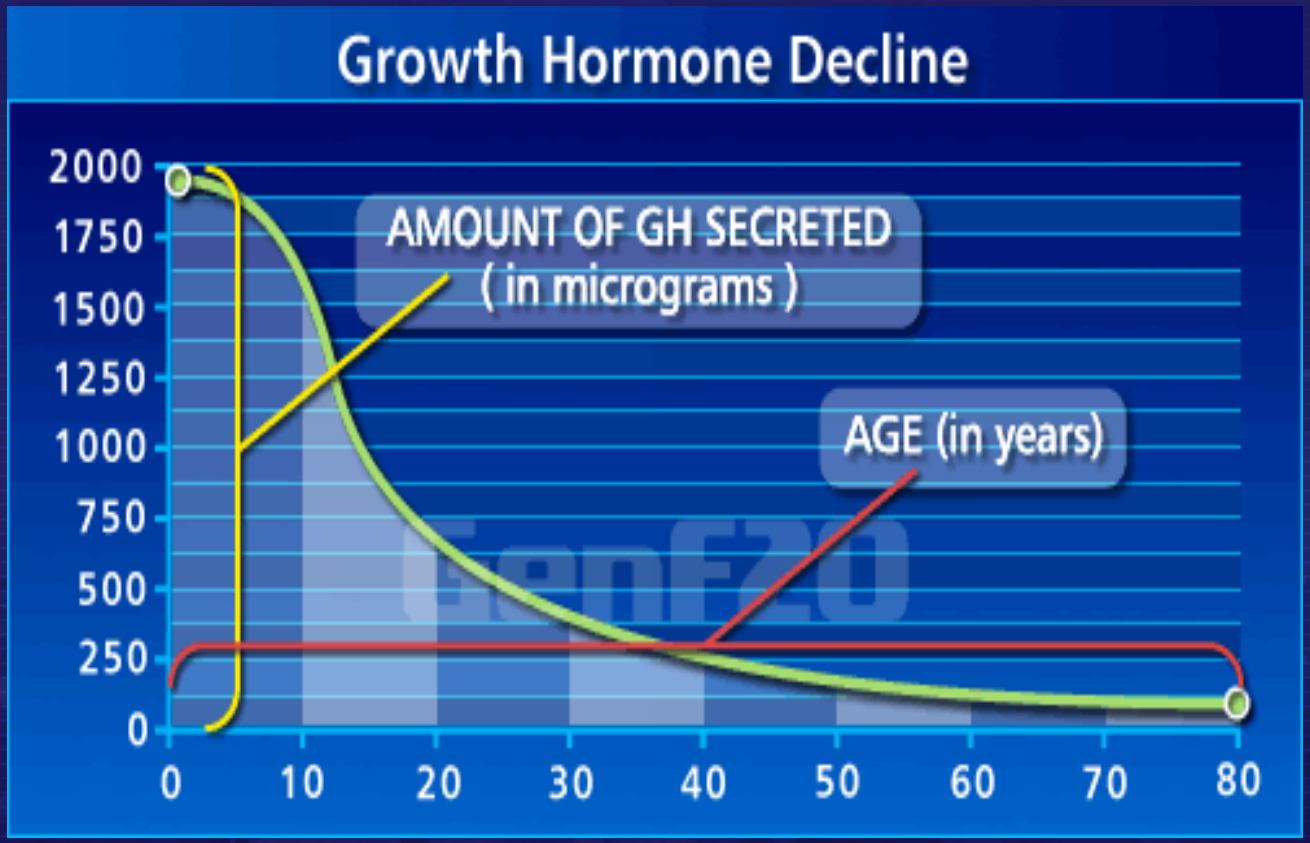


Figure 6.1: Production of growth hormone with the majority of GH released from 8pm to 4am with minor pulses throughout the day.

The GH Decline Curve.



Approximately 14% decrease per decade after 20 years.

Growth Hormone - GH

- **Reference range**: < 10 ng/ml
- **Median** = 5 ng/ml

- Therefore, it is anticipated that a patient's serum results will always be below the median when blood is drawn in the morning or early afternoon.
- This therefore, makes the use of GH as a random, single determinant blood test unreliable.

Growth Hormone - GH

Growth Hormone stimulates a number of peripheral tissues but the liver appears to be the major site of activity in producing:

- IGF-I – Primary
- IGF-II – Primary during inter-utero development.
- BP1 – 6 (six important IGF-I & IGF-II carriers)
- ALS – Acid Labile Subunit (a carrier)

Insulin-like Growth Factor-1

- **Reference range**: age determinant
- **Median** > 200 ng/ml

- As a free hormone IGF-1 has an 8-10 minute half-life.
- When bound to IGFBP-3 it has a 20-24 hour half-life.
- Present laboratory testing measures the total amount of IGF-1 in the serum, both free and bound.

IGF-Binding Factor-3

- **Reference range**: 1600 – 6500 ug/ml
- **Median** > 4050 ug/ml

- Growth hormone stimulates the liver to produce IGFBP-3. A logarithmic relationship exists between nocturnal production of GH and the level of IGFBP-3.
- Quercetin, Estradiol and Retinoic Acid can increase the production of BP-3 as well as damage to the liver can decrease the production of both IGF-1 and IGFBP-3.

IGFBP-1 to IGFBP-6

Primary Functions	
BP-1	IGFBP-1 has been proposed as an acute regulator of IGF-I bioactivity. Low circulating levels of IGFBP-1 are associated with well-known risk factors of cardiovascular disease.
BP-2	IGFBP-2 preventing adipogenesis and improved insulin sensitivity.
BP-3	IGFBP-3 has strong anti-cancer benefits in the nucleus.
BP-4	IGFBP-4 has strong anti-Colon Cancer, apoptotic affects.
BP-5	IGFBP-5 levels decrease with age and is a key component of the IGF-system in bone. Thus, it is the predominant IGFBP form stored in bone, where it is bound with high affinity to hydroxyapatite and extracellular matrix proteins. (bone healing effects of IGF1-BP5)
BP-6	Predominantly found in serum and cerebrospinal fluid IGFBP-6 having a higher affinity for IGF-II than IGF-I. IGFII-BP6 has been shown to be **neuroprotective and promote neurogenesis**.

Case 1a

- Male, 40yrs. MVA with LOC. GCS 13. 6 months post-TBI.

Growth Hormone	0.03 ng/ml	<5 ng/ml
IGF-1	203 ng/ml	>200 ng/ml
IGFBP-3	4100 ng/ml	4000 ng/ml

This patient is 6 months post-TBI and has borderline levels of IGF-1 and BP-3. In the study by Schneider (2006), it was noted that only GH continued to decline over the initial year post-TBI. Therefore, this patient should be monitored for a continued decrease in GH production.

Case 1b

- Female, 54yrs. MVA without LOC. 3 years post-TBI.

Growth Hormone	0.27 ng/ml	<5 ng/ml
IGF-1	111 ng/ml	>200 ng/ml
IGFBP-3	2700 ng/ml	>4000 ng/ml

This patient is 3 years post TBI and has low levels of IGF-1 and BP-3. Either an initial trial of secretagogue or a Glucagon Stimulation Test (GST) would be advised.

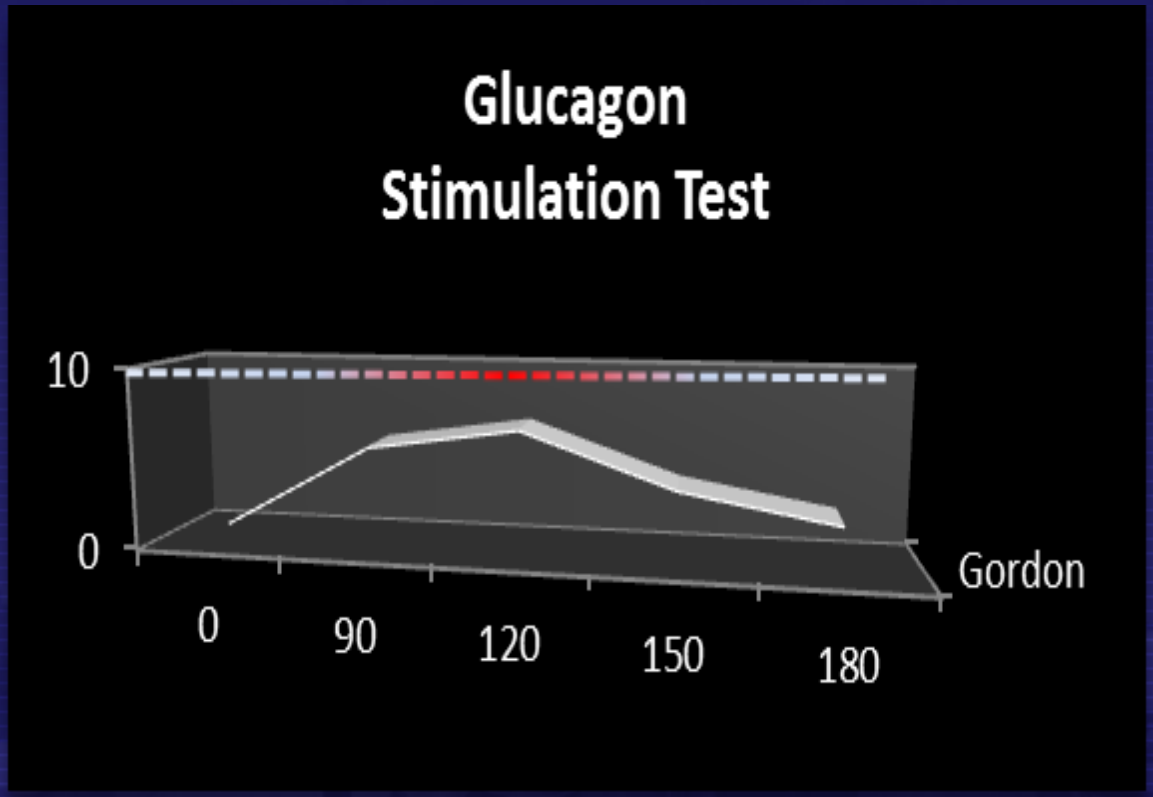
Case 1c

- Male, 66yrs. Slip and fall with LOC. 9 years Post-TBI.

Growth Hormone	0.09 ng/ml	<5 ng/ml
IGF-1	87 ng/ml	>200 ng/ml
IGFBP-3	1845 ng/ml	>4000 ng/ml

This patient has a significant deficiency of the GH/IGF-1 system. At this patients age there is significant elevated risk of cardiovascular disease, depression, and cognition problems.

Case 1 c2



Time	GH
Minutes	mU/l
0	0.05
90	4.95
120	5.37
150	2.33
180	.54

A subnormal GH response indicating GH deficiency is defined as a peak of less than 9mU/l (3ug/l); the Growth Hormone Research Society 1998.

Case 1e

- Male, 54yrs, MCA with coma for 3 weeks. Awakes with anosmia and hypogeusia.

Growth Hormone	15.4 ng/ml	5 ng/ml
IGF-1	539 ng/ml	>200 ng/ml
IGFBP-3	7467 ng/ml	4000 ng/ml

Hypothalamic dysregulation of GH via damage to the Paraventricular nucleus where Somatostatin is produced. Other considerations: Pituitary Adenoma and supplementation with rhGH.

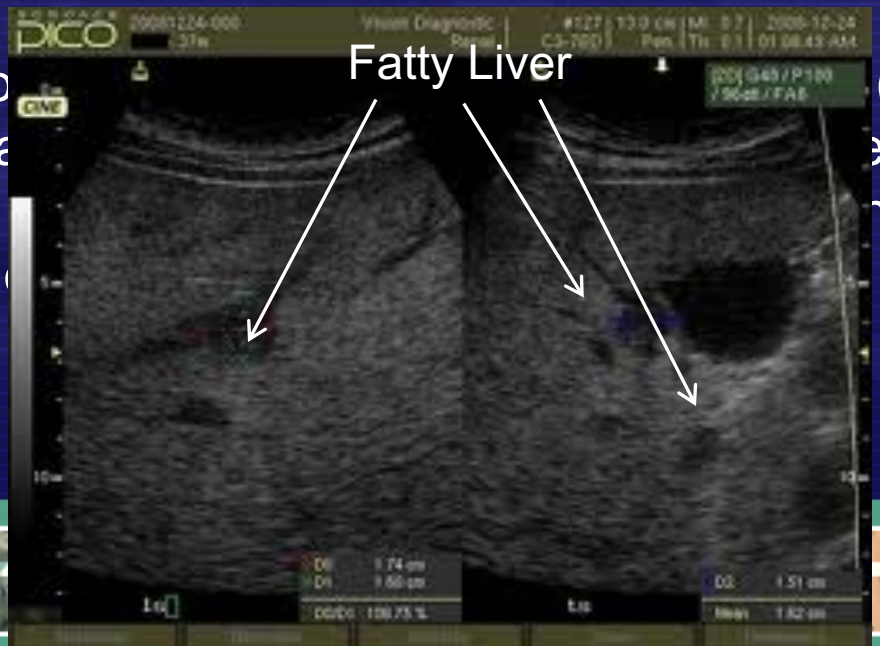
Case 1f

- Female, 57yrs, Head-on MVA with coma for 15 days. Seen at 18 months.

Growth Hormone	0.44 ng/ml	5 ng/ml
IGF-1	139 ng/ml	> 200ng/ml
IGFBP-3	4867 ng/ml	> 4000 ng/ml

GH is at a relatively normal morning level, but the IGF-1 is below 200 ng/ml.

The BP-3 is abo **(1)** that during the night an ample a e liver's production of BP-3, **(2)** that high estrogen level or (4) inflammati

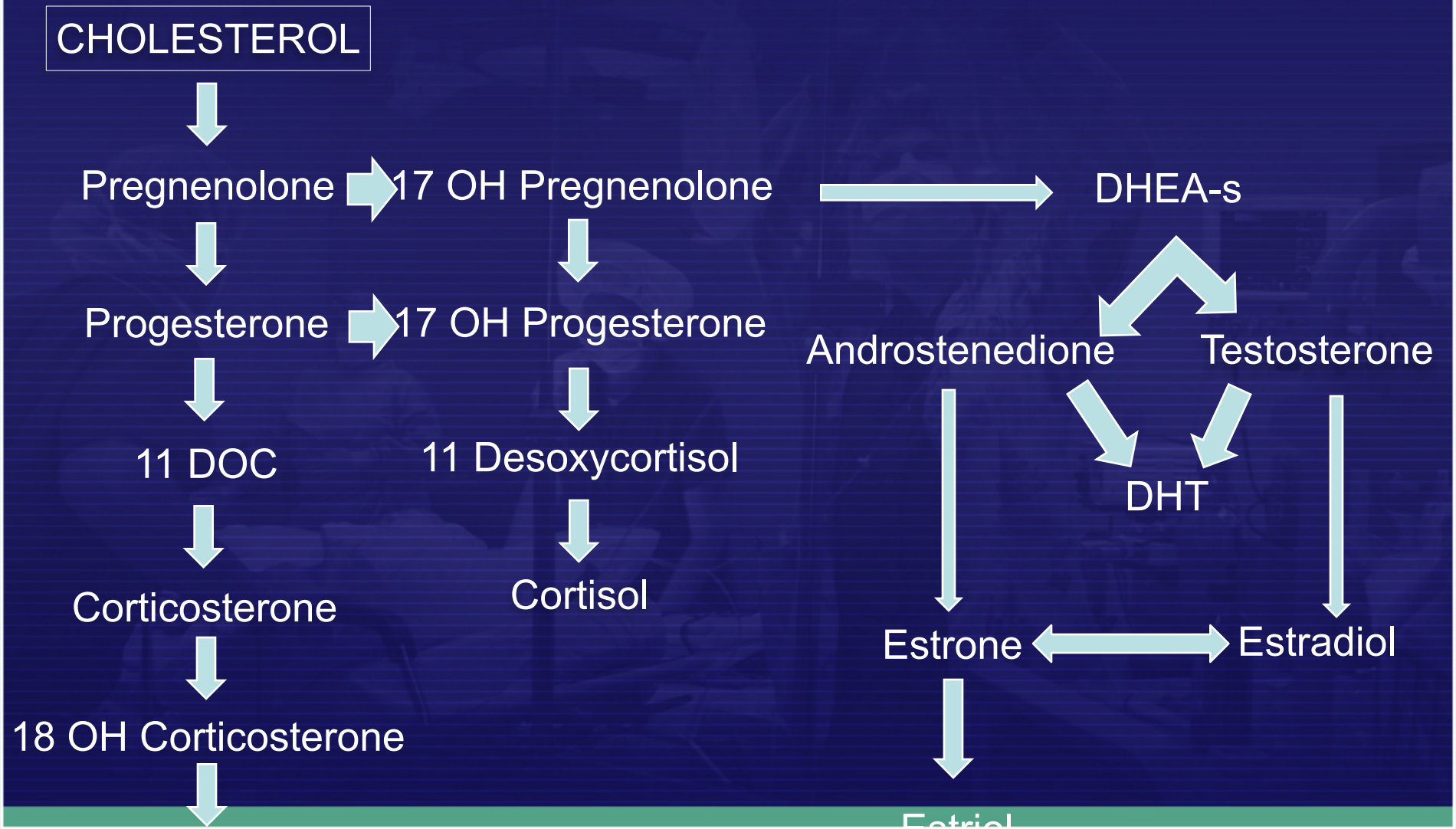


Testosterone

Nine (9) parameters of the Testosterone system :

1. Dehydroepiandrosterone-sulfate
2. Total Testosterone
3. Free Testosterone
4. Dihydrotestosterone
5. Sex Hormone Binding Globulin
6. Estradiol
7. Estrone
8. Luteinizing Hormone
9. Follicular Stimulating Hormone

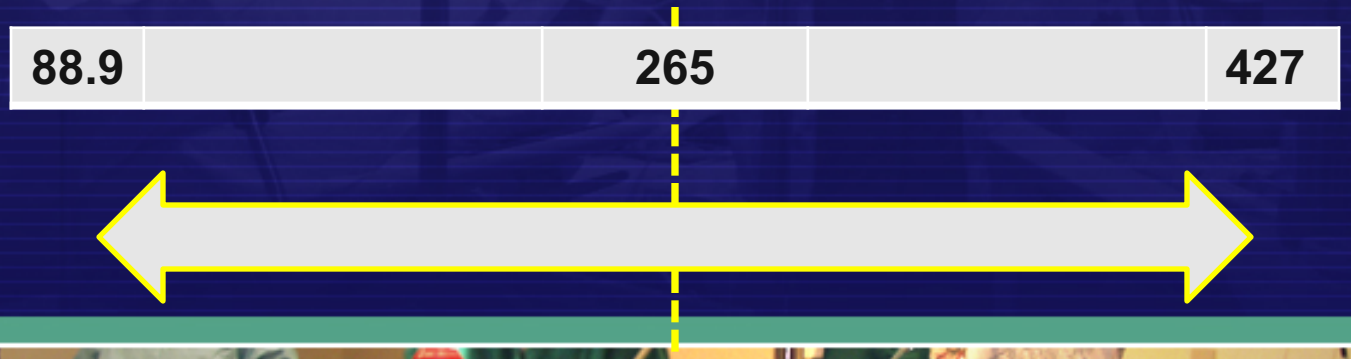
Hormone Cascade



Dehydroepiandrosterone

- Reference Ranges: 250 ng/dl (M) and 18-205ng/dl (F).
- Median: < 250 ng/dl (M) and 115 ng/dl (F).

- DHEA is sulfated to DHEA-s, the active form of DHEA.
- Produced in the Brain, Adrenals, and Gonads.



Total Testosterone

- **Reference Range**:
- **Median: 690ng/ml (M) and 44ng/ml (F)**

- The total testosterone, like total cholesterol, is a composite number of different forms of testosterone; SHBG-(T), Albumin-(T), TG-(T), and Epitestosterone[1].
- Approximately 60 to 70% binds to SHBG, 30 to 40% with albumin, and only about 2% circulates in the free form.
- Overall, TT is a poor marker for the ability of (T) to get into the brain or tissues and cells.

1. **Epitestosterone** is a natural steroid, an inactive epimer of the hormone testosterone.

Free Testosterone

- Reference Range: 1.9 -27ng/dl.
- Median: Male 12-14 ng/ml; Female 2-4ng/ml.

❖ Free Testosterone is the pre-active form of testosterone that passes the BBB and enters peripheral tissues and cells through the AR receptors and the SHBG-(fT) receptors.

DiHydroTestosterone

- Reference Ranges: 11-95ng/dl (M) and <30ng/dl (F).
- Median: < 53 ng/dl (M) and <30 ng/dl (F).

- DHT is believed to be the active form of Testosterone.
- (T) is converted by 5-α Reductase[1,2] to DHT[1,2].
- Elevated levels of DHT in the blood cause oily skin, acne, enlargement of prostate, and testicular atrophy.
- Does not cross the BBB, but is made in the brain.
- 5-α Reductase inhibitors pass the BBB and cause depression, fatigue, and sexual dysfunction. *Finasteride and Dutasteride*.

Sex Hormone Binding Globulin

- Reference Range: Male 1.9 -27ng/dl. Female 20-130 ng/ml
- Median: Male 45 pg/ml; Female 75 ng/ml.

- The primary ligand carrier protein for Testosterone and Estrogen.
- Elevated levels will bind the free hormones (Testosterone).
- Once thought to inactivate the hormone when bound, has now been found that the SHBG-Hormone has a specific cell wall receptor that functions similar to the Androgen Receptor.

Sex Hormone Binding Globulin

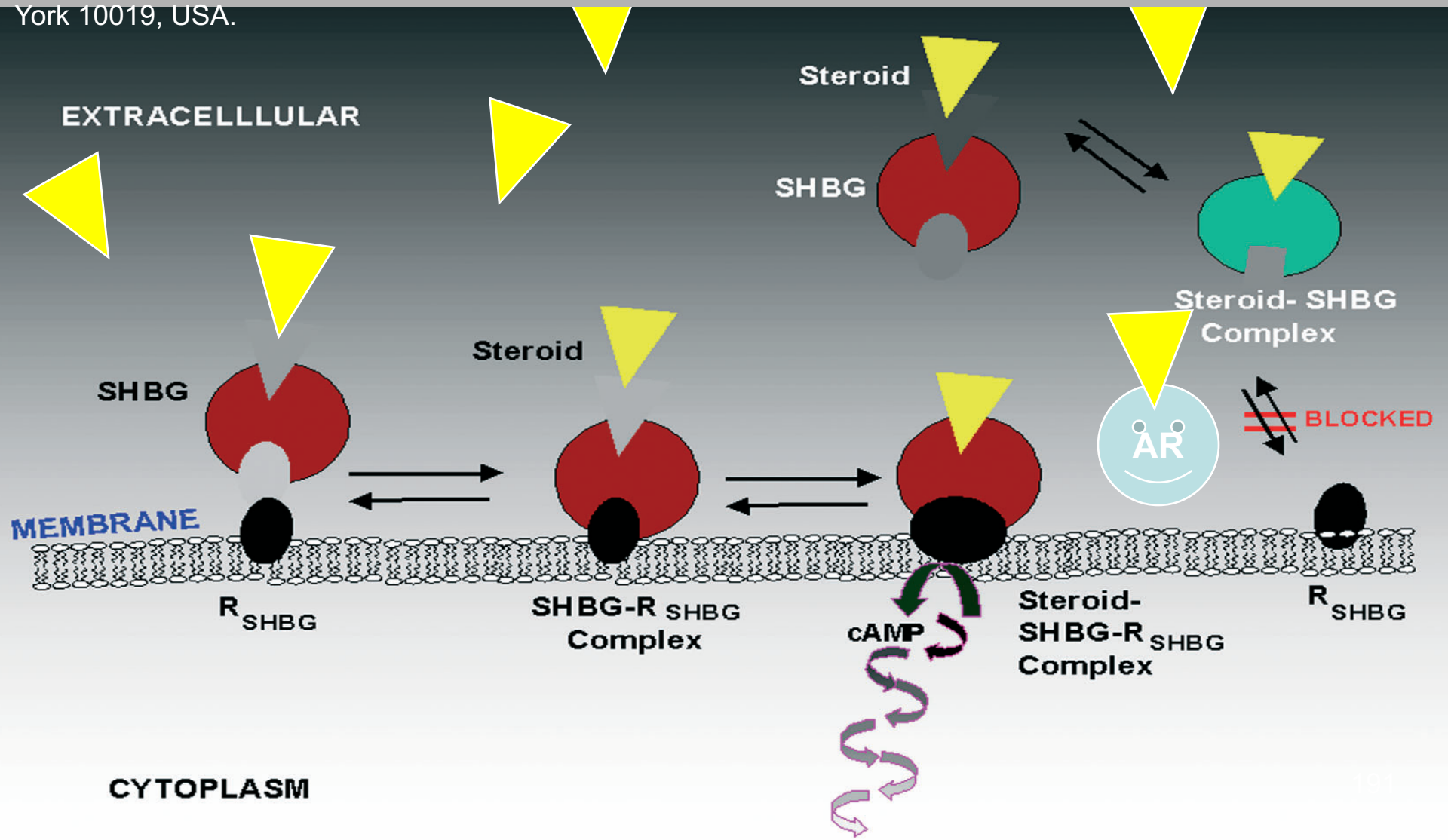
Table 2. Conditions and Medications Associated With Alterations in SHBG*[4]

Conditions That Decrease SHBG and Lower Total T Level	Conditions That Increase SHBG and Raise Total T Level
Moderate obesity	**Aging**
Nephrotic syndrome	**Hepatitis, hepatic cirrhosis**
Hypothyroidism	Hyperthyroidism
Acromegaly	HIV disease
Medications That Decrease SHBG and Lower Total T Level	**Medications That Increase SHBG and Raise Total T Level**
Androgens	Anticonvulsants
Anabolic steroids	Estrogens
Glucocorticoids	
Progestins	

*Conditions in bold print are particularly common conditions that are associated with alterations in SHBG levels.
SHBG = sex hormone–binding globulin, T = testosterone.

BEYOND CARRIER PROTEINS; Sex hormone-binding globulin is synthesized in target cells.

Journal of Endocrinology (2002) **175,** 113–120 . **S M Kahn, D J Hryb, A M Nakhla, N A Romas** and **W Rosner.** Dept of Medicine, St Luke's/Roosevelt Hospital Center, and College of Physicians and Surgeons, Columbia University, New York, New York 10019, USA. Dept of Urology, St Luke's/Roosevelt Hospital Center, and College of Physicians and Surgeons, Columbia University, New York, New York 10019, USA.



Luteinizing Hormone

- **Reference Range**: 0.7 to 8.6mIU/ml (M). In females the range can be 2.4-12.6 in Follicular phase, 14-95.6 in Ovulation phase, **1.0 – 11.4 in Luteal phase** and 7.7 – 58.5 in Post-menopausal phase. Ideal timing for female blood draw is day 21 or Luteal Phase.
- **Median**: 5.1 mIU/ml (M) and in females the median must be established for each phase of the menstrual history.

❖ When LH is below the median it means that the target hormones that regulate LH (estrogen and testosterone) are at their peak causing negative feedback.

❖ Otherwise, it LH is below the median and the target hormone is low, there is damage to the Hypothalamic-Pituitary Axis.

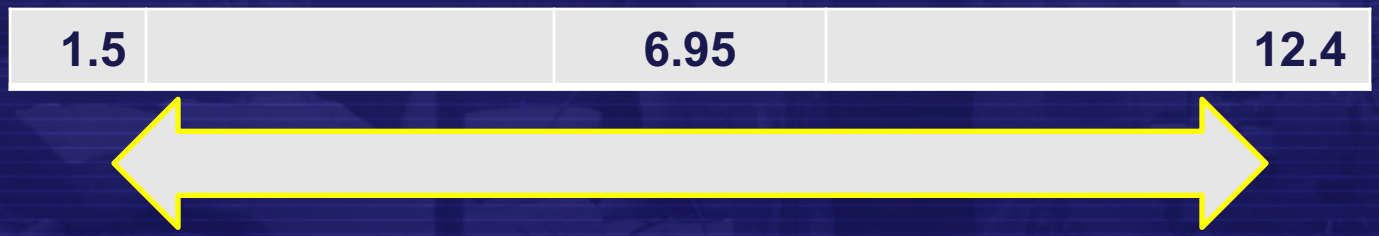
Luteinizing Hormone

- **Article**

- **Article**

Follicle Stimulating Hormone

- Reference range: 1.5 to 12.4mIU/ML (M). Female 3.5-12.5 in Follicular phase, 4.7-21.5 in Ovulation phase, 1.7 – 7.7 in Luteal phase, and 25.8 to 134.8 in the Post-menopausal phase.
- Median: 6.95mIU/ml (M) 4.7mIU/ml (F)

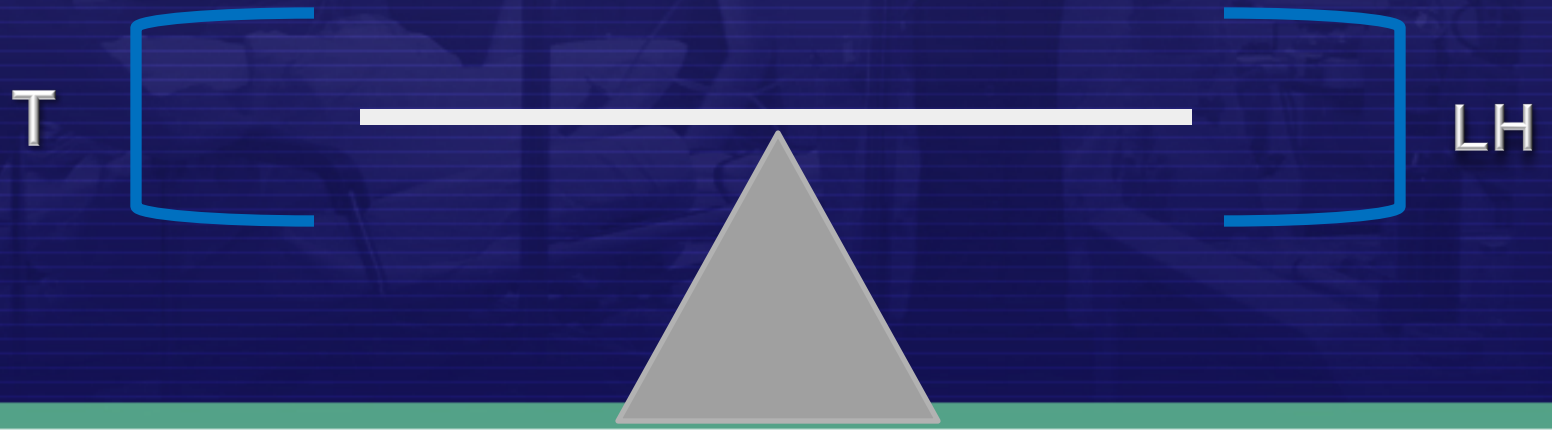


Testosterone Summary-1

Testosterone	LH/FSH	Comment
▲	▼	This pattern can represent either a natural endogenous production of testosterone or a reflection of exogenous supplementation.
▼	▲	This is most likely Primary Testicular or Ovarian failure.
▼	▼	This is the classical pattern seen in Central Hypogonadism as well as in a patient with hyperprolactinemia where LH is shut down causing a drop in Testosterone production. The hint is lactation.

Testosterone Summary-2

- In an ideal Testosterone production scenario; if a perfect equilibrium existed between the negative and positive feedback loops, then Luteinizing Hormone (LH) would be at the median of the range.
- Sufficient amounts of testosterone suppress LH below the Median while insufficient amounts of Testosterone cause LH to be above the Median.



Case 2a

- Male, 40yrs. MVA with LOC. GCS 13. 22 months later.

- The important Free-Testosterone and Total Testosterone are below the medians with a non-reactive LH.
- This is the classical Central Hypogonadism picture.
- Testosterone replacement is required here.
- Also, the low DHEA-s needs to be increased for additional protection of neuronal myelin and cardiovascular protection from Ischemic Heart Disease.

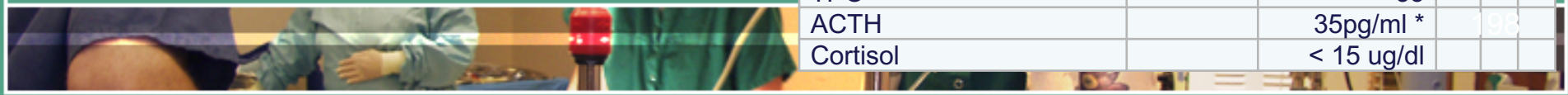
Male Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	23 L	245 ug/dl*
Estrone (E1)	2.37 N	< 60 pg/ml*
Estradiol (E2)	5.60 N	<25 pg/ml*
Progesterone	0.65 LN	0.8 ng/ml*
Pregnenolone	27 LN	110 ng/dl*
EP Ratio		< 250
Testosterone Free	3.45 L	12-14 pg/ml*
Testosterone Total	193 L	<690 ng/ml*
Dihydrotestosterone (DHT)	22 N	< 55 ng/Dl*
Sex Hormone Binding Gb	14 N	< 75 pg/ml*
FSH	1.20 L	7 mIU/ml*
LH	0.70 L	5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc	67 LN	95 mcg/dL*
Insulin	78.6 H	< 30mIU/L
Vitamin D3	23 L	>60 ng/dl*
TSH		<2.5 mcu/ml*
T3, Free		> 2.5 pg/ml
T4, Free		> 1.5 ng/ml
rT3		80-250 pg/ml
T3/rT3 Ratio		>1.06
TPO		<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl

Case 2b

- Female, 54yrs. MVA with impact of air bag causing facial trauma. No LOC but dazed and confused. LNMP age 51.

Primary Ovarian Failure with an EP Ratio of 733 (elevated).

Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	135	195 ug/dl*
Estrone (E1)	17	< 200 pg/ml*
Estradiol (E2)	5	90 pg/ml*
Progesterone	0.03	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio	733	< 250
Testosterone Free	0.05	2-4 pg/ml*
Testosterone Total	13	<44 ng/ml*
Dihydrotestosterone (DHT)	12	< 30 ng/Dl*
Sex Hormone Binding Gb	27	< 75 pg/ml*
FSH	39	7 mIU/ml*
LH	17	5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc		95 mcg/dL*
Insulin		< 30mIU/L
Vitamin D3		>60 ng/dl*
TSH		<2.5 mcu/ml*
T3, Free		> 2.5 pg/ml
T4, Free		> 1.5 ng/ml
rT3		80-250 pg/ml
T3/rT3 Ratio		>1.06
TPO		<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl



Case 2c

- Male, 66yrs. Slip and Fall, no LOC. Laceration to left temporal skull. GCS 15

Tests	Results	Median
DHEA-s	225 ug/dl	245 ug/dL
Testosterone Total	367 ng/dl	690 ng/ml
Testosterone Free	5.85 ng/dl	14 pg/ml
DHT	42 ng/dl	30 ng/dL
LH	9.7 mIU/ml	5.1 mIU/ml
FSH	3.2 mIU/ml	7.0 mIU/ml

Either due to this injury or just an accumulation of life's traumas to the HP Axis, this Male appears to have a partial primary hypogonadism with elevated LH and low-normal testosterone.

Case 2d

- Male, 38 yrs. MCA with LOC, GCS 12.
- What is the patient on and what problem do you see?

DHEA-s	67 ug/dl	245 ug/dL
Testosterone Total	578 ng/dl	690 ng/ml
Testosterone Free	12.35 ng/dl	14 pg/ml
DHT	132 ng/dl	30 ng/dL
LH	<1.0 mIU/ml	5.1 mIU/ml
FSH	<1.0 mIU/ml	7.0 mIU/ml

The patient is on a topical Testosterone product that is converting rapidly to DHT causing depression of DHEA-s, LH and FSH. If you looked further you might find Erythrocytosis and PSA elevation.

Estrogens

- Measuring both Estrone (E1) and Estradiol (E2) with progesterone (PROG) will allow for the calculation of the EP Ratio.
- Estrogen Dominance as a co-morbid factor to TBI can cause greater disturbance in neurochemistry especially with GABA.

Estrone (E1)

- DHEA is metabolize down three pathways:
  1. DHEA to Androstenedione then Estrone (E1).
  2. DHEA to Testosterone and then Estradiol (E2).
  3. DHEA to the active form DHEA-s.
- Estrone and Estradiol are converted back and forth through a sulfinated intermediary.
- Levels of E1 and E2 are regulated by the presence of enzymes and the feedback loops.
- HRT with primary and secondary prohormones (DHEA, Testosterone, and so forth) can influence the enzymatic pathways causing imbalances.

Estrone (E1)

- Reference range: **Males**: < 60pg/ml **Females**: < 40 pg/ml
- Median: Male <30pg/ml Female: < 20pg/ml

Comment: If E1 is elevated causing the EP Ratio to be elevated. Using 7-Keto DHEA will decrease it.

Estradiol (E2)

- E2 is a direct metabolite of Testosterone and represents the most active form of Estrogen.
- Extremely important in both central and peripheral biochemical processes it is important to maintain a balance between this group of hormones (Estrogens) and all the others.
- Supplementing with Estradiol can lead to a decrease in production of Testosterone, DHEA, Progesterone, Cortisol, and Pregnenolone with a transient increase in Cholesterol.
- Therefore, an important hormone to monitor with any protocols of HRT.

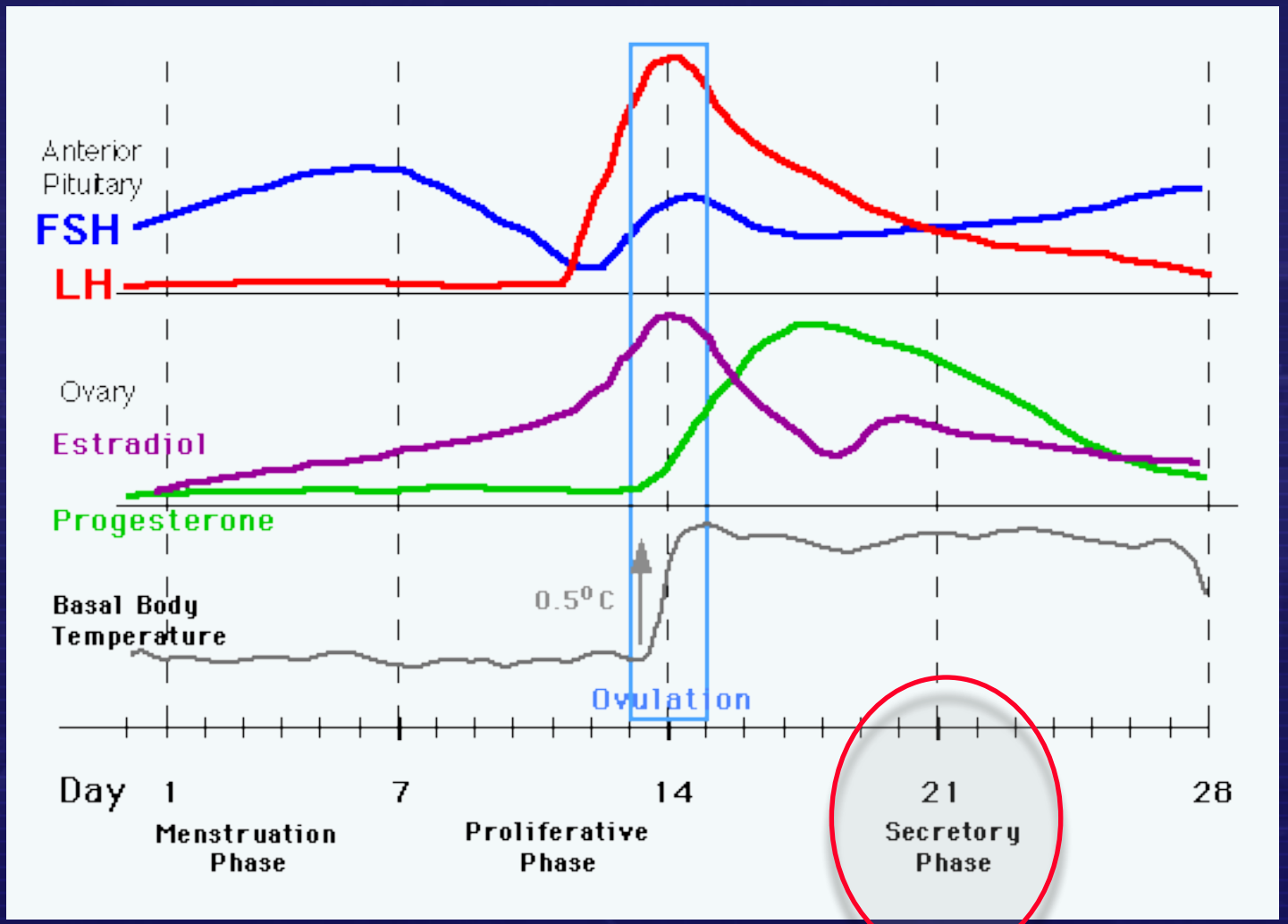
Estradiol (E2)

- Reference Range: **Males**: 7.6-42.6 pg/ml. **Females**: Follicular phase 12.5-166 pg/ml, Ovulation phase 85.8-498 pg/ml, Luteal phase 43.8 – 211 pg/ml, *Postmenopausal <5.0 – 54.7 pg/ml.*
- Median Range: **Males**: <25pm/ml
- Median Range: **Females**: Luteal phase 127.4 pg/ml
- Median Range: **Post menopausal women**: <90pg/ml with adjustment for any symptoms. EP Ratio must be maintained below 250.

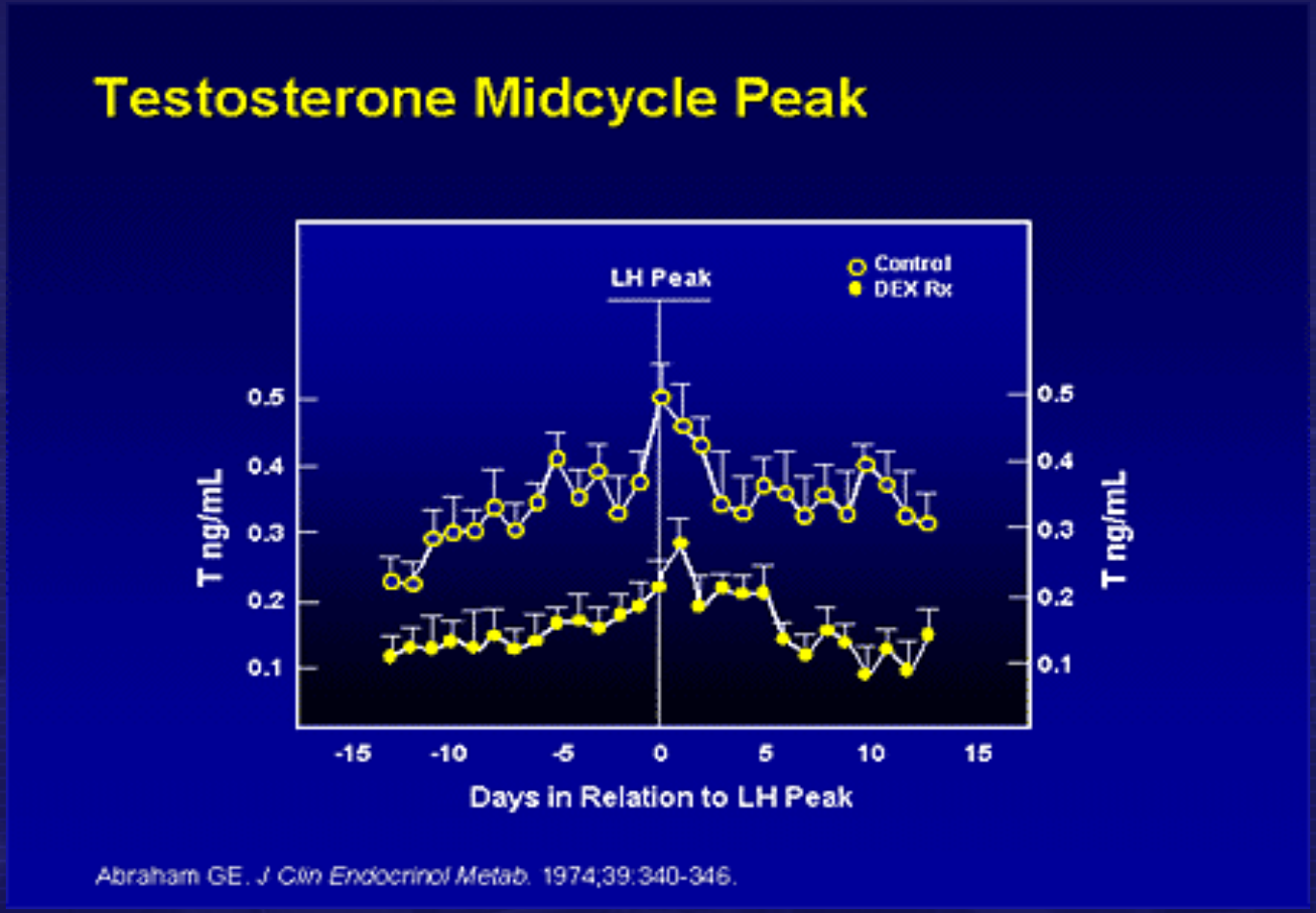
Summary for Estrogens

- Optimal time to perform lab testing is day 21, but as you become more adept at the female menstrual cycle you'll be able to use any day and interrelate all of the hormones into an understandable picture.

Standard Menstrual Cycle Chart



LH-Testosterone Spikes



The Mid-cycle spike of Testosterone correlates with ovulation.

Pregnenolone

- Reference range: **Males**: 205 ng/dl **Females**: 31-98 ng/dl
- Median: Male < 110 ng/ml Female: 64.5ng/dl

❖ Pregnenolone (PREG) is one of the most important rate limiting precursor hormones made from Cholesterol. It is the "Mother of all Hormones" for its production of Pregnenolone, Progesterone, Cortisol, Cortisone, DHEA, DHT,

WARNING: The use of Estrogen in women or Testosterone in Men without supplementation of Pregnenolone will lead to Deficiency within 4-6 months with symptoms.

❖ Additionally, pregnenolone produces Allopregnenolone which is neuroprotective as an anti-oxidant and neuroregenerative hormone.

❖ Patients with Alzheimer's disease have a deficiency of ALLO, in the frontal lobes (executive functions).

Progesterone

- Reference Ranges: Male 0.85 ng/ml Females: Follicular phase 0.2-1.5 ng/ml, Ovulation phase 0.8-3.0 ng/ml, Luteal phase 1.7-27.0 ng/ml, postmenopausal 0.1-0.8 ng/ml.
- Median Range: Male: 0.85 ng/ml
- Median Range: Female Luteal phase 14.35 ng/ml
- Median Range: Postmenopausal Varied but .6-.8 ng/ml

- Primarily in vivo, evidence that Progesterone can play an important role in promoting and enhancing repair after traumatic brain injury and stroke.

The Estrogen-Progesterone Ratio

- The EP Ratio is a measurement of **Estrogen Dominance**. The Millennium HC has been studying this relationship since 2005 looking at this ratio as it pertains to the psychological, physiological, and physical well-being of its female patients.
- In symptomatic, peri- and post-menopausal women; a ratio above 250, is associated with symptoms and a decrease in quality of life issues.
- In symptomatic women less than 40 yrs of age this ratio coincidentally corresponds to an elevation in the EP Ratio usually above 1000!

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The EP Ratio Formula

(Estrone + Estradiol) / Progesterone = 250 or less.

(E1 + E2)/PROG = < 250

e.g., E1 of 254ng/ml. E2 of 113ng/ml. Prog of 0.23ng/ml

(254 + 113)/0.23 = **1595**

EP Ratio Symptoms

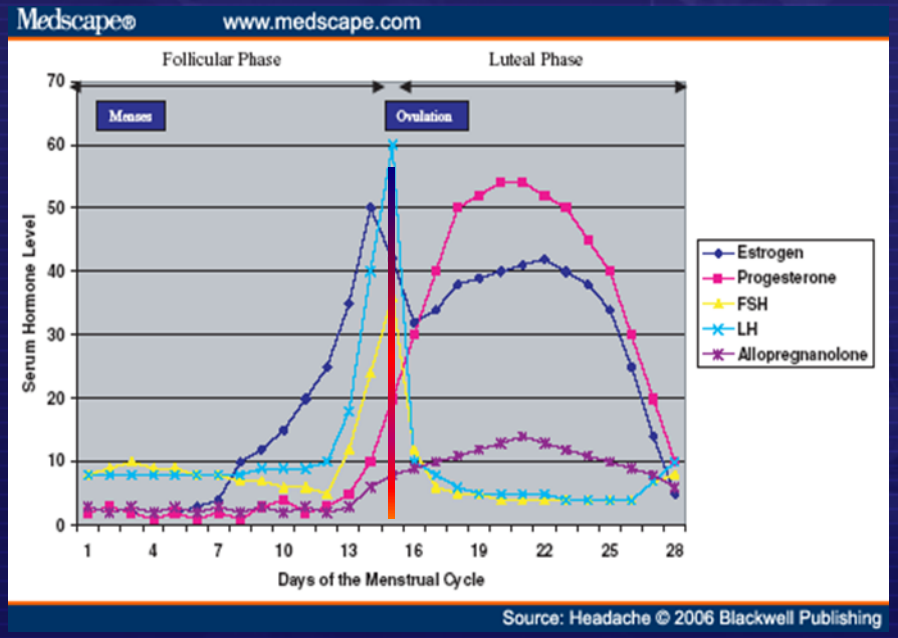
Symptoms	< 250	250- 1000	1000-5000	> 5000
Head Aches/ Migraines	Intermittent	Mild	Moderate	Severe
Sleep Issues	Intermittent	Mild	Moderate	Severe
Sleep Deprivation	NP	Intermittent	Mild	Moderate
Bloating	NP	NP	Mild	Moderate
Mood Swings/Irritability	NP	Mild	Moderate	Severe
Anxiety	NP	Intermittent	Mild	Severe
Depression	NP	Intermittent	Mild	Severe
Panic Attacks	NP	Intermittent	Mild	Severe
Mastalgia	Intermittent	Mild	Severe	Severe

The Millennium Health Group started looking at the relationship between estrogens and progesterone in 2005 based upon the recognition that those female patients that had symptoms were on an Estrogen-Only replacement regimen as provided by their HCP. Knowing the relationship between progesterone and GABA(up-regulation) and the opposite affect estrogen (down-regulation), it became clear that there must be an ideal ratio between E1 & E2 and Progesterone.

Case 3a – Where is she in her menstrual cycle?

Ovulatory Phase

Because: **FSH, LH-Testosterone, Estrogen-Progesterone**

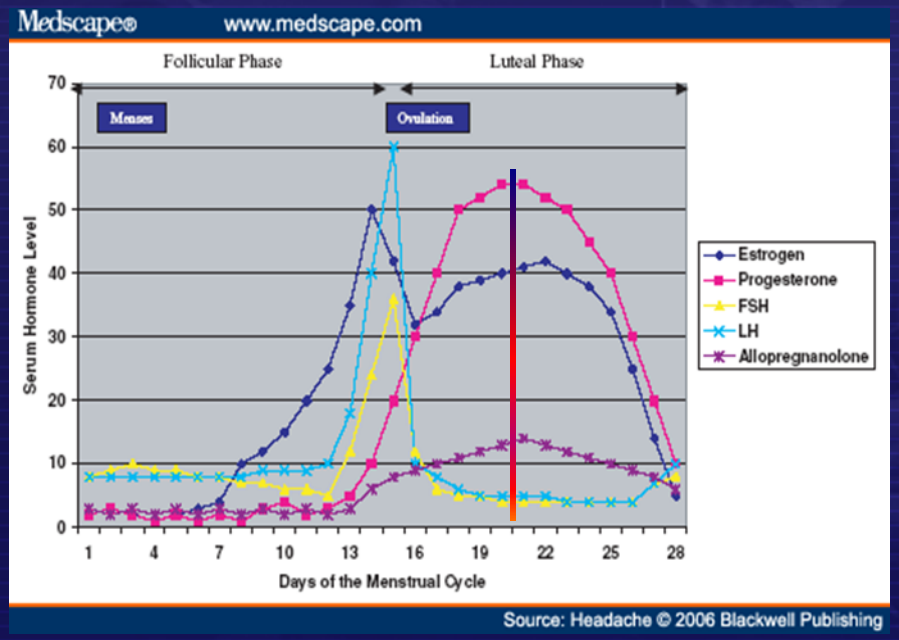


Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	143 L	195 ug/dl*
Estrone (E1)*	36 N	< 200 pg/ml*
Estradiol (E2)*	187.3 HN	90 pg/ml*
Progesterone*	1.17 LN	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio*	190 N	< 250
Testosterone Free*	2.54 N	2-4 pg/ml*
Testosterone Total	13 N	<44 ng/ml*
Dihydrotestosterone (DHT)	22 N	< 30 ng/Dl*
Sex Hormone Binding Gb	103 HN	< 75 pg/ml*
FSH*	11.2 H	7 mIU/ml*
LH*	15.7 H	5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc		95 mcg/dL*
Insulin		< 30mIU/L
Vitamin D3		>60 ng/dl*
TSH		<2.5 mcu/ml*
T3, Free		> 2.5 pg/ml
T4, Free		> 1.5 ng/ml
rT3		80-250 pg/ml
T3/rT3 Ratio		>1.06
TPO		<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl

Case 3b – Where is she in her menstrual cycle?

Luteal Phase

Because: **FSH, LH-Testosterone, Estrogen-Progesterone**



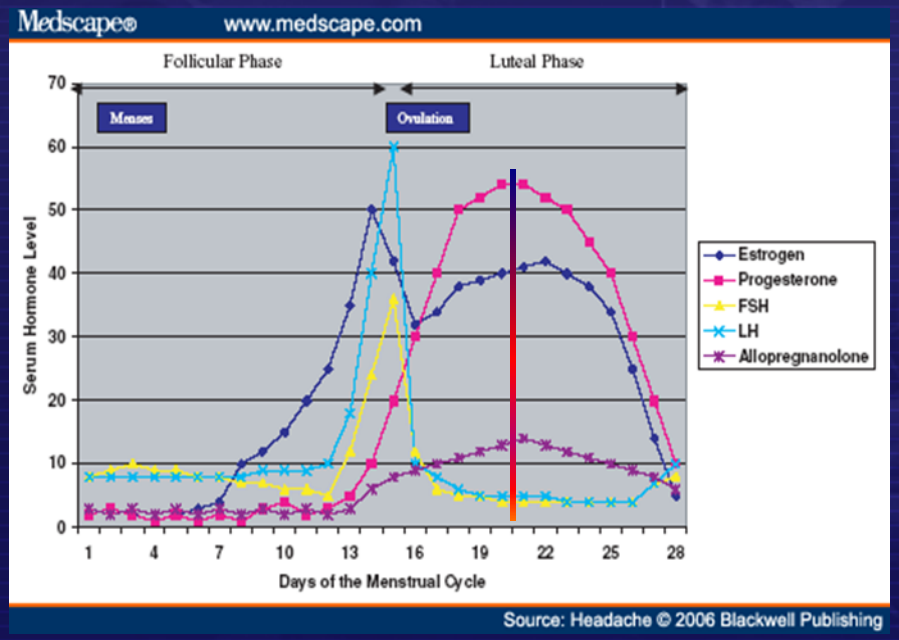
Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	121 LN	195 ug/dl*
Estrone (E1)*	8 N	< 200 pg/ml*
Estradiol (E2)*	68 LN	90 pg/ml*
Progesterone*	9.7 HN	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio*	6.6 N	< 250
Testosterone Free*	0.18 LN	2-4 pg/ml*
Testosterone Total	11 N	<44 ng/ml*
Dihydrotestosterone (DHT)	16 N	< 30 ng/Dl*
Sex Hormone Binding Gb	58 N	< 75 pg/ml*
FSH*	4.2 LN	7 mIU/ml*
LH*	7.4 HN	5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc		95 mcg/dL*
Insulin		< 30mIU/L
Vitamin D3		>60 ng/dl*
TSH		<2.5 mcu/ml*
T3, Free		> 2.5 pg/ml
T4, Free		> 1.5 ng/ml
rT3		80-250 pg/ml
T3/rT3 Ratio		>1.06
TPO		<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl

Case 3c

23 y/o female. Head aches, abdominal bloating 7-10 days prior to menses, fatigues, dulling, emotional volatility. On-set of menstruation and her symptoms improve over 24 hours.

Estrogen Dominance.

- 100mg of Progesterone on days 15-25 of her cycle resolved the problems.



Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	223 HN	195 ug/dl*
Estrone (E1)*	243 HN	< 200 pg/ml*
Estradiol (E2)*	167.3 HN	90 pg/ml*
Progesterone*	0.07 LN	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio*	5861 H	< 250
Testosterone Free*	0.45 LN	2-4 pg/ml*
Testosterone Total	13 N	<44 ng/ml*
Dihydrotestosterone (DHT)	22 N	< 30 ng/Dl*
Sex Hormone Binding Gb		< 75 pg/ml*
FSH*	7.2 N	7 mIU/ml*
LH*	4.7 LN	5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc		95 mcg/dL*
Insulin		< 30mIU/L
Vitamin D3		>60 ng/dl*
TSH		<2.5 mcu/ml*
T3, Free		> 2.5 pg/ml
T4, Free		> 1.5 ng/ml
rT3		80-250 pg/ml
T3/rT3 Ratio		>1.06
TPO		<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl

Vitamin D (25-OH, Total)

- Vitamin D3: > 60ng/ml to optimize benefits

Relative Vitamin D Insufficiency in Hashimoto's Thyroiditis. Thyroid. Volume: 21 Issue 8: August 2, 2011Gonca Tamer, M.D. Department of Endocrinology and Metabolism Goztepe Education and Research HospitalTellikavak sok. No. 8, A blok, D:24. Istanbul 34738. Turkey

- Vitamin D insufficiency, defined as serum levels of 25-hydroxyvitamin D lower than 30 ng/mL, has been reported to be prevalent in several autoimmune diseases such as multiple sclerosis and type 1 diabetes mellitus.
- Vitamin D insufficiency is associated with HT. Further studies are needed to determine whether vitamin D insufficiency is a casual factor in the pathogenesis of HT or rather a consequence of the disease.

Thyroid Hormones

- Both peripheral and central conditions of Thyroid hormone production are commonly missed due to the belief that the TSH (Thyroid Stimulating Hormone) Test is sufficient.
- Unfortunately, we have found that there is a need for a comprehensive evaluation of the HPT (Hypothalamic-Pituitary-Thyroid Axis) to avoid missing many of the conditions that are now being addressed like:

I. Subclinical Hypothyroidism

Aspects	T4	T3
Potency	1x	10x
Protein Bound	10-20d	1d
Half-Life	5-7 days	< 24 hrs.
Secretion	100 ug/d	6 ug/d

Relationship between thyroid function and ICU mortality: a prospective observation study

. Critical Care 2012, 16: R11. Feilong Wang, Wenzhi Pan, Hairong Wang, Shuyun Wang, Shuming Pan and Junbo Ge. Dept of Emergency, Xinhua Hospital of Shanghai Jiaotong, No. 1665, Kongjiang Road, Shanghai, 200092, China. Dept of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital of Fudan U., No. 180, Fenglin Road, Shanghai, 200032, China

Table 3

Univariate odds ratios of variables for predicting ICU mortality[a]

Predictor	Standard β value	OR	95% CI	*P* value
TT3	-0.953	0.386	0.2889 to 0.516	< 0.001
TT4	-0.699	0.497	0.387 to 0.637	< 0.001
FT3	-1.129	0.323	0.239 to 0.436	< 0.001
FT4	-0.425	0.654	0.508 to 0.842	0.001
rT3	0.275	1.316	1.060 to 1.636	0.013
TSH	-0.263	0.769	0.537 to 1.100	0.151
T3/rT3	-0.765	0.465	0.230 to 0.940	0.031
Log(NT-proBNP)	0.930	2.530	1.876 to 3.425	< 0.001
Log(CRP)	0.707	2.028	1.563 to 2.632	< 0.001
APACHE II score	1.355	3.877	2.869 to 5.237	< 0.001

[a]APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CRP, C-r

Order of importance: FT3-TT3-T3/rT3 Ratio – T4.

Thyroid Stimulating Hormone

- Reference range: 0.5 – 4.5 mIU/ml
- Median: 2.5 mIU/ml

- Above the median, the hypothalamus has sensed that serum T4 is not optimal and attempts to increase it.
- Below the median it means that there is an adequate or even excessive amount of T4 in the circulation except when there is a central hypothyroidism (or GH deficiency).
- This can be confirmed with findings of below the median levels of T4 and/or T3.

Free T4

- Reference range: 0.9 – 1.7 ng/dl
- Median: 1.3 ng/dl

- Tetraiodothyronine (T4) is the major thyroid hormone produced by the thyroid gland under the direction of TSH.
- Under homeostatic regulation the production of T4 represents nearly 90% of thyroid production.
- **When both TSH and T4 are low expect to find a central issue (TSHi will be below 1.3)**

The TSH Index

This has helped me to recognize central vs peripheral thyroid condition:

- **TSH Index = (0.1345*T4) + TSH**
- Range = 1.3 – 4.1
- When it is Below 1.3 it suggests a HP axis issue.
- When above 4.1 it suggests a peripheral issue (Cortisol▲, HMT╬, Selenium ▼, Iodine▼).

Free T3

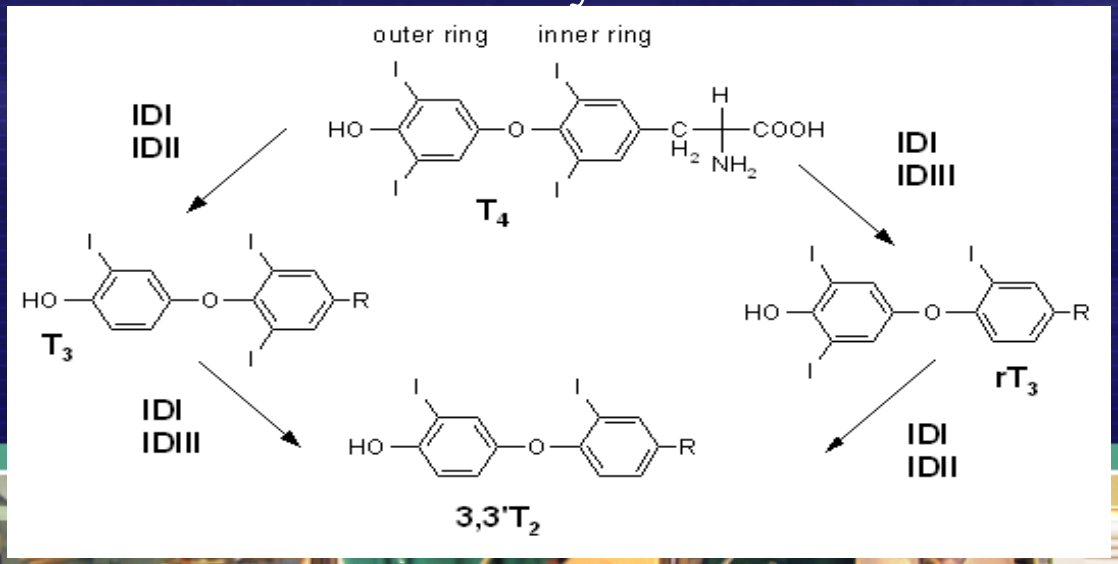
- Reference range: 1.3 – 4.6 pg/ml
- Median: 2.95 pg/ml

- Per Dr. Ronald Swerdloff, UCLA-Harbor General, Director of Endocrinology. The laboratory test called the Free T3 consists of both free T3 and free rT3 it is the Total Free T3 in the serum.
- T3 is the activate form of Thyroid Hormone and is derived from T4 by mono-deiodination at the 5' Iodide site of the outer ring.
- Selenium, zinc, Vit B6 and B12, iron, Vit D and iodine as they are all required by the 5-deiodinase enzyme responsible for proper T3 production from T4.

rT3

- Reference range: 80-250 pg/ml
- Median: 165 pg/ml

- Reverse T3 is derived from the deionization of the inner ring or 5’ iodine.
- rT3 is 3-5’-3’-Triiodothyronine and
- T3 is 3-3’-5’ – Triiodothyronine.



B-12 deficiency
Low Ferritin
Low Iron
High Cortisol

T3/rT3 Ratio

- The T3/rT3 Ratio being > 1.06 assures the patient of an adequate amount of active T3 for intracellular use.
- At below 1.06 it confirms the present of the **Low T3 Syndrome.** **(≥ 2.0 OPTIMAL SO FAR)**
- The abnormal rT3 still can function as a THr-ligand and block the accessibility of the normal and active T3.
- Although the measurement of T3 (Total T3) and or T4 (Total T4) can be normal if the ratio of rT3 is high, therefore causing a low T3/rT3 ratio, the patient will be symptomatic.
- Investigation into the causation for high levels of rT3 is **mandatory** in order to improve upon the patients symptoms and quality of life.

Serum T3 and rT3 Concentration after Surgical Operation. T he Lancet Volume 306, Issue 7948, Dec 1975, W. A. Burra, E. G. Blacka, R. S. Griffithsa, R. Hoffenberga, H. Meinholdb and K. W. Wenzelba Dept of Medicine, University of Birmingham, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom b Klinik für Radiologie, Nuklearmedizin und Physikalische Therapie Klinikum Steglitz, Freie Universität Berlin, Hindenburgdamm 30, 1000, Berlin 45, Germany

- Serum-triiodothyronine (T3) concentrations fell rapidly after surgery in six out of seven initially euthyroid patients.
- Simultaneous increases in reverse triiodothyronine (rT3) concentrations suggested that the peripheral monodeiodination of thyroxine (T4) proceeds by an alternative pathway in the postoperative period.

Let's see; who thinks it might be due to Cortisol elevation??

TPO

- Reference range: < 35 mIU/ml

- Thyroid peroxidase or thyroperoxidase (TPO) is an enzyme expressed mainly in the thyroid that liberates iodine for addition onto tyrosine residues on thyroglobulin for the production of thyroxine (T_4) or triiodothyronine (T_3).
- Thyroid Peroxidase is a marker for Hashimoto's thyroiditis the leading cause of hypothyroidism in the United States.
- 10% of postpartum women develop it as do;
- 25% of Diabetes Mellitus Type I individuals.

Thyroid Hormone Summary

- It is imperative that all new patients be completely assessed as to their levels of all thyroid related chemistry.
- The traditional use of TSH alone or TSH/T4 levels leaves a blind spot in our abilities to better treat the patients.
- Many times the depression associated with TBI is a Thyroid related co-factor with Testosterone. Don't miss the opportunity to make and be the difference.

Case 4a

- Male, 32 yrs. MVA with LOC, GCS 11.

- TSH below 1.0 with both T4 and T3 below the median of the range.
- Elevated rT3 with a T3/rT3 Ratio below 1.06.
- This is the **Low T3 Syndrome** possibly caused by an elevation in cortisol along with pituitary trauma.

TSHi = 0.996 = Central

Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S		195 ug/dl*
Estrone (E1)		< 200 pg/ml*
Estradiol (E2)		90 pg/ml*
Progesterone		5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio		< 250
Testosterone Free		2-4 pg/ml*
Testosterone Total		<44 ng/ml*
Dihydrotestosterone (DHT)		< 30 ng/Dl*
Sex Hormone Binding Gb		< 75 pg/ml*
FSH		7 mIU/ml*
LH		5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc		95 mcg/dL*
Insulin		< 30mIU/L
Vitamin D3		>60 ng/dl*
TSH	**0.875 N**	<2.5 mcu/ml*
T3, Free	**2.1 LN**	> 2.5 pg/ml
T4, Free	**0.90 LN**	> 1.5 ng/ml
rT3	**217 HN**	80-250 pg/ml
T3/rT3 Ratio	**0.96 L**	>1.06
TPO	**13.0 N**	<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl

Case 4b

- Female, 38 yrs. MCA with LOC, GCS 12

TSH is above the median with both T4 and T3 below the median of the range.

rT3 above the median with a normal T3/rT3 ratio.

TPO is elevated making this case Hashimoto's Disease.

Note the low Vitamin D3.

TSHi = 4.57 = Peripheral

Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S		195 ug/dl*
Estrone (E1)		< 200 pg/ml*
Estradiol (E2)		90 pg/ml*
Progesterone		5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio		< 250
Testosterone Free		2-4 pg/ml*
Testosterone Total		<44 ng/ml*
Dihydrotestosterone (DHT)		< 30 ng/Dl*
Sex Hormone Binding Gb		< 75 pg/ml*
FSH		7 mIU/ml*
LH		5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc		95 mcg/dL*
Insulin		< 30mIU/L
Vitamin D3	**17 L**	>60 ng/dl*
TSH	**4.38 HN**	<2.5 mcu/ml*
T3, Free	**2.45 N**	> 2.5 pg/ml
T4, Free	**1.44 N**	> 1.5 ng/ml
rT3	**176 HN**	80-250 pg/ml
T3/rT3 Ratio	**1.58 N**	>1.06
TPO	**267 H**	<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl

Case 4c

- Male, 41 yrs. MCA with LOC, GCS 12

- TSH below the median, fT4 almost at the median, fT3 above the median, Ratio is optimal, TPO is negative.
- What to do?

TSHi = 2.47 = Normal

Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S		195 ug/dl*
Estrone (E1)		< 200 pg/ml*
Estradiol (E2)		90 pg/ml*
Progesterone		5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio		< 250
Testosterone Free		2-4 pg/ml*
Testosterone Total		<44 ng/ml*
Dihydrotestosterone (DHT)		< 30 ng/Dl*
Sex Hormone Binding Gb		< 75 pg/ml*
FSH		7 mIU/ml*
LH		5.1 mIU/ml
Prolactin		14 ng/ml*
Zinc		95 mcg/dL*
Insulin		< 30mIU/L
Vitamin D3		>60 ng/dl*
TSH	**2.23 LN**	<2.5 mcu/ml*
T3, Free	**3.1 N**	> 2.5 pg/ml
T4, Free	**1.47 N**	> 1.5 ng/ml
rT3	**196 HN**	80-250 pg/ml
T3/rT3 Ratio	**1.58 N**	>1.06
TPO	**7.0 N**	<35
ACTH		35pg/ml *
Cortisol		< 15 ug/dl

ACTH and Cortisol

- TBI is associated with an acute elevation in the Corticotropin Releasing Hormone (CRH) from the Hypothalamus.
- Elevation in the CRH, aside from increasing the release of ACTH from the pituitary, also causes a **decrease in LH and TSH release.**
- The subsequent adrenal release of Cortisol also increases the production of rT3 from T4 with a corresponding drop in the T3 levels.
- Not until Cortisol is corrected can there be an improvement in the production of T3.

ACTH

- Reference Ranges: 7.2 – 63.3pg/ml
- Median (AM): 35 pg/ml

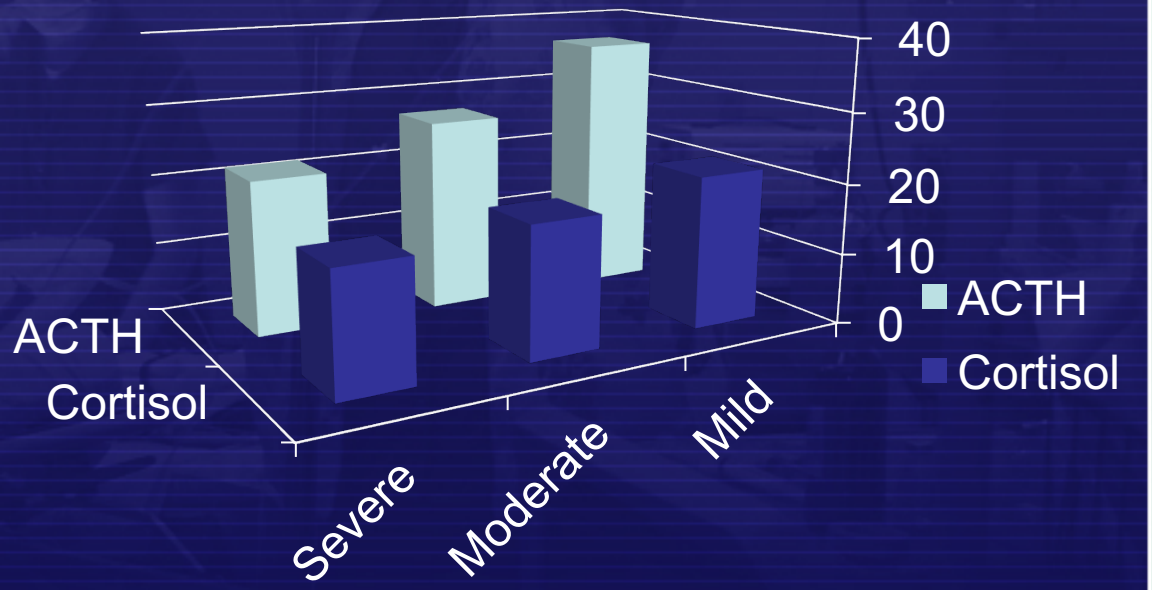
Cortisol

- Morning (AM): 6.2 - 19.4 ug/dl
  - AM Median: 15 ug/dl
- Afternoon (PM): 2.3 - 12.3 ug/dl
  - PM Median: 7.3 ug/dl

Pituitary functions in the acute phase of Traumatic Brain Injury: Are they related to severity of the injury or mortality?

Brain Injury, April 2007; 21(4): 433–439. FaithTanriverdi, Casanueva, et al. Dept of Endocrinology, Neurosurgery, Erciyes University Medical School, Kayseri, Turkey, and Dept of Medicine School of Medicine and Complejo Hospitalario Universitario de Santiago, Santiago de Compostela University, Santiago de Compostela, Spain

15% of Moderate to Severe TBI develop 1° or 2° Adrenal failure within 7-60 days.



Case 5a – 2 years post

A. Male, 18 yrs. MCA with LOC < 90min, GCS 10.

Cortisol Labs	Results	Ranges
ACTH	6.4 pg/ml	< 35 pg/ml
Cortisol (am)	21.8 pg/ml	< 15 pg/ml

Case 5b – 2 years post

B. Male, 22 yrs., Blast Trauma with LOC < 30 sec, GCS 15.

Cortisol Labs	Results	Ranges
ACTH	47.2 pg/ml	< 35 pg/ml
Cortisol (am)	17.5 pg/ml	< 15 pg/ml

ACTH- and Non-ACTH-Mediated Regulation of the Adrenal Cortex: Neural and immune inputs.

The Journal of Clinical Endocrinology & Metabolism. Vol. 84, No. 5 1999. S. R. Bornstein and G. P. Chrousos. Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892.

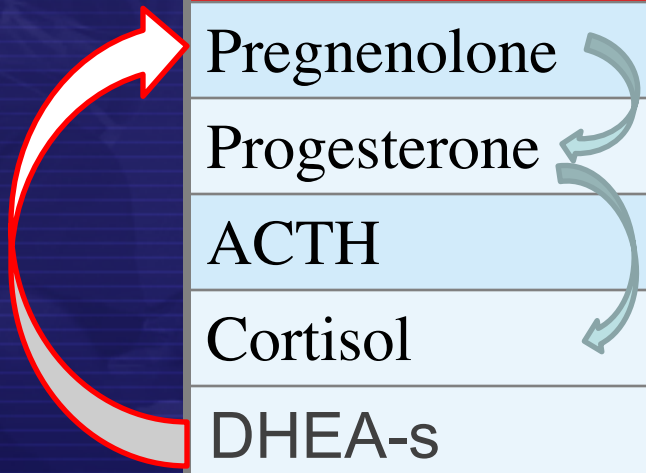
Two peripheral systems for the regulation of Cortisol:

1. **Traditional**: CRH from the hypothalamus, inducing ACTH released from the pituitary causing an increase in adrenal cortical production and release of Cortisol.
2. **Non-Traditional**: Catecholamines stored in the splanchnic nerves can induce Cortisol production by release of dopamine, epinephrine, and norepinephrine and a wide variety of neuropeptides. (exercise and body trauma)

- Due to the non-ACTH regulation of the adrenal cortex, you can have low levels of ACTH with high levels of Cortisol.

Case 5c

- Male, 38 yrs. Pedestrian vs automobile with LOC less than 1 hours. GCS ?



PSS	Results	Median
Pregnenolone	127 ng/dL	110 ng/dL
Progesterone	1.9 ng/ml	0.8 ng/ml
ACTH	34.7 pg/ml	35 pg/ml
Cortisol	2.95 ug/dL	15.0 ug/dL
DHEA-s	114.6 ug/dl	245 ug/dL
Free Testosterone	9.31 ng/ml	14 ng/ml

Preservation of the species by sacrificing libido for dealing with stressors.

Pregnenolone Steal Syndrome

- This syndrome can be found in patients with chronic fatigue, adrenal fatigue and adrenal insufficiency.
- It is a phenomenon where the 'super hormone' pregnenolone is used as the raw material to make the stress hormone cortisol instead of **your** other hormones. Pregnenolone can be normal or elevated with a low to low-normal DHEA or;
- **both pregnenolone and DHEA can be low to low normal.**
- Under issues of stress the body will take as much of the Pregnenolone (DHEA too) it can to make Cortisol.
- If there is a deficiency in Pregnenolone, Progesterone, or even 11 DOC, and DHEA will be reduced in production in favor of the adaptogenic Cortisol.

Prolactin

- Reference Range: Male:4.1-18.4ng/ml. Female: 3.4-24.1.
- Median: Males: 11.25 ng/ml Females: 13.75 ng/ml

- Prolactin like growth hormone is under negative control by the presence of Prolactin Inhibiting Factor (PIF) like GH is under the negative presence of Somatostatin (SRIF or SS).
- The normally functioning Hypothalamus releases PIF to suppress the release of Prolactin from the Pituitary.
- Damage to the hypothalamus can cause a decrease in the production/release of PIF enabling the anterior pituitary to freely produce and release Prolactin.
- Otherwise, in an individual with elevated levels of Prolactin, consider a Pituitary Adenoma as the cause if there is no history of head trauma. Perform an MRI of the Pituitary Gland.

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Case 6a

- Male, 52 yrs. MVA with LOC, Coma for 3 weeks. He subsequently develops depression and panic attacks within a year. He is on Wellbutrin XR.

Labs	Results	Ranges
Prolactin	2.3 ng/ml	15.0 ng/ml*

- Hypothalamic control over the pituitary release of Prolactin is by negative inhibition by the primarily Prolactin Inhibitory Factors – **Dopamine** and second by GABA.

- Results support findings that **dopaminergic over-activity in panic disorder** as compared with major and minor depression.

Biological Psychiatry. Vol. 32, No.11, Dec. 1992, Pages 1004–1011

Posterior Pituitary Hormones

- The resiliency of posterior pituitary hormones to trauma is derived from the absence within the gland of trophic cells that make Oxytocin and Vasopressin.
- The posterior pituitary consists mainly of neuronal projections (axons) of magnocellular neurosecretory cells extending from the supraoptic and paraventricular nuclei of the hypothalamus.
- By the time a patient sees us, their posterior pituitary dysfunction is already under treatment.
- Therefore, as a general rule, we do not pursue PP hormonal issues.

Summary

- Only through a comprehensive hormonal assessment will you be able to offer the patient optimal treatment.
- Learn the female cycle of hormone production and not just what to anticipated at day 21.
- Use the EP Ratio to guide in both replenishment and balancing of estrogens and progesterone.
- Interrelate the results of each hormone to the others to understand the full scope of the condition. -

Hippocrates: a pioneer in the treatment of head injuries.

Neurosurgery. 2005 Jul;57(1):181-9; discussion 181-9. Panourias IG, Skiadas PK, Sakas DE, Marketos SG.

Corpus Hippocraticum a collection of 60 early Ancient Greek medical works strongly associated with the physician Hippocrates.

Hippocrates found that "the lesions, at the bregma, are more mortal, and with medical treatment escape from death more difficult here than any other part of the head," whereas patients sustaining blows to the posterior and occipital areas generally held a more favorable course.

Four Humors

- Hippocrates believed that certain human moods, emotions and behaviors were caused by the four bodily fluids called "humors", which were (1) blood, (2) yellow bile, (3) black bile and (4) phlegm.
- Essentially, Hippocrates was not so far off, if we consider the four major hormones - somatotropin, gonadotropin, thyrotropin and corticotrophin - as the “humors” that we now see as influencing our neuropsychology and physical well-being.

Phineas Gage

September 13, 1848

The 3 meter iron rod that was blow behind his left eye and up through his skull. He lived 12 years post injury dying in status epilepticus.

A historical case o o the frontal lobe causing significant lity changes.

http://en.wikipedia.org/wiki/Phineas_Gage

Symptomatology associated with mTBI

The 10 Top Symptoms associated with Mild TBI:

1. Fatigue (100% of patients)
2. Excessive sleepiness and/or disturbed sleep patterns.
3. Inattention with difficulty concentrating
4. Impaired memory
5. Faulty judgment with slowed thinking.
6. Depression w/wo Anxiety and Panic Attacks.
7. Irritability with emotional outbursts of Anger.
8. Diminished libido.
9. Difficulty switching between two tasks.
10. Alcohol Abuse w/wo Drugs.

Neuropsychological sequelae of diffuse traumatic brain injury.

Brain Injury, 2005 Feb;19(2):101-8 Fork M, Bartels C, Ebert AD, Grubich C, Synowitz H, Wallesch CW. [1]Department of Neurology, Otto-von-Guericke-University, Magdeburg, Germany.

- In TBI, neurobehavioral alterations have been seen as the primary factor attributing to long-term disability, which frequently include: difficulty remaining employed, maintaining social relationships and participating in other social roles.
- In most cases of **mild TBI**, the cognitive sequelae are overshadowed by limitations caused by debilitating psychiatric problems such as depression, suicidal ideation, anxiety, agitation, anger, paranoia, sexual dysfunction and alcohol/drug abuse.

Can Traumatic Brain Injury Cause Psychiatric Disorders? The Journal of Neuropsychiatry and Clinical Neurosciences 2000; 12:316–327. Robert van Reekum, M.D., F.R.C.P.C. Tammy Cohen, B.A.(H) Jenny Wong, B.A.(H) Department of Psychiatry and Kunin-Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care; Division of Geriatric Psychiatry, University of Toronto; **(2000)**

- Traumatic brain injury may cause psychiatric illness.
- The evidence is convincing for a strong association between TBI and mood and anxiety disorders.

Axis II psychopathology in individuals with traumatic brain injury.

. BRAIN INJURY , 2000, Vol. 14, No. 1 , Pages 45-61 Mary. R. Hibbard, Jennifer Bogdany, Suzan Uysal, Karen Kepler, Jonathan M. Silver, Wayne A. Gordon, and Lisa Haddad

Condition	Patient	Control
Border-line Personality Disorder	34%	
Obsessive-compulsive	27%	
Paranoid	26%	
Avoidance	26%	
Anti-social personality	21%	

Table 7.1 Hibbard reported a rate as high as 66% for personality disorders among subjects with TBI. Brain Injury 2000, 14(1) pg 45-61.

Axis I and II Psychiatric Disorders after Traumatic Brain Injury: a 30-year Follow-Up Study

Am J Psychiatry. **2002**; 159(8):1315-21 Koponen S; et al. O Department of Psychiatry, Turku University Central Hospital, Finland

- Traumatic brain injury seems to make patients particularly susceptible to depressive episodes, delusional disorder, and personality disturbances.

Axis I	48.3%
Major Depression	26.7%
Alcohol (Substance) Abuse	11.7%
Panic Disorder	8.3%
Phobias	8.3%
Paranoia	8.3%

Depression

What we have over-looked

Hormones and Depression	Results
Testosterone and Depression	70,400
Estrogen and Depression	99,300
Progesterone and Depression	53,600
Thyroid and Depression	235,000
DHEA and Depression	15,700
Growth Hormone and Depression	19,100

Table 7.1: A search on Google Scholar for published articles associating a specific hormone deficiency with the presence of depression yielded the following number of articles. The date range was between 2000-2012 and the articles were not screened for accuracy. MLG

A Boolean logic search of Google Scholar using "Hormone-X and Depression" yielded the above results. These were not screened for accuracy.

Diagnostic criteria for Depression

- The Diagnostic and Statistical Manual Text Revision-4 (DSM-IV, 2000), outlines the necessary symptoms which a patient must experience to be diagnosed with major depression (MDD).
- These include a depressed mood or loss of pleasure for two weeks, and
- the presence of four or more of the following symptoms: change in appetite or weight loss, insomnia or hypersomnia, fatigue or loss of energy, being restless or slowed down to a degree that is observable by others, feeling worthless, being unable to concentrate, having suicidal thoughts, planning or attempting suicide.

Predictors of New-Onset Depression after Mild Traumatic Brain Injury.

Rao, Vani., Et al. *J Neuropsychiatry Clin Neurosci* . 2010 ; 22(1): 100–104.Division of Geriatric Psychiatry & Neuropsychiatry, Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD.

- Mild-TBI is the most common form of TBI. Most people recover after mTBI but a small percentage continues to have persistent problems, predominantly **depression**.
- Of **43 mTBI patients**, followed longitudinally for one year the prevalence of new-onset depression was found to be **18%**.
- **Older age** and presence of **frontal subdural hemorrhage** were the only two significant findings noted in the depressed group compared to the non-depressed group.

Treatment for Depression after Traumatic Brain Injury: A Systematic Review

. Journal of Neurotrauma 26:2383–2402 (December 2009). Jesse R. Fann, Tessa Hart, and Katherine G. Schomer. Depts of Psychiatry and Behavioral Sciences, Rehabilitation Medicine, and Epidemiology, and Model Systems Knowledge Translation Center, Center for Technology and Disability Studies, University of Washington, Seattle, Washington. Moss Rehabilitation Research Institute, Elkins Park, Pennsylvania.

- More than half of all individuals who experience TBI will become depressed in the year after their injury,
- and less than half of those who do become depressed are likely to receive adequate treatment*.

*Note: Hormone assessment and replenishment.

The Bio-behavioral correlates of Post-Traumatic Brain Injury Depression. Journal Neuroscience Nurse **2000** Jun;32(3):169-76 Jean-Bay E University of Michigan, USA.

- ***Traumatic brain injury*** (TBI) leaves the survivors often with lifelong impairments affecting:
- Memory
- Cognition
- Language
- Mood (depression/anxiety)
- as well as physical functioning and altered metabolism.

Depression: A repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition?

Neurosci Biobehav Rev. 2011 January ; 35(3): 742–764 Karen Wager-Smith and Athina Markou. Department of Psychiatry School of Medicine University of California, San Diego 9500 Gilman Drive La Jolla, CA , USA.

- While depression is a relatively common diagnosis affecting about 20 percent of the general population (20%);
- individuals surviving TBI appear to be significantly more susceptible to varying degrees of depression, as evidenced by incidence rates ranging upwards to 77 percent (77%).

Atypical depression in growth hormone deficient adults, and the beneficial effects of growth hormone treatment on depression and quality of life. European Journal of Endocrinology 151 325–332. Tripti Mahajan1, Anna Crown, Stuart Checkley, Anne Farmer and Stafford Lightman Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol, UK and Institute of Psychiatry, London, UK

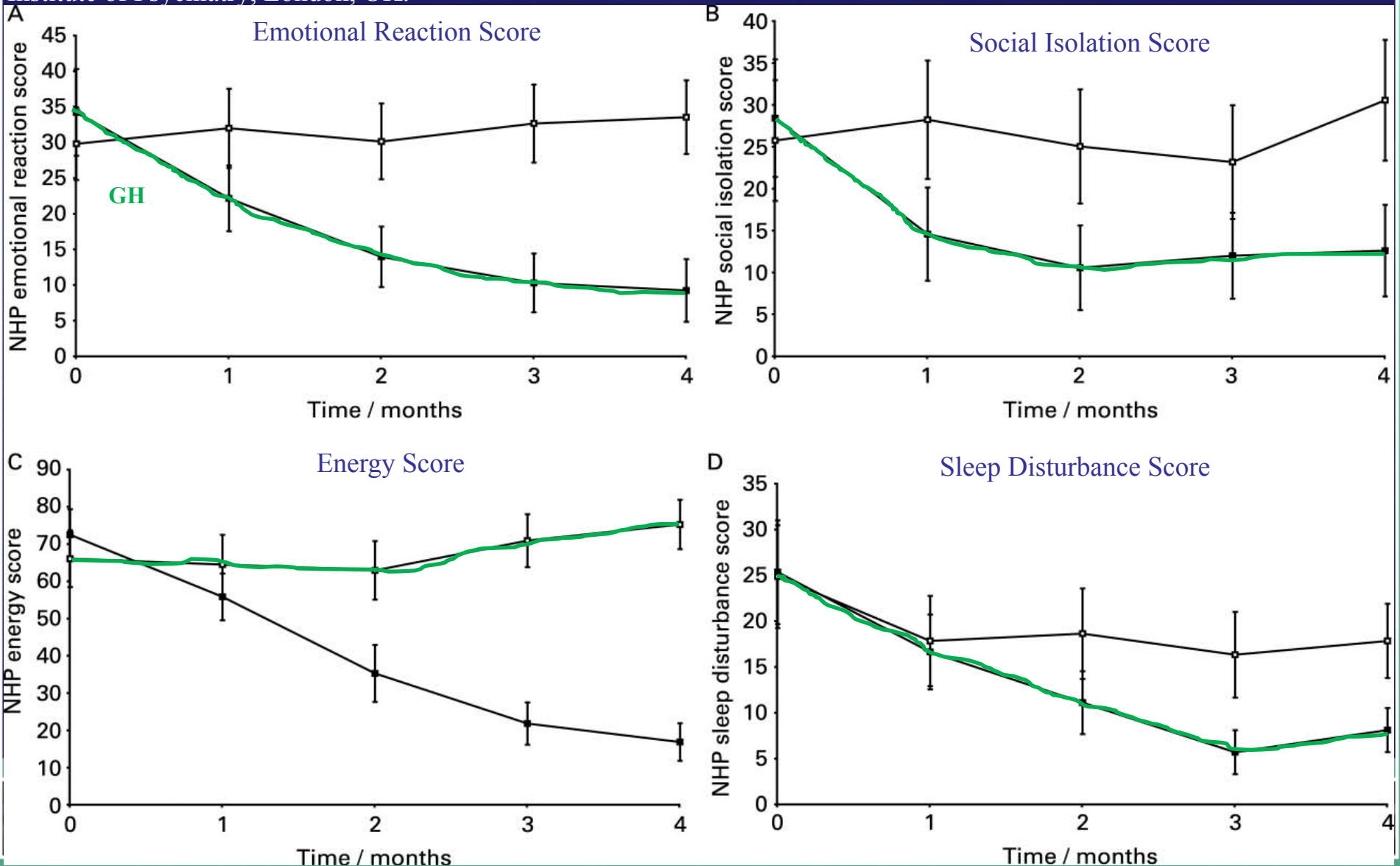
- 61% of the patients with Adult Onset Growth Hormone Deficiency were found to have atypical depression at baseline.
- There were significant improvements in the depression rating scale scores after 2 months of GH therapy, with significant improvements in emotional reaction and social isolation scores from 1 month, and in energy levels and sleep disturbance from 2 and 3 months respectively.

Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy. J Endocrinol Investigation. 2010 Dec;33(11):770-5. Maric NP, Doknic M, Pavlovic D, Pekic S, Stojanovic M, Jasovic-Gasic M, Popovic V

- GH-deficient TBI patients are depressed and have cognitive impairment.
- GH therapy induced reduction of depression, social dysfunction, and certain cognitive domains.
- Our preliminary data support the necessity of conducting randomized placebo-controlled trials on the effects of GH therapy on neuropsychological and psychiatric status in GHD TBI patients.

Atypical depression in growth hormone deficient adults, and the beneficial effects of growth hormone (rhGH) treatment on depression and quality of life.

European Journal of Endocrinology (2004) 151 325–332 Tripti Mahajan, Anna Crown, Stuart Checkley, Anne Farmer and Stafford Lightman, Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Institute of Psychiatry, London, UK.



Low testosterone levels in elderly men with dysthymic disorder.

Am J Psychiatry **2002** Mar;159(3):456-9. Seidman SN; Araujo AB; Roose SP; Devanand DP; Late Life Depression Clinic, New York State Psychiatric Institute, New York, NY 10032, USA.

- A decline in hypothalamic-pituitary-gonadal axis function is often seen in elderly men, and dysthymic disorder is a common finding.
- Median Testosterone levels varied for those with dysthymic disorder (295 ng/dl), major depressive disorder (425 ng/dl), and no depression (423 ng/dl).
- **Conclusion:** Total testosterone levels were lower in elderly men with dysthymic disorder than in men with major depressive disorder and men without depressive symptoms. Dysthymic disorder in elderly men may be related to HPG axis hypofunction.

Low free testosterone levels are associated with prevalence and incidence of depressive symptoms in older men

Clinical Endocrinology (2010) 72, 232–240. Devina Joshi, Natasja M. van Schoor, Willem de Ronde, Laura A. Schaap, Hannie C. Comijs, Aartjan T. F. Beekman, and Paul Lips,EMGO Institute, VU University Medical Center, Amsterdam, the Netherlands, Dept of Endocrinology, VU University Medical Center, Amsterdam, the Netherlands and Dept of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands

- **Free testosterone levels below 4.9 pg/ml** are associated with depressive symptoms, and
- **Free testosterone levels below 6.3 pg/ml** predict the onset of depressive symptoms.
- Range of Free Testosterone (Access Medical Lab):

Median = 12-14 pg/ml.

Use of Endocrine Hormones for Treating Depression.

Robert H. Howland, MD J. Psychosocial Nursing and Mental Health Services Psychopharmacology Dec 2010,Vol 48, Iss 12:3-16

- Thyroid hormone augmentation is effective for non-responders to antidepressant agents.
- Estrogen may improve mild mood symptoms in perimenopausal women but may not be effective alone for major depression.
- Evidence of the antidepressant effects of testosterone in men is inconsistent.
- DHEA-s has an important role in mood regulation and may have significant antidepressant effects.

Double-Blind Treatment of Major Depression With Dehydroepiandrosterone.

American Journal of Psychiatry 1999; 156:646–649. Owen M. Wolkowitz, M.D., Victor I. Reus, M.D., Audrey Keebler, B.A., Nicola Nelson, B.A., Mirit Friedland, B.A., Louann Brizendine, M.D., and Eugene Roberts, Ph.D.

- Open-label or single-blind treatment studies as early as 1952 noted that DHEA treatment improved mood, energy, confidence, interest, and activity levels in patients with “inadequate personality” or “emotional and constitutional immaturity”.
- In a 1994 double-blind trial, Morales et al. demonstrated a significant DHEA-induced increase in sense of well-being in middle-aged and elderly healthy volunteers.

Double-Blind Treatment of Major Depression With Dehydroepiandrosterone

(Am J Psychiatry 1999; 156:646–649). Owen M. Wolkowitz, M.D., Victor I. Reus, M.D., Audrey Keebler, B.A., Nicola Nelson, B.A., Mirit Friedland, B.A., Louann Brizendine, M.D., and Eugene Roberts, Ph.D.

- DHEA-treated subjects showed a significantly greater antidepressant response than did those who received placebo, as indicated by change in Hamilton depression scale ratings.
- The mean percentage change in Hamilton depression scale ratings in the DHEA group was 30.5%, compared with 5.3% in the placebo group..

Prevalence and Management of Treatment-Resistant Depression. Journal of Clinical Psychiatry 2007;68[suppl 8]:17–25. Charles B. Nemeroff, M.D., Ph.D.

Thane and Rush:	Stages of Treatment Resistant Depression
Stage 1	Failure of an adequate trial of 1 class of major antidepressant.
Stage 2	Failure of adequate trials of 2 distinctly different classes of antidepressants.
Stage 3	Stage 2 plus failure of a 3rd class of antidepressants, including a tricyclic.
Stage 4	Stage 3 plus failure of an adequate trial of a MOA inhibitor.
Stage 5	Stage 4 plus failure of an adequate course of electroconvulsive therapy.

Table 7.1: Adapted from Thane and Rush. J Clinical Psychiatry 1997;58 (suppl 13): 23-29.

Treatment Resistant Depression

1. Testosterone Gel Supplementation for Men With Refractory Depression: A Randomized, Placebo-Controlled Trial Harrison G. Pope, Jr., M.D.; Geoffrey H. Cohane, B.A.; Gen Kanayama, M.D., Ph.D.; Arthur J. Siegel, M.D.; James I. Hudson, M.D., Sc.D. Am J Psychiatry 2003;160:105-111

2. Intramuscular testosterone supplementation to selective serotonin reuptake inhibitor in treatment-resistant depressed men: randomized placebo-controlled study. SN Seidman, M Miyazaki, SP Roose - Journal of clinical psychopharmacology, 2005

3. Safety and Efficacy of Testosterone Gel 1% Augmentation in Depressed Men With Partial Response to Antidepressant Therapy. Claudia A. Orengo, MD, PhD Veterans Affairs Medical Center, Houston, TX, Menninger Dept of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, Veterans Affairs South Central Mental Illness Research, Education, and Clinical Center. J Geriatr Psychiatry Neurol March 2005 18: 20-24,

4. Augmentation with testosterone in men with treatment resistant depression and a history of substance abuse dependence. Unterseher, *OU-Tulsa Research Forum 2010--April 8*. 2010.

5. Testosterone supplementation for depressed men: Current research and suggested treatment guidelines. Kanayama, Gen, et al. Experimental and Clinical Psychopharmacology 15.6 (2007): 529.

6. Low-dose transdermal testosterone augmentation therapy improves depression severity in women. Miller, Karen K., et al. " CNS Spectr 14.12 (2009): 688-694.

Suicide Tendency

Serotonin brain circuits involved in major depression and suicide.

Victoria Arango, Mark D. Underwood and J. John Manx. Dept of Neuroscience, New York State Psychiatric Institute, Dept of Psychiatry, Dept of Anatomy and Cell Biology, Columbia University College of physicians and Surgeons, 1051 Riverside Drive, New York, NY 10032, USA

- A classical relationship exists between the development of depression and the incidence of suicide.
- Suicide is a potentially preventable public health problem. In 2009, the last year for which statistics are available, suicide was the 10th leading cause of death in the U.S. That year, there were nearly 37,000 suicides, and 1 million people attempted suicide, according to the Centers for Disease Control.
- Men take their lives nearly four times the rate of women, accounting for 79% of suicides in the U.S.

Testosterone levels in suicide attempters with bipolar disorder.

Psychiatr Res. 2012 October;46(10). Leo Sher, M.D., Michael F. Grunebaum, M.D., Gregory M. Sullivan, M.D., Ainsley K.Burke, Ph.D., Thomas B. Cooper, M.S., J. John Mann, M.D., and Maria A. Oquendo, M.D. New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons, New York, NY. James J. Peters Veterans' Administration Medical Center and Mount Sinai School of Medicine, New York, NY

- Depressed men have lower plasma or serum testosterone levels although this association is not observed consistently.
- Hypogonadal men frequently show depressive symptoms, and testosterone replacement improves these symptoms.
- Testosterone and other androgens might have anti-depressant properties.
- It has been shown in 2003, that the use of testosterone gel produced anti-depressant effects in depressed men with low testosterone levels.

Anxiety

Anxiety is an unpleasant state of inner turmoil, often accompanied by nervous behavior, such as pacing back and forth, somatic complaints and rumination. It is the subjectively unpleasant feelings of dread over anticipated events, such as the feeling of imminent death.

Testosterone's analgesic, anxiolytic, and cognitive-enhancing effects may be due in part to actions of its 5 alpha-reduced metabolites in the hippocampus.

Behav Neurosci **2004** Dec;118(6):1352-64. Edinger KL; Frye CA Department of Psychology, The University at Albany-SUNY, Albany, NY 12222, USA.

- Testosterone (T) may decrease **anxiety** and enhance cognitive performance via conversion to Dihydrotestosterone(DHT) or 3-Alpha Andosterone.

Notes: Patients on 5-AR blockers subsequently develop central deficiency of these active metabolites of Testosterone and Pregnenolone with documented affects on personality with depression.

Low Pregnenolone sulphate plasma concentrations in patients with generalized social phobia. Psychology Medicine **2002** Jul;32(5):929-33. Heydari B; Le Melledo JM Department of Psychiatry, University of Alberta Hospital, Edmonton, **Canada**.

- Aside from low Pregnenolone-s being associated with Social Phobia, it was also a correlation in male patients suffering from generalized **anxiety** disorder (GAD).

Psychopathology in Women and Men: Focus on Female Hormones

Am J Psychiatry **1997**; 154:1641–1647. Dr. Seeman, Clarke Institute of Psychiatry, University of Toronto, 250 College St., Toronto, ON, Canada M5T 1R8

- Estrogens are neuroprotective with respect to neuronal degeneration, growth, and susceptibility to toxins.
- The cyclic fluctuations of estrogens and progesterone enhance the response to stress, which confers susceptibility to depression and **anxiety**.

Obsessive-Compulsive Disorder and Traumatic Brain Injury: Behavioral, Cognitive, and Neuroimaging Findings

Marcelo L. Berthier, M.D., Jaime Kulisevsky, M.D., Alexandre Gironell, M.D., and Oscar L. López, M.D. Dept of Medicine and Dermatology, University of Malaga, Malaga, Spain; Dept of Neurology, Sant Pau Hospital, Autonomous University of Barcelona, Barcelona, Spain; and Dept of Neurology and Alzheimer's Disease Research Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

- Post-traumatic OCD has a relatively specific pattern of symptoms even in patients with mild TBI and is associated with a variety of other psychiatric disorders, particularly non-OCD **anxiety.**
- The patterns of cognitive deficits and MRI findings suggest dysfunction of **frontal-subcortical circuits**.

Cognitive Functioning, Cortisol Release, and Symptom Severity in Patients with Schizophrenia

BIOL PSYCHIATRY 2000;48:1121–1132. Deborah J. Walder, Elaine F. Walker, and Richard J. Lewine. Departments of Psychology and Psychiatry, Emory University, Atlanta, Georgia.

- It has been suggested that the relation between cortisol levels and symptom severity is due to the augmenting effects of cortisol on dopamine activity.
- Elevation of Dopamine can increase symptoms of Anxiety and Panic Attacks.

MHC Notes: The presence of a LOW Prolactin level can be a tip-off in a patient with treatment resistant anxiety. Having a high dopamine (Prolactin inhibiting factor) will suppress the production of Prolactin from the Anterior Pituitary.

Agitation

Emotional state of excitement or restlessness.

Measurement and Treatment of Agitation Following Traumatic Brain Injury : II . A Survey of the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation. Archives Phys Med Rehabil Vol 78, September 1997. Lisa P. Fugate, MD, Lisa A. Spacek, BA, Laura A. Kresty, MS, Charles E. Levy, MD, Jane C. Johnson, MA, W. Jerry Gysiw, MD

- Noted is a high prevalence rate for agitation in patients with TBI.
- **Unfortunately, and in light of the 9 specific medications that are used to treat the agitation, there is no standardized means of measurement.**
- Treatment strategies differ significantly between general physiatrists and those who specialize in the treatment of patients with TBI.

Patterns of agitated behaviour during acute brain injury rehabilitation.

Brain Injury, September 2010; 24(10): 1214–1221. Melissa T. Nott et al., Brain Injury Rehabilitation Service, Westmead Hospital, Wentworthville, NSW, AU, Faculty of Health Sciences, The University of Sydney, Sydney, NSW, AU, and Dept of Rehabilitation Medicine, Sydney Medical School, The University of Sydney, Sydney, NSW, AU.

- Agitated behavior is present along a continuum with varying levels of behavioral disturbance characterized by inattention, disinhibition, emotional lability, impulsivity, motor restlessness and aggression.

Aggression

Aggression is overt, often harmful, social interaction with the intention of inflicting damage or other unpleasantness upon another individual. It is a virtually universal behavior among animals. It may occur either in retaliation or without provocation. In humans, frustration due to blocked goals can cause aggression.

Aggression after Traumatic Brain Injury: Prevalence & Correlates

Rao, Vani., Et al. *J Neuropsychiatry Clin Neurosci*. (2009) ; 21(4): 420–429. Division of Geriatric Psychiatry & Neuropsychiatry, Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD.

- Aggression after TBI is common but not well defined.
- Seventy-six (76) participants with first-time TBI were seen within 3 months of injury and evaluated for aggression.
- The prevalence of aggression was found to be **28.4%** and to be predominantly verbal aggression.
- Post-TBI aggression was associated with new-onset major depression, poorer social functioning, and increased dependency on activities of daily living.

Changes in brain testosterone and Allopregnanolone biosynthesis elicit aggressive behavior. PNAS, Feb 8, 2005, Vol. 102 No. 6 2135–2140. Graziano Pinna*, Erminio Costa, and Alessandro Guidotti Psychiatric Institute, Dept of Psychiatry, College of Medicine, University of Illinois, Chicago, IL 60612

- The administration of Testosterone down-regulates the production of Allopregnanolone which is associated with **irritability**, **impulsive aggression**, and signs of **major depression**.
- Allopregnenolone is a metabolite of pregnenolone which is affected in neurodegeneration secondary to neuroinflammation.

MHC Note: High peripheral doses of T can convert to DHT in the CNS and precipitate Panic and Anxiety. It appears that the mechanism is the decrease in ALLO-P.

Psychosis

Psychosis refers to an abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality".

The Role of Estrogen and Other Hormones in the Pathophysiology and Treatment of Schizophrenia

Schizophrenia Research and Treatment Volume **2012**, Article ID 540273. Emily Hayes, Emorfia Gavrilidis, and Jayashri Kulkarni
Monash Alfred Psychiatry Research Centre, The Alfred Hospital and Monash University School of Psychology, Psychiatry and Psychological Medicine, Melbourne, VIC 3004, Australia

- The theory that many serious mental illnesses, in particular psychoses such as schizophrenia, may have a significant hormonal etiological component is fast gaining popularity and the support of scientific evidence.
- **Estradiol** has been found to significantly influence the dopaminergic, serotonergic, and glutamatergic systems, meaning that it may have **properties similar to those of atypical antipsychotic drugs**.

Revisiting Thyroid Hormones in Schizophrenia.

Journal of Thyroid Research Volume 2012, Article ID 569147. N. Santos, et., at. Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Campus de Gualtar, Braga, Portugal, Dept of Pathology, Leiden University Medical Center, Leiden, The Netherlands Institute of Medical Psychology, Faculty of Medicine, U. of Coimbra, Coimbra, Portugal

- Research on thyroid function in schizophrenia, relating the interrelations between the pituitary-thyroid axis (PTA) and major neuro-signaling systems showed pathophysiology that included serotonergic, dopaminergic, glutamatergic, and GABAergic networks, as well as myelination and inflammatory processes.
- The available evidence supports that thyroid hormones deregulation is a common feature in schizophrenia and that the implications of thyroid hormones homeostasis in the fine-tuning of crucial brain networks warrants further research*.

* Oligodendrocyte precursor stem cells

Sexual Dysfunction

Sexual dysfunction or **sexual malfunction** is difficulty experienced by an individual or a couple during any stage of a normal sexual activity, including physical pleasure, desire, preference, arousal or orgasm.

Brain processing of visual sexual stimuli in treated and untreated hypogonadal patients

Psychoneuroendocrinology 2005 Jun;30(5):461-82.
Redoute J; et al.Inserm U 483, Universite Pierre et Marie Curie, Boite 23, 9 quai Saint-Bernard, 75252 Paris Cedex 05, France.

- Using PET Scan, the Left Inferior Frontal Gyrus was found to increase in activity with VSS* only in Controls and Testosterone treated males and not in the Hypogonadal individuals.

*visual sexual stimuli

Female sexual dysfunction and use of hormone therapy in postmenopausal women

Semin Reprod Med **2005** May;23(2):180-7. Kovalevsky G Dept of Obstetrics and Gynecology, Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, 601 Colley Avenue, Norfolk, VA

- Female sexual function is highly complex and deeply influenced by non-hormonal factors such as emotional intimacy and culture.
- Although, the lack of estrogen may lead to sexual dysfunction primarily by causing vaginal atrophy and dyspareunia, and
- low testosterone causes diminished libido.

Head injury and sexual dysfunction. Brain Injury, 1996, VOL. 10, NO. 10, 703-717.

Mark L. Elliott, Laurel S. Biever. Ohio State University, Columbus, OH, USA

- Head trauma, especially a deceleration injury, often results in damage to the frontal lobes, pituitary and/or the limbic system, increasing the chance that a sexual problem will arise after head injury.
- Changes in sexual interest/desire are cited as the most common sexual problem after head injury.
- Patients with a *Basal Frontal Lobe* injury exhibited sexual disinhibition and increased sexual drive manifested as exhibitionism.

Cognition

Cognition is the set of all mental abilities and processes related to knowledge: attention, memory and working memory, judgment and evaluation, reasoning and "computation", problem solving and decision making, comprehension and production of language, etc. Human cognition is conscious and unconscious, concrete or abstract, as well as intuitive and conceptual. Cognitive processes use existing knowledge and generate new knowledge.

Thyroid Hormones Are Associated with Poorer Cognition in Mild Cognitive Impairment (MCI).

Dementia and Geriatric Cognitive Disorders 2010;30:205–211 a Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Mölndal , Sweden; b Depts of Neurology and Medicine, State University of New York, Downstate Medical Center, Brooklyn, N.Y. , USA

- Among those with MCI, Total T3 levels were inversely associated with cognitive performance across all domains.
- Those with relatively high T-T3 levels showed impairment in memory as well as in visuospatial and executive functions.
- Those with TT3 levels at or below the lower boundary of the normal range performed comparably to healthy controls.

MHC Notes: This stresses the need to maintain physiologic levels of all thyroid hormones during replenishment therapies with timely and appropriate laboratory testing.

Hormones and Cognition: Current Concepts and Issues in Neuropsychology.

Neuropsychology Review, Vol. 9, No. 4, 1999 David M. Erlanger, Kenneth C. Kutner, and Alan R. Jacobs, Dept of Neurosciences, Columbia University, New York, New York. Dept of Neurology, Weill Medical College of Cornell University, New York, New York.

- In pediatric, adolescent, and adult patients, research has consistently shown profound effects of hormonal dysregulation on behavior, affect, and cognition. These effects may be due to severe syndromes or even to subclinical endocrine dysfunction.
- Researchers and clinicians are increasingly studying hormones for their potential in diagnosing and treating cognitive problems associated with a variety of conditions that affect the central nervous system.

Neurosteroids in the Hippocampus: Neuronal Plasticity and Memory

Schumacher M. Stress **1997** Oct;2(1):65-78

- Pregnenolone sulfate, has been found to regulate neurotransmission in the hippocampus thereby exerting a strong influence on learning and memory processes.

Pregnenolone sulfate and aging of cognitive functions: behavioral, neurochemical, and morphological investigations. Horm Behav **2001** Sep;40(2):215-7 Mayo W; INSERM U259, Institut Francois Magendie, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France.

- Cerebral Pregnenolone correlated with cognitive performance which improved with replacement in deficient older adults.
- Noted was an increase of Acetylcholine in the amygdala, cerebral cortex and hippocampus.

Androgen Effects on Cognitive Function.

Suzanne Craft, et al William Bremner Geriatric Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, WA; University of Washington School of Medicine, Seattle, WA

- Androgen receptors are present throughout the brain, where they are known to affect brain development and synaptic organization.
- Recent evidence suggests that androgens have ongoing effects in the mature brain that may impact cognitive function and spatial memory in men.

Cognitive changes associated with supplementation of testosterone or DHT in mildly hypogonadal men: a preliminary report. J Androl 2003 Jul-Aug;24(4):568-76. Cherrier MM; Craft S; Matsumoto AH Department of Psychiatry and Behavioral Sciences, University of Washington Medical School, Seattle, Washington 98108, USA.

- The results suggest that beneficial changes in cognition can occur in hypogonadal men using T replacement levels and DHT treatment, and these changes in cognition can be reliably measured during a relative steady-state dose level.

17-alpha-estradiol: a brain-active estrogen?

Endocrinology 2005 Sep;146(9):3843-50. Toran-Allerand CD; et al. Department of Anatomy and Cell Biology, Columbia University College of Physicians and Surgeons, 650 West 168th Street, Black Building, Room 1615, New York, New York 10032, USA

- In the brain 17-alpha-estradiol elicits rapid and sustained activation of the MAPK/ERK and phosphatidylinositol 3-kinase-Akt signaling pathways;
- and is found to be **neuroprotective**, after an ischemic stroke and oxidative stress, and in Alzheimer's disease; and influences spatial memory and Hippocampal-dependent synaptic plasticity.

Relationship between testosterone supplementation and insulin-like growth factor-I levels and cognition in healthy older men.

Psychoneuroendocrinology 2004 Jan;29(1):65-82. Cherrier MM; Department of Psychiatry and Behavioral Sciences, University of Washington Medical School, 1959 NE Pacific, Box 356560, Seattle, WA 98195, USA

- Testosterone, Estradiol and IGF-I may have independent and selective effects on cognitive functioning.
- Positive associations between Testosterone levels and cognition are consistent with an effect of androgen treatment.

Fatigue after TBI: Association with neuroendocrine abnormalities. Brain Injury, June 2007; 21(6): 559–566. Tamara Bushnik, Jeffrey Englander, & Laurence Katznelson. Rehabilitation Research Center, PM&R, Santa Clara Valley Medical Center, San Jose, CA, USA, and Pituitary Center, Depts. of Neurosurgery and Medicine, Stanford University Medical Center, Stanford, CA, USA.

- The prevalence of fatigue does not appear to change over time, in a study of individuals with TBI living in the community,
- 68% reported fatigue at 2 years post-injury and,
- at 5 years post-injury 73%, reported problems with fatigue.

Loss of **hypocretin** (orexin) neurons with traumatic brain injury. Ann Neurol . 2009 October ; 66(4): 555–559. Christian R. Baumann1, Claudio L. Bassetti1, Philipp O. Valko, Johannes Haybaeck, Morten Keller, Erika Clark, Reto Stocker4, Markus Tolnay, and Thomas E. Scammell. Dept. of Neurology, Dept. of Neuropathology, Dept. of Forensic Medicine, and Dept. of Surgical Intensive Care, University Hospital, Zurich, Switzerland. Dept. of Neurology, Beth Israel Deaconess Medical Center, Boston, USA

- **Chronic, daytime sleepiness** is a major, disabling symptom in patients with traumatic brain injury (TBI).
- Loss of the hypothalamic neurons that produce the wake-promoting neuropeptide **hypocretin (orexin)** causes the severe sleepiness of **narcolepsy**,
- The partial loss of these cells may contribute to the sleepiness of Parkinson's disease and other disorders.
- This study found that the number of hypocretin neurons is significantly reduced in patients with severe TBI.
- Constant fatigue is the #1 symptom across TBI.

NMDA Receptor Function and Physiological Modulation

 K Zito, University of California at Davis, Davis, CA, USA V Scheuss, Max-Planck-Institute for Neurobiology, Martinsried, Germany

- The NMDA receptor belongs to a family of ionotropic receptors characterized by high affinity for glutamate, a high unitary conductance, high calcium permeability, and a voltage-dependent block by magnesium ions.
- The basics of excitatory neurotransmission to the complexities of learning and memory, the N-methyl-D-aspartate (NMDA) receptor can be considered one of the fundamental neurotransmitter receptors in the brain.
- NMDA receptor activation leads to opening of an ion channel that is selective for cations, resulting in the influx of Na and Ca2 ions and efflux of K ions.

Summary

- Each diagnostic label that we use to describe a Neuro-psychiatric condition has a neurosteroid or neuroactive steroid in its core relationship.
- We have medications that influence receptors allowing for increases and decreases in neurochemical transmissions thereby influencing emotional expressions.
- As a group, the appropriate replenishment of all NS and NAS can accomplish the same results without the costly side-effects.