Introduction: 2017AD



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Traumatic Brain Injury:

A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.



Introduction to TBI - Neuroendocrinology

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Disclosure

The following potential conflict of interest relationships are germane to my presentation:

Equipment: **N/A**
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Consultant: Secretropin Rx
Consultant: University Compounding Pharmacy.

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Status of off label use of devices, drugs or other materials that constitute the subject of this presentation: N/A

Disclaimer

- This course is called: ***Traumatic Brain Injury – A Clinical Approach to Diagnosis and Treatment,*** and therefore, we will not be discussing hospitalized patients.
- This course and the book were designed to address the 80-85% of patients who sustained a mild Traumatic Brain Injury (mTBI) and are considered highly functional ; **until they decompensate**.
- Many of these mTBI patients do develop an array of symptoms that have been generically categorized under the headings of **TBI and PTS**.

The Journey Begins

- **This 1 day program** will take you through a group of related lectures that will build one on top of the other forming a foundation.
- **The end-game** is to have you understand the progression and treatment of traumatic brain injury based upon the content of these lectures.
- **Neurotrauma** is usually thought of in 3 dimensions (causation, intensity, affects) but there is a fourth dimension of **TIME**.

The Journey Begins

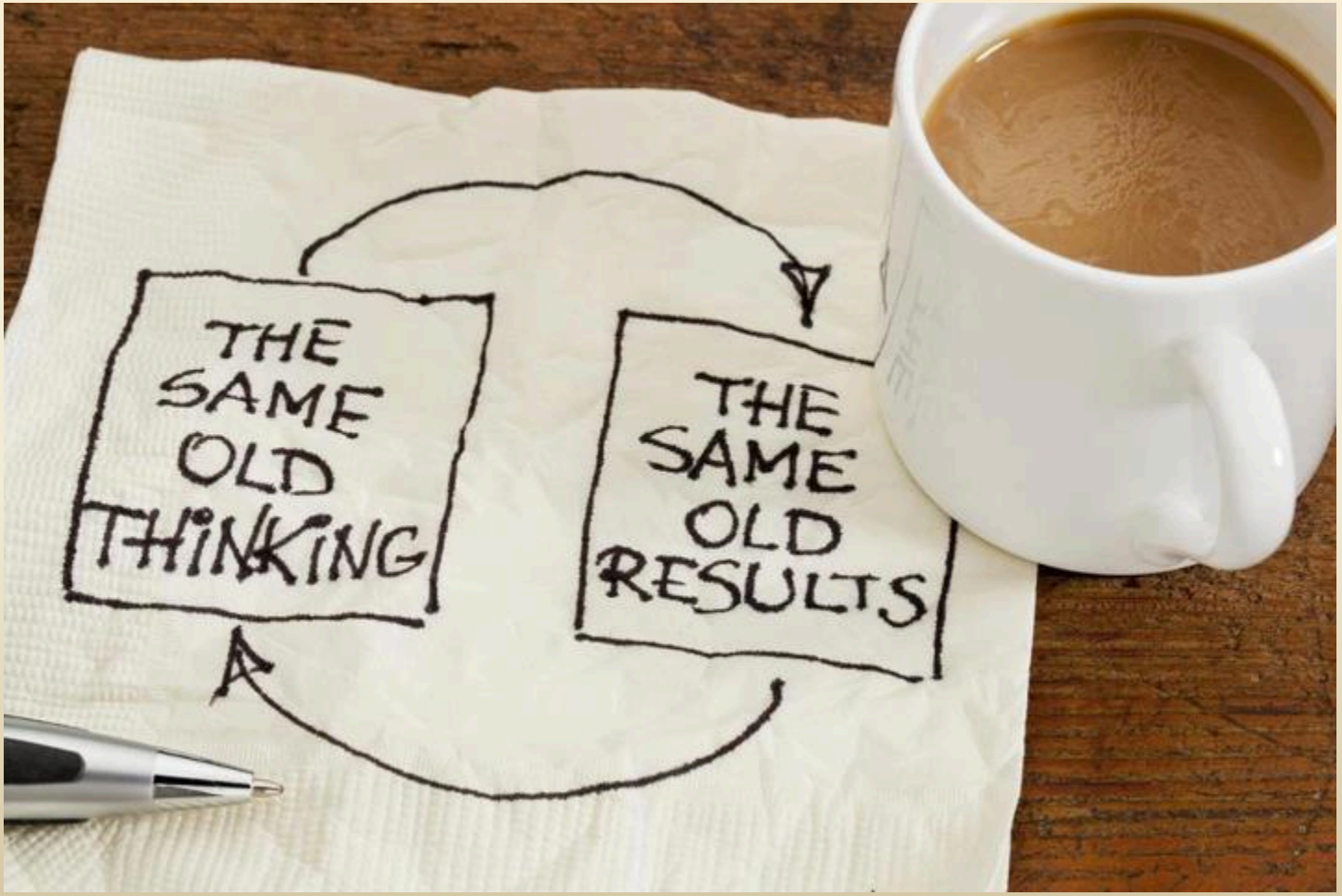
Rules of engagement:

There are no rules, just engage.

(1) Raise your hand. (2) When called upon please stand and identify yourself. (3) Ask your question or make a comment and then sit down.

Let's Begin

The Journey Begins



The Journey Begins

The Paradigm Shift has begun!



The Journey Begins

- Many individuals are under the false perception that only a head trauma that causes transient unconsciousness or a coma are valid TBIs.
- Furthermore, subclinical traumas can culminate, **in time**, with the same clinical symptomatology that is seen in someone who has had loss of consciousness.

Comparison of Concussive Symptoms, Cognitive Performance, and Psychological Symptoms Between Acute Blast-Versus Non-blast-Induced Mild Traumatic Brain Injury. Journal of the International Neuropsychological Society (2011), 17, 36–45.

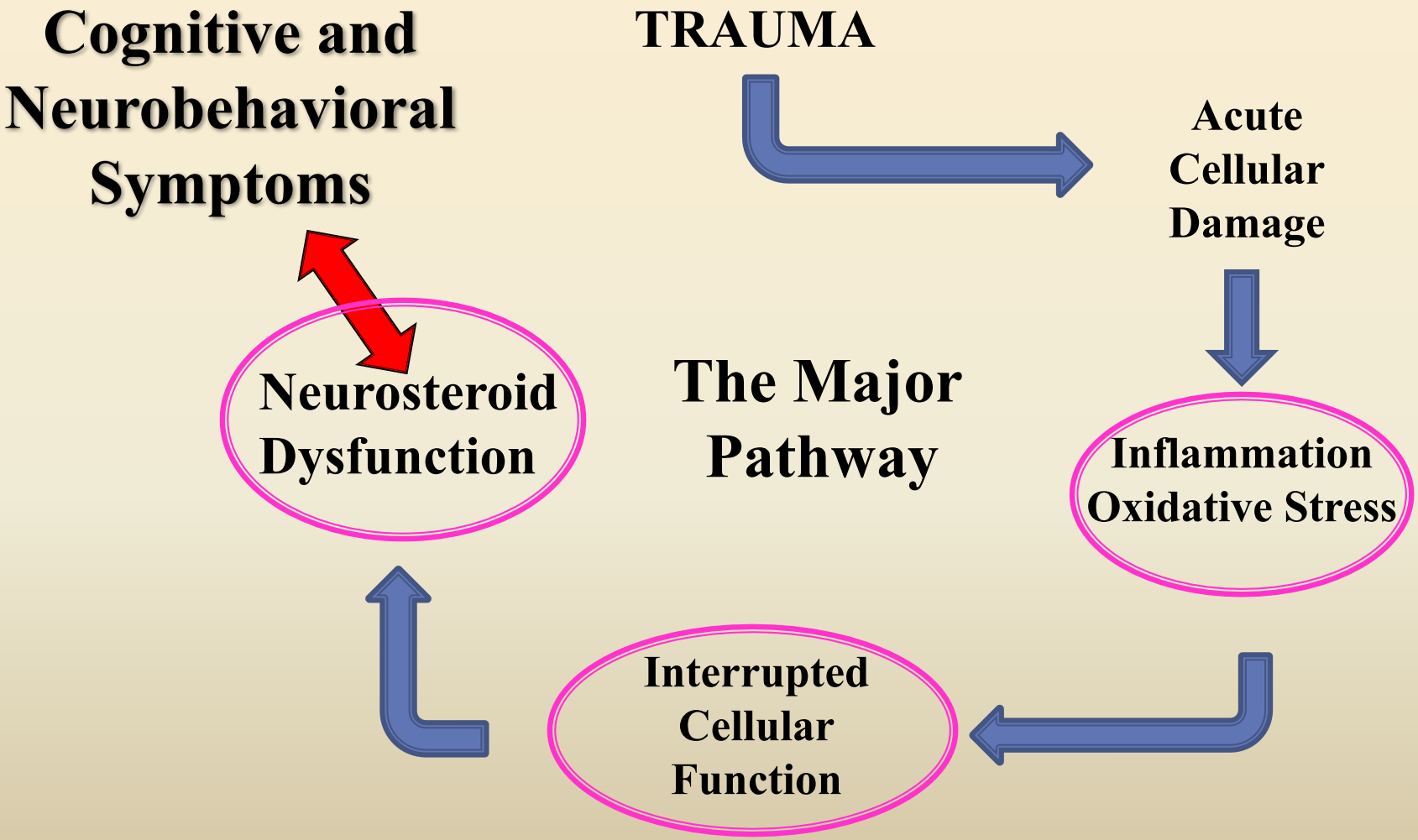
Cynthia A. Luethcke, et al. Dept of Psychiatry, U of Texas Health Science Center at San Antonio, Texas

- Results suggest that there are few differences in **concussive symptoms**, **psychological symptoms**, and **neurocognitive performance** between blast and non-blast mTBIs, although clinically significant impairment in cognitive reaction time for both blast and non-blast groups is observed.
- MLG: Again, we cannot guess who will develop sequalae from TBI, but we can measure its impact on the neuroendocrine system.

The immunology of traumatic brain injury: a prime target for Alzheimer's disease prevention. Journal of Neuroinflammation 2012, 9:185. Brian Giunta, Demian Obregon, Renuka Velisetty, Paul R Sanberg, Cesar V Borlongan and Jun Tan.

- It has been suggested that a long-term process of amyloid-beta (Aβ) metabolism is initiated by Traumatic Brain Injury (TBI).
- The inflammatory-based progression of TBI has been shown to be active in humans for up to **17 years post TBI**.
- Inflammation inhibits microglial clearance of the amyloid-beta allowing it to accumulate and create further inflammation and destruction.

The Journey Begins



NFL Fatalities

What we know is that people with repetitive head trauma become suicidal.

Paul Oliver	29 y/o	09-2013	Gunshot	Chest
Junior Seau	43 y/o	07-2012	Gunshot	Chest
Jovan H. Belcher	25 y/o	07-2012	Gunshot	Head
Kurt Crain	47 y/o	04-2012	Gunshot	-
Ray Easterling	62 y/o	04-2012	Gunshot	-
O.J. Murdock	25 y/o	07-2012	Gunshot	Chest
Dave Duerson	50 y/o	02-2011	Gunshot	Chest
Kenny McKinley	23 y/o	09-2010	Gunshot	-
Andre Waters	44 y/o	11-2006	Gunshot	Head
Terry Long	45 y/o	06-2005	Anti-freeze	
Juston Strzelczyk	36 y/o	09-2004	MVA in Chase	
Mike Webster	50 y/o	09-2002	MI?	-

We Know: There are Higher Rates of Dementia in Former N.F.L. Players - NYTimes.com

Dementia Risk Seen in Players in N.F.L.

Study By ALAN SCHWARZ , September 2009

- A study commissioned by the NFL reports that Alzheimer's disease or DAT appear to have been diagnosed in the league's former players more often than in the national population — including a rate of **19 times the normal rate** for men ages 30 - 49.

410,000 Veterans Administration visits in 2012 for PTSD (TBI)

- **We Know** that a large number Veterans are returning with symptoms of PTSD based upon the number of recorded visits to VA Hospitals for psychosocial behavioral issues.*
- **We Know** that **20-33%** of returning veterans have symptoms of PTSD (mTBI). **The Nation. April 16, 2013**
- **We Know** that the use of polypharmacy does nothing to help with the underlying cause of the neuro-psychopathology associated with TBI.

*

That depends if you believe the Scheduling Records recently reported by the Veteran's Administration!!

One death-a-day: Military suicides reach terrifying rate.

- **We Know**: that more US soldiers are dying from suicide than from enemy fire according to findings released by the Dept. of Defense.
- The suicide rate for active duty soldiers in 2012 was around one per day.
- Approximately 40 veterans/soldiers and 113 civilians a day at a rate of one suicide every 9.5 minutes.

What we don't know?

1. Was your birth an easy one?
2. Have you every had an injury that involved your head?
3. Have you ever had any situation that caused jarring of the head or of your body?
4. While learning to walk? Falling out of bed?
5. Roller skates? Bicycling? Motor Vehicle?
6. Skier (water or snow)?
7. Military service? Combat? – ***Combat Trauma Syndrome***
8. Sports? Football? Basketball? Soccer? Rugby?
9. Frequently exposed to ionizing radiation (x-rays).

We have not been asking enough of the right questions!

The Next 8 hours:

1. Introduction: An over-view of the program
2. Neurology:
    a. Understand what disruption of the brains architecture means in terms of functionality.
3. Neuropathology:
    a. Traumatic insults to the brain in terms of the physical components of Phase I and,
    b. the inflammatory and biochemical impacts generated as Phase II.

The Next 8 hours:

4. Neuroendocrinology:
    a. The releasing and trophic hormones that regulate glandular hormones.
    b. The missing Neurosteroids (NS)
5. Neurolaboratory
    a. Neurosteroid and Neuroactive Steroid testing.
    b. Interpretation on an individualized basis.

The Next 8 hours:

6. Neuropsychology
    a. The impact of inflammation and neuro- and neuroactive steroid production on cognitive and emotional behaviors.
7. Supplementing for TBI
    a. Promoting a Neuro-Permissive Environment; a potential mechanism for repair.

The Next 8 hours:

8. Treatment and case studies
    a. Putting it all together.
    b. Walking through case histories, laboratory results and their interpretation, followed by
    c. Treatment and follow-up.

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Chapter 2: Neurology For TBI

Hippocrates 400 BCE

"Men ought to know that from nothing else but the brain comes joy, delight, laughter and **sports**, and sorrow, grief, despondency, and lamentation.“

Therefore;

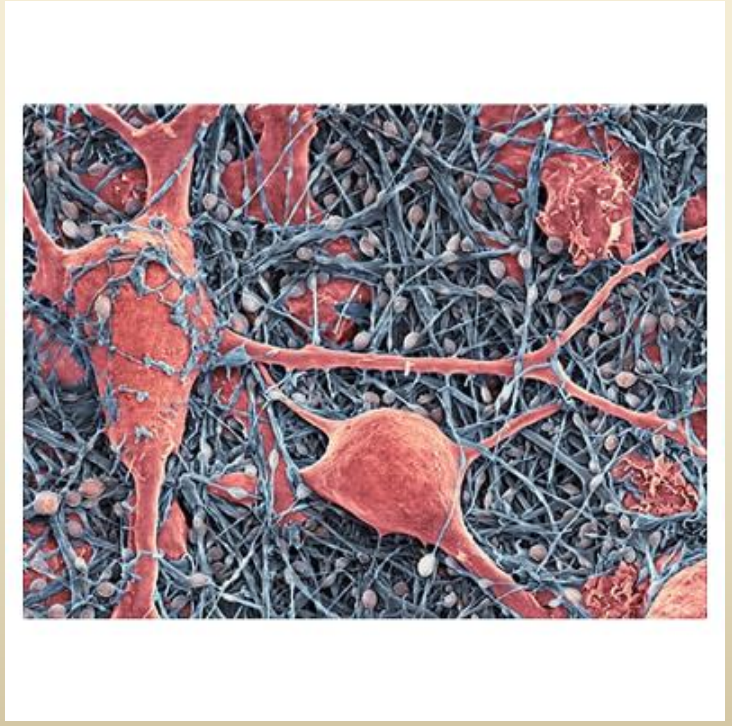
“ Women ought to know after 2500 years how to put up with our SH*T”

Introduction

- The outcome of mild closed head trauma (mTBI) on the ultimate functionality of the individual is unpredictable.
- Age and gender have been looked upon as influencing both the morbidity and mortality.
- Reports show that we can have normal appearing acute CT and MRI scans in an unconscious patient. No findings of contusion, ischemia, hematoma or structural compromise.
- Researchers are finding that impaired hypothalamic-pituitary function and general outcome can be predicted based upon the presence and degree of **Diffuse Axonal Injury** (DAI).

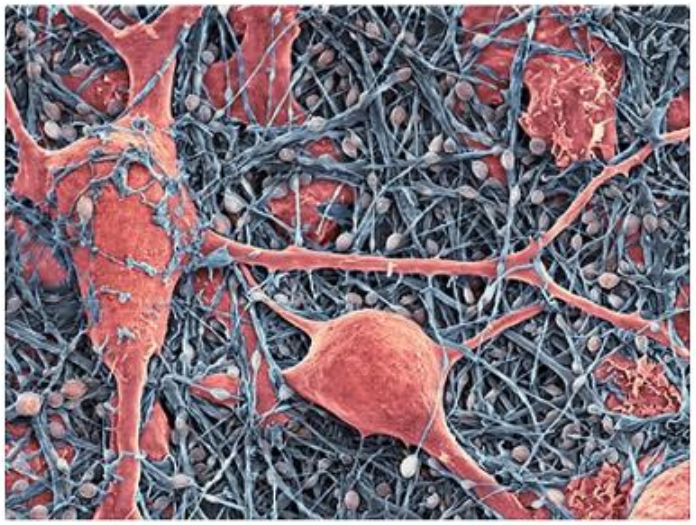
Gray and White Matters!

- The brain is an informational speedway made up of neuronal bodies (gray) and their long interconnecting appendages; axons (white).



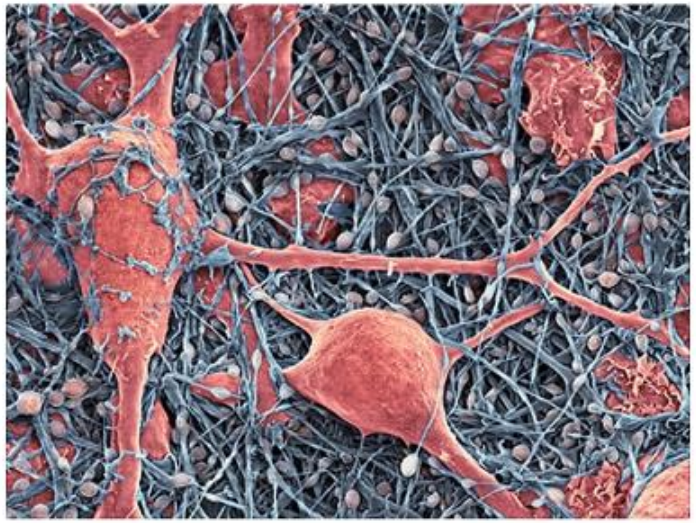
Gray Matters!

- **Gray Matter** consisting of neuronal cell bodies, neuropil (dendrites and unmyelinated axons), glial cells (astroglia and oligodendrocytes) and capillaries.



White Matters!

- **White matter** is one of the two components of the central nervous system and consists mostly of glial cells and myelinated axons that transmit signals from one region of the cerebrum to another and between the cerebrum and lower brain centers.

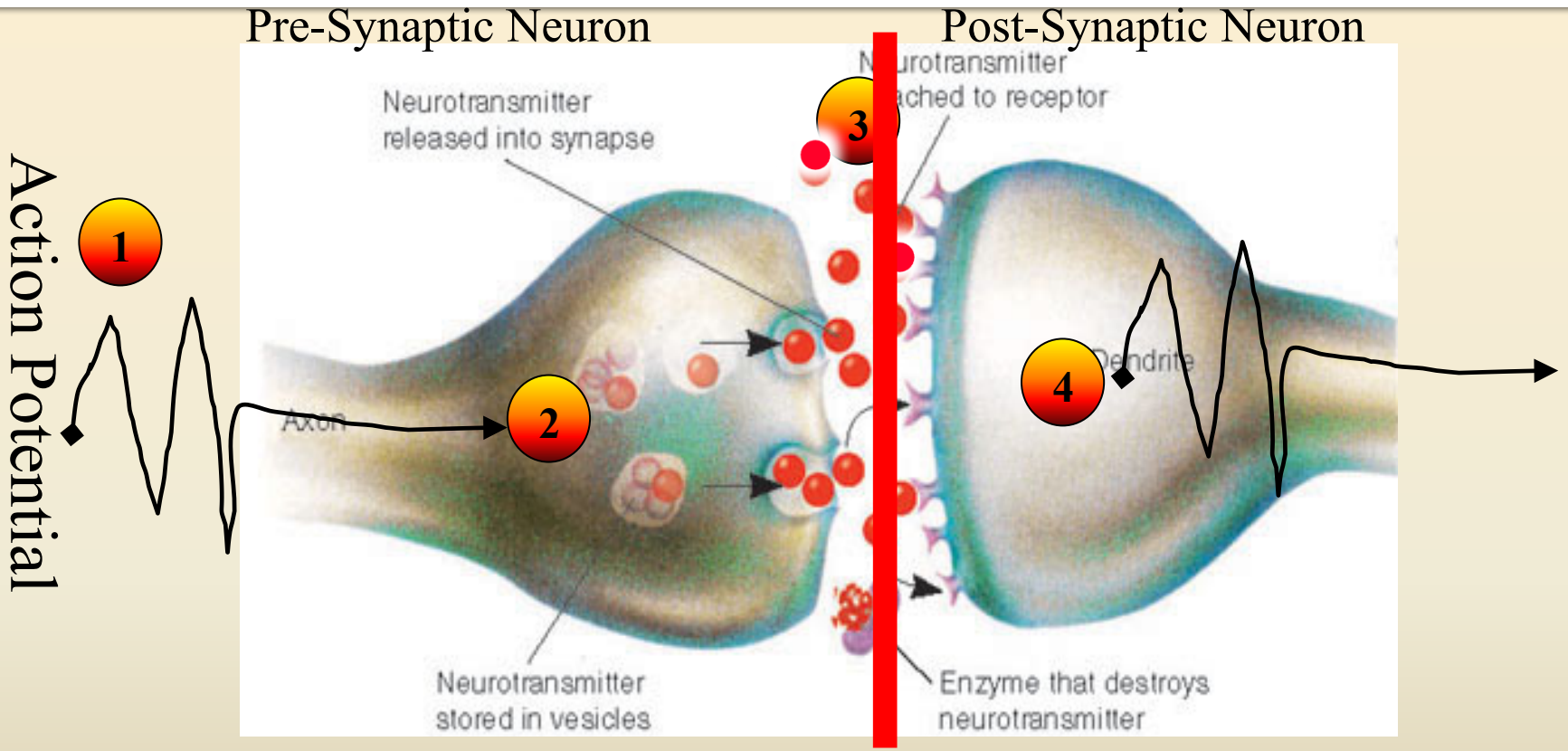


Neurons

- A neuron is an electrically excitable cell that processes and transmits information through electrical and chemical signals.
- A chemical signal occurs via a synapse, a specialized connection with other cells. Neurons connect to each other to form neural networks.
- Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia.



Neuronal Synapses



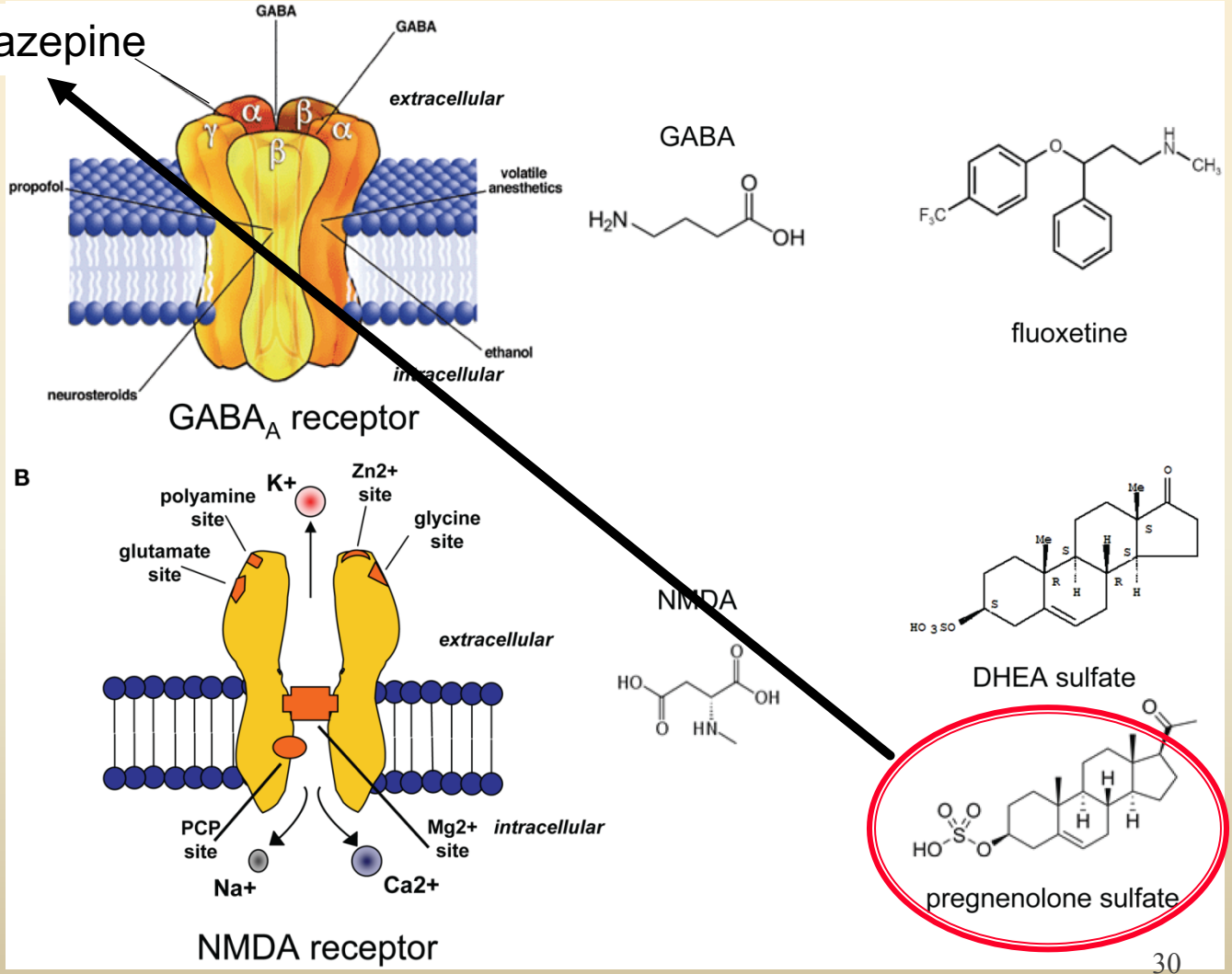
2 Neurotransmitter **diffuses** across the synapse and binds with receptor molecules on the membrane of the next neuron.

Due to inflammation and free radicals the communication is interrupted!

Neurosteroids as neuromodulators in the treatment of anxiety disorders.

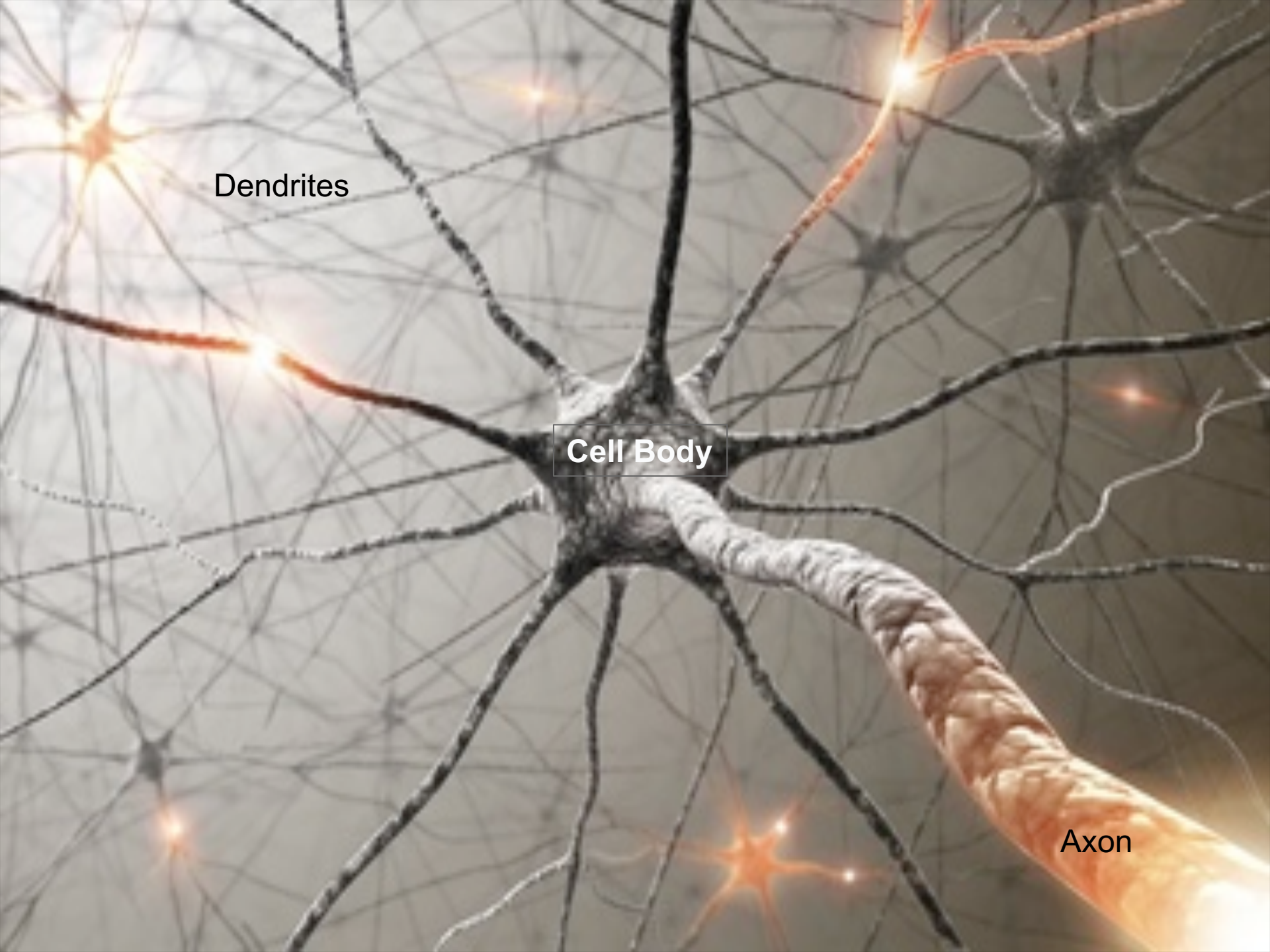
Front. Endocrinol., 2011 Patrizia Longone, et al., Rupprecht Molecular Neurobiology Unit, Experimental Neurology, Fondazione Santa Lucia, Rome, Italy. Child Neurology and Psychiatry, Dept of Neuroscience, University of Rome "Tor Vergata,", Rome, Italy. Deptt of Neuroscience, University of Rome "Tor Vergata,",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

Neuronal and synaptic communication is modulated by neurosteroids such as; estrogens, pregnenolone, allopregnenolone, progesterone, allopregnanolone, DHEA and their sulfated metabolites.



Neurons

- A typical neuron possesses a cell body, dendrite, and an axon.
- Dendrites are thin structures that arise from the cell body, often extending for hundreds of micrometers and branching multiple times, giving rise to a complex "dendritic tree".
- An axon is a special cellular extension that arises from the cell body and travels for a distance, as far as 1 meter in humans.
- The cell body of a neuron gives rise to multiple dendrites, but never to more than one axon, although the axon may branch hundreds of times before it terminates. At the majority of synapses, signals are sent from the axon of one neuron to a dendrite of another.


Dendrites
Cell Body
Axon

Glial Cells

- These are non-neuronal cells providing support to neurons in both the central and peripheral nervous systems.
- In general they have the ability to surround and hold neurons in place, supply nutrients and oxygen (A), produce myelin to insulate one neuron from another (O), and act as part of the immune system to destroy pathogens and remove dead neurons(MG).
- **Glial cells have been found to be the source of many of the Neurosteroids that we will discuss**.

Astrocytes

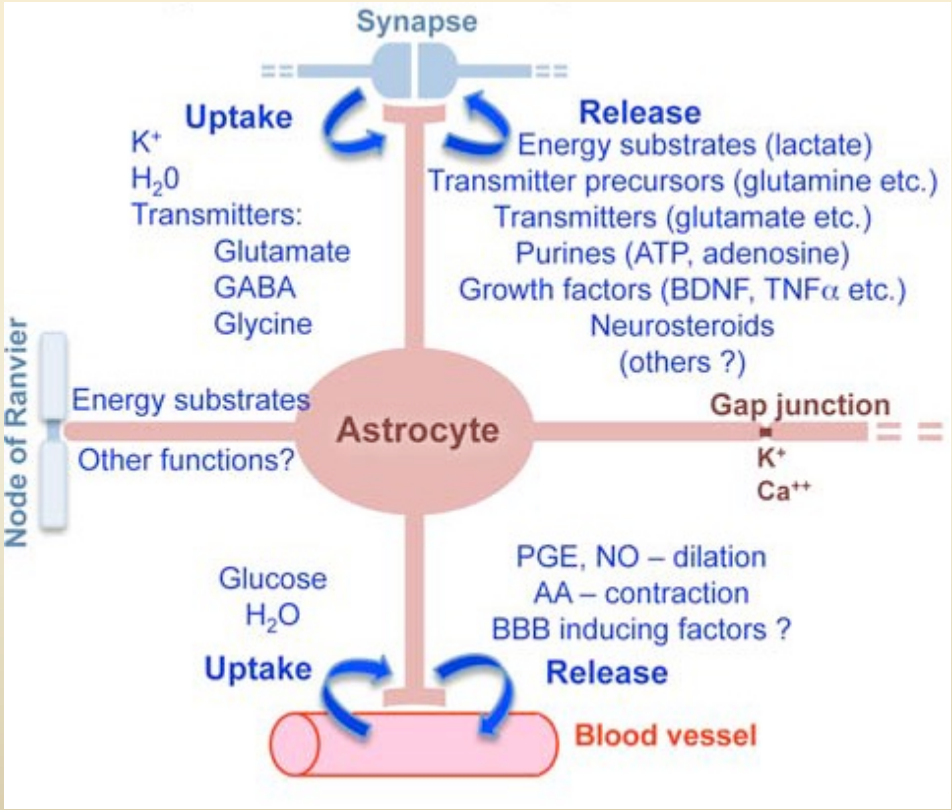
- The most abundant type of macroglial cell, astrocytes (also called astroglia) have numerous projections that anchor neurons to their blood supply.
- They regulate the external chemical environment of neurons by removing excess ions, notably potassium, and recycling neurotransmitters released during synaptic transmission.
- Astrocytes may regulate vasoconstriction and vasodilatation by producing substances such as **arachidonic acid**, whose metabolites are vasoactive.

Astrocytes: biology and pathology. Acta Neuropathol (2010) 119:7–35 Michael V. Sofroniew, Harry V. Vinters. Department of Neurobiology, David Geffen School of Medicine, University of California, 10833 Le Conte Avenue, Los Angeles, CA 90095-1763, USA

- Astrocytes are specialized glial cells that out-number neurons by fivefold[+].
- They contiguously tile the entire central nervous system (CNS) and exert many essential complex functions in the healthy CNS.
- Astrocytes respond to all forms of CNS insults through a process referred to as reactive astrogliosis, which has become a pathological hallmark of CNS structural lesions.

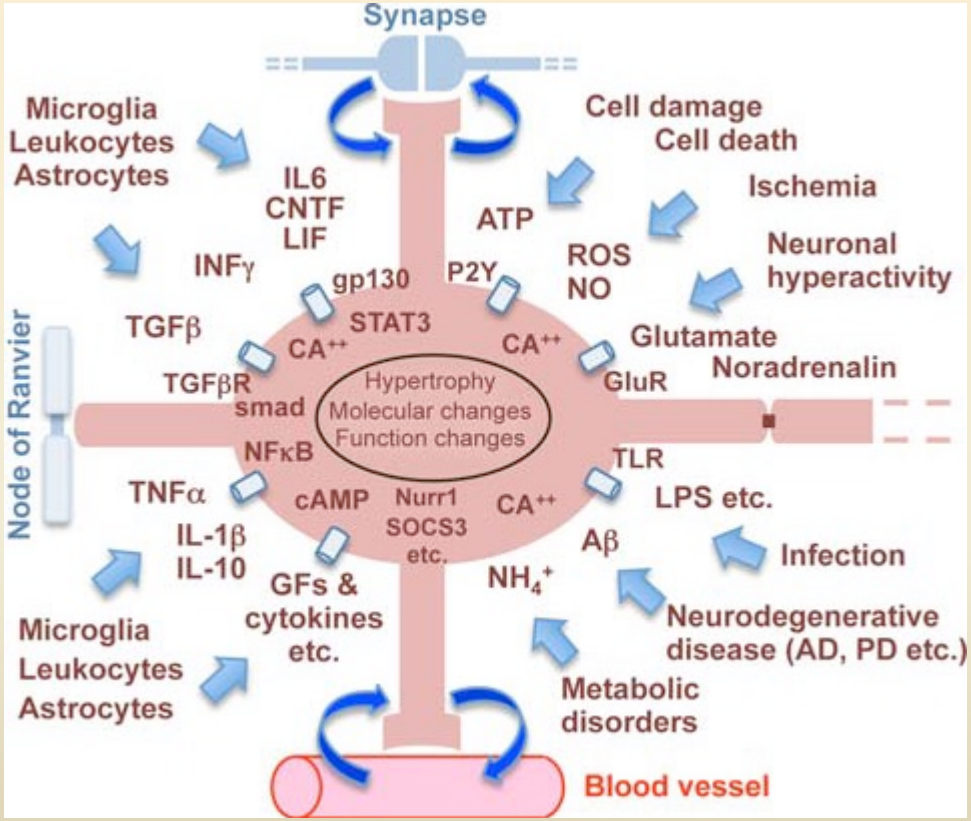
Astrocyte Functions in Healthy CNS

- Astrocytes have been found to provide more metabolic support that thought of in the past.
- They help regulate the health of the neurons as well as modulate electrochemical processes.

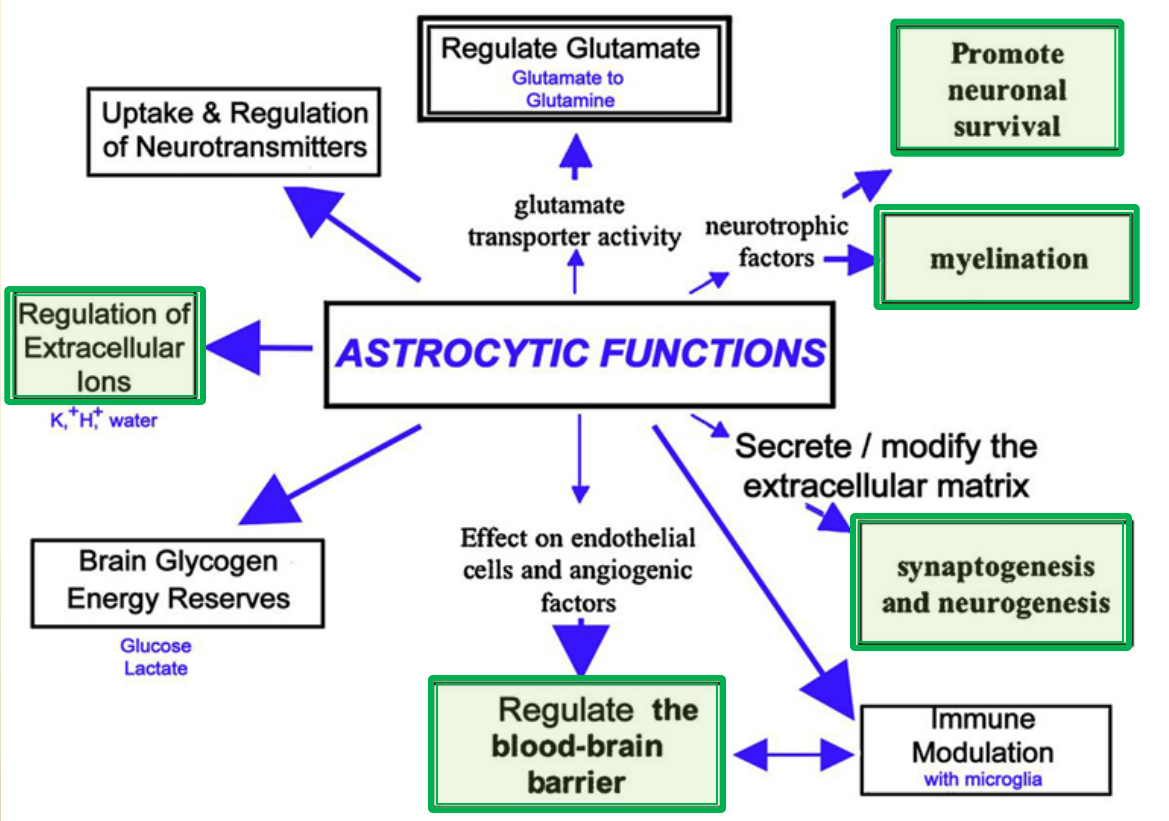


Astrocyte Functions in a Damaged CNS

- The development of a Glial Scar (reactive astrogliosis) acts as a physical impediment to the regrowth and reconnectivity of neurons.
- Early intervention to control inflammation will promote a more neuro-permissive environment fostering recovery.



Neuropermissive Environment



Oligodendrocytes

- Their main functions are to provide support and to insulate the axons in the CNS and spinal cord by producing Myelin.
- Oligodendrocytes produce the myelin sheath, which is 80% lipid and 20% protein.
- A single oligodendrocyte can extend its processes to 50 axons, wrapping approximately 1 μm of myelin sheath around each axon.
- In contrast, Schwann cells, found in the peripheral nervous system, wrap around only 1 axon.

Microglia

- Microglia constitute 15-20% of the total glial cell population within the brain.
- They act as macrophages capable of phagocytosis removing debris and bacteria. They act as the first and main form of active immune defense in the central nervous system.
- In the healthy CNS, microglia are constantly scavenging the CNS for plaques, damaged neurons, and infectious agents. (inflammation decreases this!)

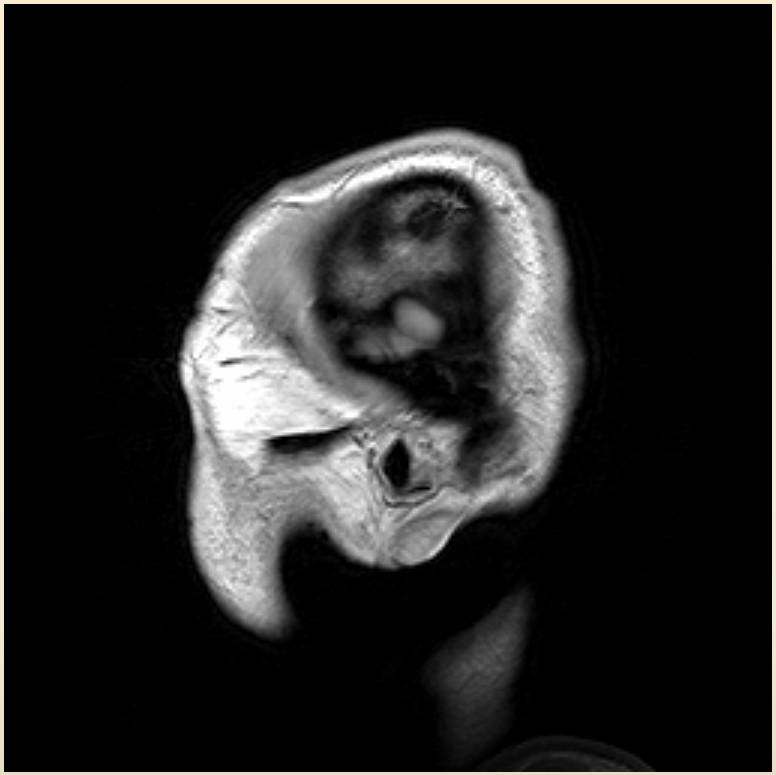
Estrogen and Microglia: A Regulatory System That Affects the Brain. J

Neurobiol 40: 484–496, 1999. Gil Mor, Jon Nilsen,Tamas Horvath, Ingo Bechmann, Santiago Brown, Luis Miguel Garcia-Segura, Frederick Naftolin, Dept of Obstetrics and Gynecology and Center for Reproductive Biology, Yale University Medical School, 333 Cedar St. FMB 202, New Haven, Connecticut 06520, USA

- The microglia are a specialized brain glial cell type, which is a target for **estrogen actions**; immune and non-immune regulatory functions are influenced directly by estrogen via expression and secretion of cytokines, and growth factors by the microglia.
- IL-1, IL-2, IL-6, TNF-Alpha, and IFN - Gamma are all products of microglia.

  - Why Aromatase inhibitors are not safe!!

What we can see and what we cannot see



Lobes of the Brain

Form and Function

- Clinical assessment of the patients symptomatology can lead to an understanding of the underlying damage.
- Knowing the key functional attributes of each lobe of the brain can help in determining where the damage is even before doing sophisticated radiologic procedures.
- If the technology is unavailable, then you can use confrontational means to assess the areas of damage.

TBI Locator

Traumatic Brain Injury Locator | 2014

A comprehensive clinical assessment of a patient, with a history of head trauma, can help predict or localize the area(s) of the brain involved. Sometime this assessment will not have a radiologic confirmation and therefore, becomes the only means to assign the probable area of injury.

Name: Date:

Brain Stem [ ] NORMAL
- ☐ Decreased vital capacity in breathing (speaking)
- ☐ Swallowing food and water (**Dysphagia**).
- ☐ Difficulty with organization/perception of the environment.
- ☐ Problems with balance and movement.
- ☐ Dizziness and nausea (**Vertigo**).
- ☐ Sleeping difficulties (Insomnia, sleep apnea).

Cerebellum [ ] NORMAL
- ☐ Loss of ability to coordinate fine movements.
- ☐ Loss of ability to walk.
- ☐ Inability to reach out and grab objects.
- ☐ Tremors.
- ☐ Dizziness (Vertigo).
- ☐ Slurred Speech (**Scanning Speech**).
- ☐ Inability to make rapid movements.

Temporal Lobe [ ] NORMAL
- ☐ Difficulty in recognizing faces (**Prosopagnosia**).
- ☐ Difficulty in understanding spoken words (**Wernicke's Aphasia**).
- ☐ Difficulty with verbal ID of objects.
- ☐ Short term memory loss.
- ☐ Interference with long term memory.
- ☐ Alteration in Libido and sexual behavior.
- ☐ Inability to categorize objects (**Categorization**).
- ☐ Right lobe damage can cause persistent talking.
- ☐ Increased aggressive behavior.

Occipital Lobe [ ] NORMAL
- ☐ Defects in vision (**Visual Field Cuts**).
- ☐ Difficulty with locating objects in environment.
- ☐ Difficulty with identifying colors (**Color Agnosia**).
- ☐ Production of hallucinations.
- ☐ Visual illusions - inaccurately seeing objects.
- ☐ Word blindness - inability to recognize words.
- ☐ Difficulty in recognizing drawn objects.
- ☐ Inability to recognize the movement of object
- ☐ Difficulties with reading and writing.

Parietal Lobe [ ] NORMAL
- ☐ Inability to attend to more than one object at a time.
- ☐ Inability to name an object (**Anomia**).
- ☐ Inability to locate the words for writing (**Agraphia**).
- ☐ Problems with reading (**Alexia**).
- ☐ Difficulty with drawing objects.
- ☐ Difficulty in distinguishing left from right.
- ☐ Difficulty with doing mathematics (**Dyscalculia**).
- ☐ Lack of self awareness and/or surrounding space (**Apraxia**) that leads to difficulties in self-care.
- ☐ Inability to focus visual attention.
- ☐ Difficulties with eye and hand coordination.

Frontal Lobe [ ] NORMAL
- ☐ Loss of simple movement of various body parts
- ☐ Inability to plan a sequence of complex movements needed to complete multi-stepped tasks, such as making coffee (**Sequencing**).
- ☐ Loss of spontaneity in interacting with others.
- ☐ Loss of flexibility in thinking.
- ☐ Persistence of a single thought (**Perseveration**).
- ☐ Inability to focus on task (Attending).
- ☐ Mood changes (**Emotionally Labile**).
- ☐ Changes in social behavior.
- ☐ Changes in personality.
- ☐ Difficulty with problem solving.
- ☐ Inability to express language (Broca's Aphasia).

Abnormal Findings in:

[ ] Frontal

[ ] Parietal

[ ] Occipital

[ ] Temporal

[ ] Cerebellum

[ ] Brain Stem

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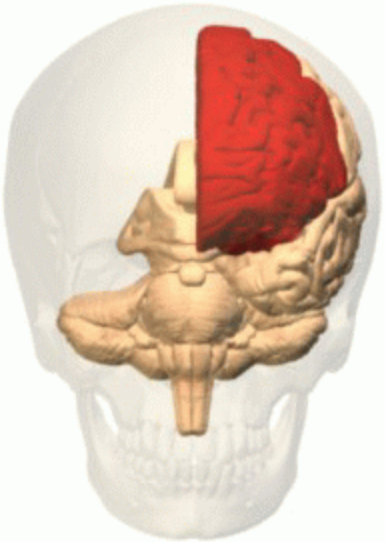
1a. Lobular Functionality
Frontal Lobes

- Mood changes (Emotionally Labile).
- Changes in social behavior.
- Changes in personality.
- Diminished Executive Functions.
- Inability to sequence complex movements.
- Loss of spontaneity in interacting with others
- Loss of flexibility in thinking.
- Persistence of a single thought (Persevera
- Inability to focus on task (Attending).
- Difficulty with problem solving.
- Inability to express language (Broca's Ap



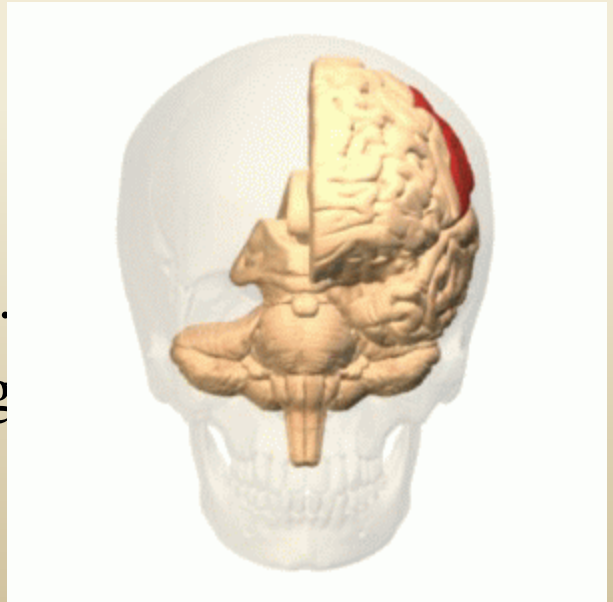
Traumatic Brain Injury Syndrome Temporal Lobes

- Increased aggressive behavior.
- Short term memory loss.
- Interference with long term memory.
- Alteration in Libido and Sexual Behavior.
- Difficulty in understanding spoken words (Wernicke's Aphasia).
- Difficulty in recognizing faces (Prosopagn
- Difficulty with verbal ID of objects.
- Inability to categorize objects (Categorizat
- Right lobe damage can cause persistent tal



Traumatic Brain Injury Syndrome Parietal Lobes

- Problems with reading (Alexia).
- Difficulty with doing mathematics (Dyscalculia).
- Inability to focus visual attention.
- Difficulties with eye and hand coordination.
- Inability to locate the words for writing (Agraphia).
- Inability to name an object (Anomia).
- Inability to attend to more than one object
- Difficulty with drawing objects.
- Difficulty in distinguishing left from right.
- Lack of self awareness and/or surrounding that leads to difficulties in self-care.



Traumatic Brain Injury Syndrome Occipital Lobes

- Production of hallucinations.
- Visual illusions - inaccurately seeing objects.
- Defects in vision (Visual Field Cuts).
- Difficulties with reading and writing.
- Difficulty with locating objects in environment.
- Difficulty with identifying colors (Color A
- Word blindness - inability to recognize wo
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- Inability to recognize the movement of obj



Cerebellum

- Loss of ability to coordinate fine movements.
- Loss of ability to walk.
- Inability to reach out and grab objects.
- Tremors.
- Dizziness (Vertigo).
- Slurred Speech (Scanning Speech).
- Inability to make rapid movements.

Brain Stem

- Decreased vital capacity in breathing, important for speech.
- Swallowing food and water (Dysphagia).
- Difficulty with organization/perception of the environment.
- Problems with balance and movement.
- Dizziness and nausea (Vertigo).
- Sleeping difficulties (Insomnia, sleep apnea).

Hypothalamus

- The main function of the hypothalamus is homeostasis.
- Measurable factors such as blood pressure, body temperature, fluid and electrolyte balance, and body weight are maintained at a precise value called the set point.
- The hypothalamus does so by regulating three interrelated functions: **endocrine secretion**, **autonomic function**, and **emotions**.

The Hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity.

Proc. Natl. Acad. Sci. USA Vol. 95, pp. 322–327, January 1998 Neurobiology. L. De Lecea, T.S.Kilduff, C. Peyron et al. Depts of Molecular Biology and Neuropharmacology, The Scripps Research Institute, La Jolla, CA; Center for Sleep and Circadian Neurobiology, Stanford University, Stanford, CA; Dept of Neurosurgery, Yale University, New Haven, CT ; Institute of Basic Medical Sciences, Dept of Biochemistry, University of Oslo, P.O. Box 1112, Blindern, N-0317 Oslo, Norway; and The Jackson Laboratory, Bar Harbor, ME 04609.

- Narcolepsy appears to be due to the sudden drop in the production of Orexin-Hypocretin.
- Damage to the cells of the dorsal and lateral hypothalamus leads to a variable deficiency in the production of Hypocretin (Orexin).
- In traumatic brain injury, it appears to be the cause for the primary complaint of fatigue and daytime somnabulance.
- Hypocretin has been found to be a potent neurotransmitter in the CNS regulating the ??RAS??
- New sleep medication: **Suvorexant blocks Orexin receptors 1 and 2.**

Loss of hypocretin (orexin) neurons with traumatic brain injury.

Ann Neurol . 2009 October ; 66(4): 555–559. Christian R. Baumann, et al, Dept. of Neurology, University Hospital, Zurich, Switzerland. Dept of Neuropathology, University Hospital, Zurich, Switzerland. Dept of Forensic Medicine, University Hospital, Zurich, Switzerland. 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 for many patients with traumatic brain injury (TBI) but thus far, its etiology is not well understood.
- Extensive loss of the hypothalamic neurons that produce the wake-promoting neuropeptide hypocretin (orexin) causes the severe sleepiness of narcolepsy, and partial loss of these cells may contribute to the sleepiness of Parkinson's disease and other disorders.

Inflammation of the Hypothalamus Leads to Defective Pancreatic Islet Function

. J. Biol. Chem. 2011, 286:12870-12880. Vivian C. Calegari, Adriana S. Torsoni, Emerielle C. Vanzela, Eliana P. Araújo, Joseane Morari, Claudio C. Zoppi, Lourenço Sbragia, Antonio C. Boschero and Lício A. Velloso

- Type 2 diabetes mellitus results from the complex association of Insulin Resistance and Pancreatic β-Cell Failure.
- Many of the neural inputs that control β-cell activity are generated in the hypothalamus.
- The autonomic signals generated with hypothalamic inflammation can impair pancreatic islet function, and may explain the link between obesity and defective insulin secretion and the Metabolic Syndrome(Insulin Resistance) in TBI Cases.

The Limbic System

- Is a collection of structures from the cerebrum, diencephalon, and midbrain, including the hippocampus, amygdalae, anterior thalamic nuclei, septum, limbic cortex and fornix.
- It appears to be primarily responsible for our **emotional life**, and has a great deal to do with the formation of long-term **memories and provides motivation**.

A revised limbic system model for memory, emotion and behaviour.

Neuroscience and Biobehavioral Reviews 37 (2013) 1724– 1737. Marco Catania,Flavio Dell'Acquaa,Michel Thiebaut de Schottena,, Natbrainlab, Dept of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College London, UK. Dept of Neuroimaging Sciences, Institute of Psychiatry, King's College London, NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London, UK.

- The limbic system is a group of interconnected cortical and subcortical structures dedicated to linking visceral states and emotion to cognition and behavior.
- The role of the limbic structures includes controlling social interactions and behavior, consolidating memories, and forming emotions.

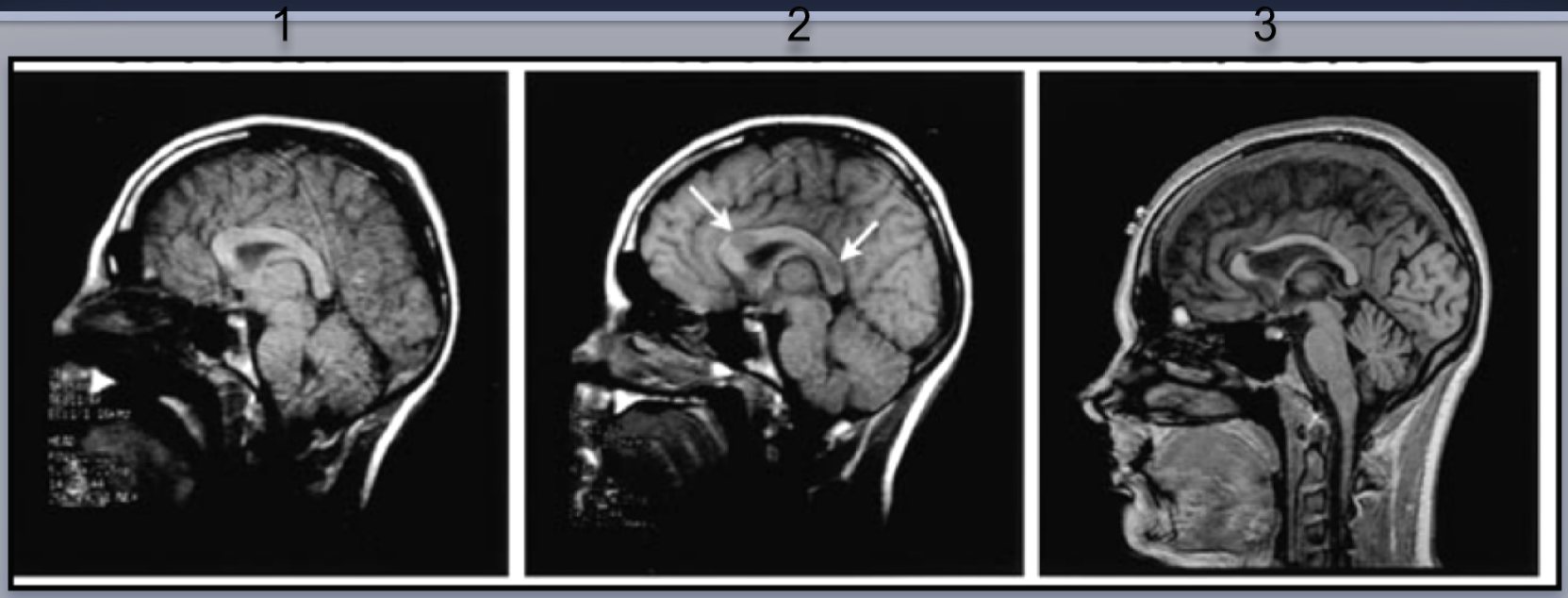
Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis

. Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 1201 – 1213.
James P. Herman, Michelle M. Ostrander, Nancy K. Mueller, Helmer Figueiredo . Dept of Psychiatry, Psychiatry North, ML 0506 2170 East Galbraith Road, University of Cincinnati College of Medicine, Cincinnati, OH, Dept of Cell Biology, Neurobiology and Anatomy, University of Cincinnati College of Medicine, Reading, OH

- Limbic dysfunction and hypothalamo-pituitary-adrenocortical (HPA) axis dysregulation are key features of Affective Disorders.
- *Affective disorders* are a set of psychiatric diseases, also called *mood disorders*. The main types of *affective disorders* are **depression, bipolar disorder, and anxiety disorder**.

The lesion(s) in traumatic brain injury: implications for clinical neuropsychology

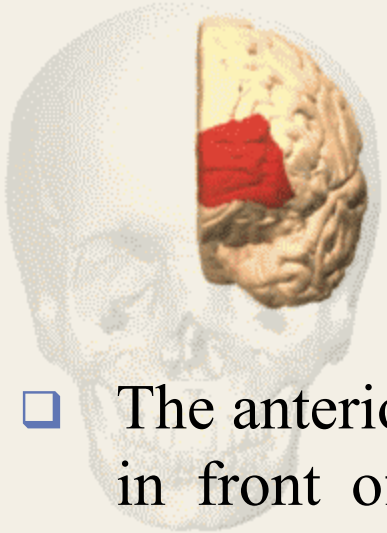
. Archives of Clinical Neuropsychology 16 (2001) 95-131. Erin D. Bigler
Departments of Psychology and Neuroscience, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA



(1) DOI (2) 5-days Post-TBI (3) 4-years Post-TBI

Damage to the corpus callosum from Coup-counter coup in this patient in a front end collision:

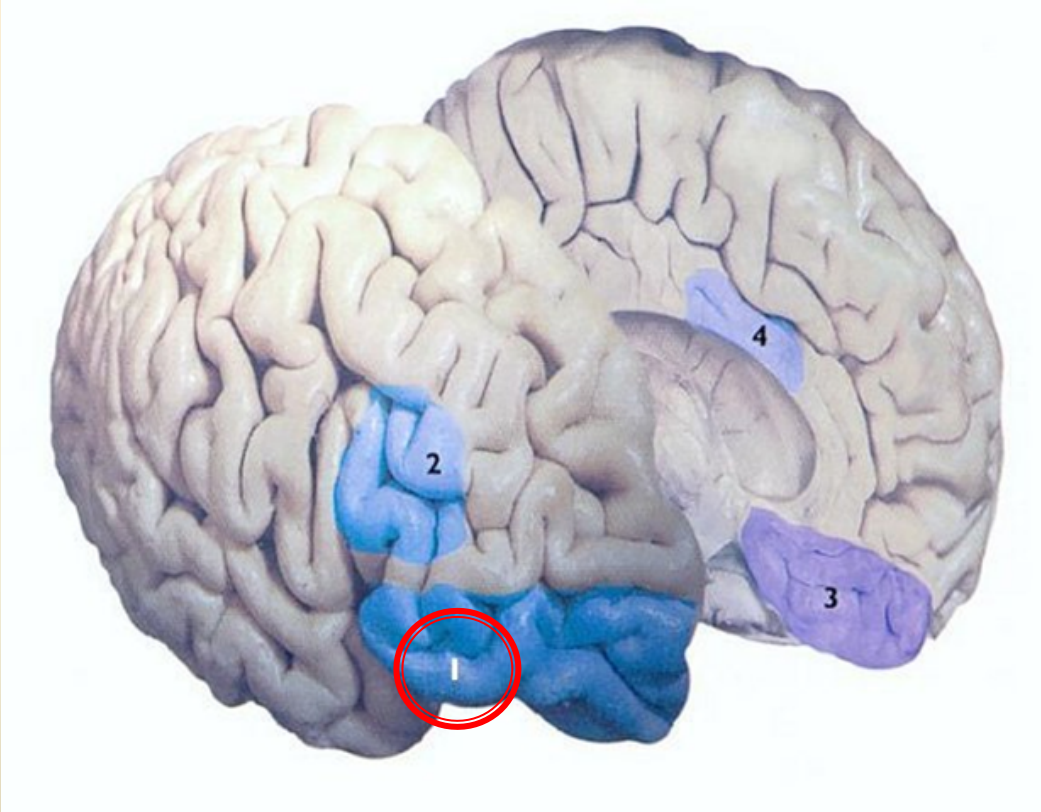
This patient developed anger, rage, and violent emotional outbursts.



Prefrontal Cortex

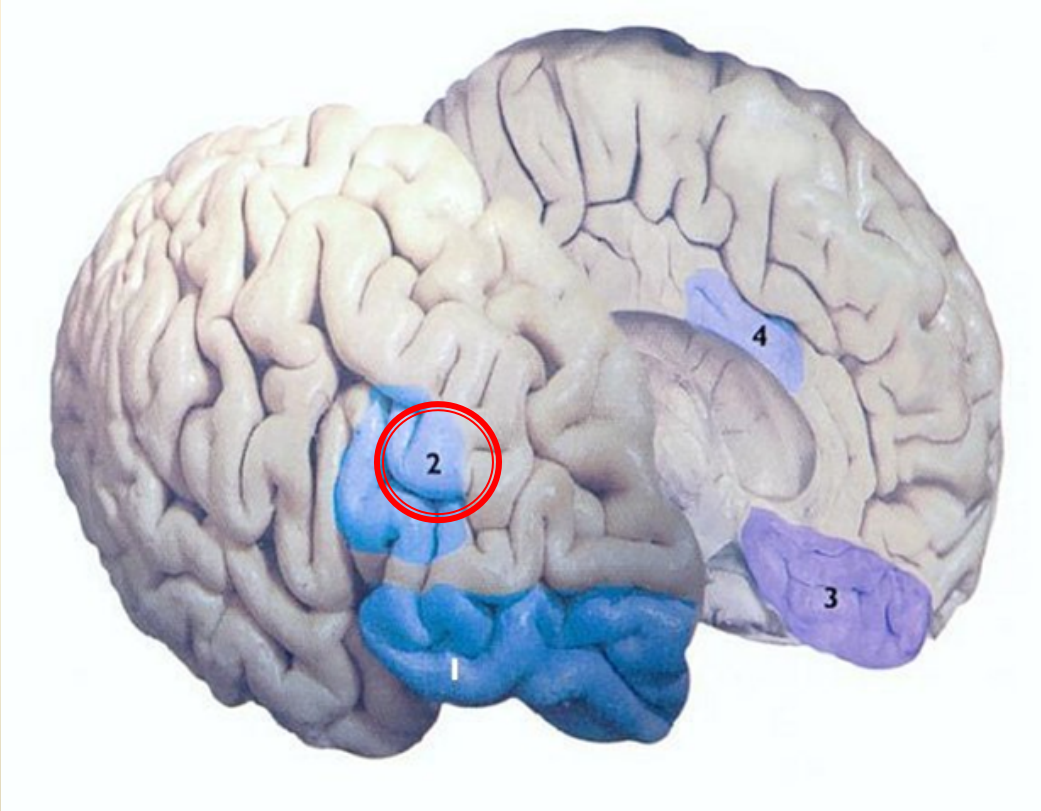
- The anterior part of the frontal lobes (prefrontal cortex), lying in front of the motor and premotor areas is implicated in planning, complex cognitive behavior, personality expression, decision making, and moderating social behavior; Executive Functions.
- Executive function relates to abilities to differentiate among conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social "control" (the ability to suppress urges that, if not suppressed, could lead to socially unacceptable outcomes).

Frontal Lobe Functioning in Health



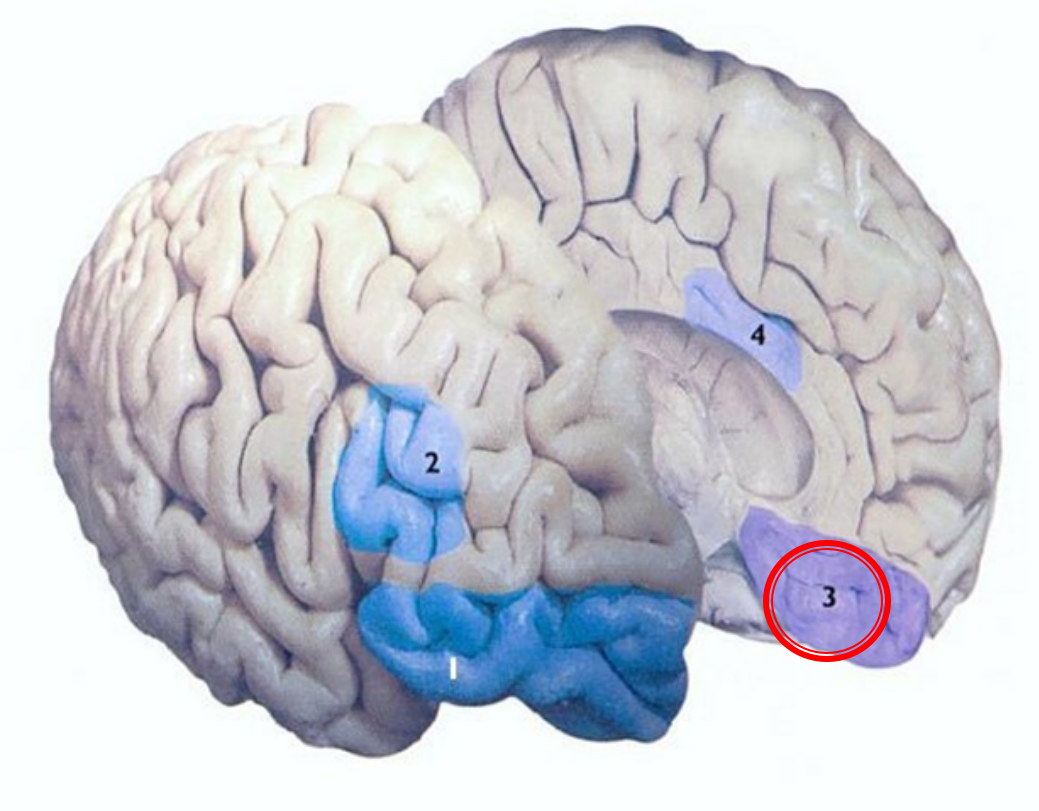
1 : **Orbito-Frontal Cortex** - This area inhibits inappropriate action, freeing us from the tyranny of our urges and allowing us to defer immediate reward in favor of long-term advantage.

Frontal Lobe Functioning in Health



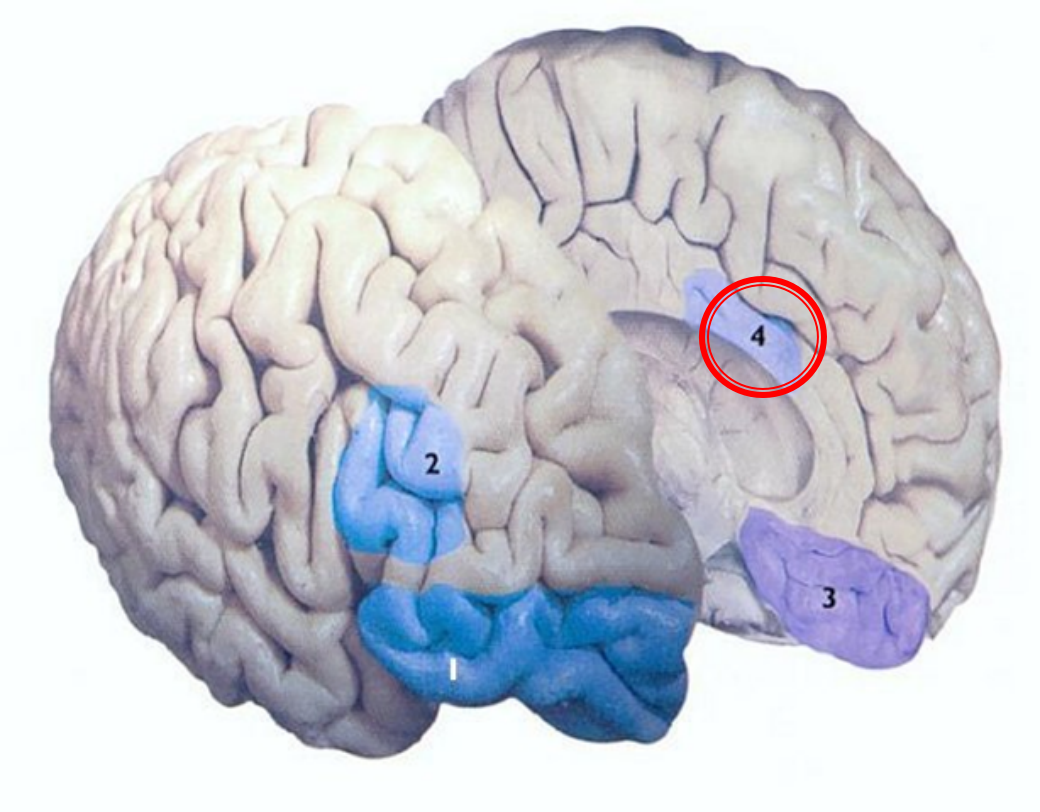
2 : Dorsolateral prefrontal cortex - Things are held "in mind" here, and manipulated to form plans and concepts. This area also seems to choose to do one thing rather than another.

Frontal Lobe Functioning in Health



3 : Ventromedial cortex - This is where emotions are experienced and meaning bestowed on our perceptions.

Frontal Lobe Functioning in Health



4 : Anterior cingulate cortex - It helps focus attention and "tune in" to own thoughts.

Hippocampal Volume and Mood Disorders After Traumatic Brain Injury

BIOL PSYCHIATRY 2007;62:332–338. Ricardo E. Jorge, Laura Acion, Sergio E. Starkstein, and Vincent Magnotta. Departmentof Psychiatry;Departmentof Radiology, University of Iowa, Iowa City, Iowa; and the Department of Psychiatry.

- TBI is characterized by pathological changes in cortical areas, subcortical nuclei, and white matter tracts with dystrophic neurons in the **CA1** subfields of the hippocampus, lasting up to 2 weeks after trauma.
- Quantitative analysis demonstrated **progressive neuronal loss** in the cerebral cortex and hippocampus over 1 year after injury.
- The occurrence of mood disorders during the first year after TBI appears to be associated with this reduction in hippocampal volumes (also memory recall and the ability to learn new information).

The Cingulate Gyrus

- It is an integral part of the limbic system, which is involved with **emotion formation** and **processing**, **learning,** and **memory**.
- The combination of these three functions makes the cingulate gyrus highly influential in linking **behavioral outcomes to motivation**.
- Daniel Coleman, author of ***Emotional Intellect*** puts the function as "Lets just say that the CG tries to help us put logic around our emotions. **Good luck**!"

Amygdala.1

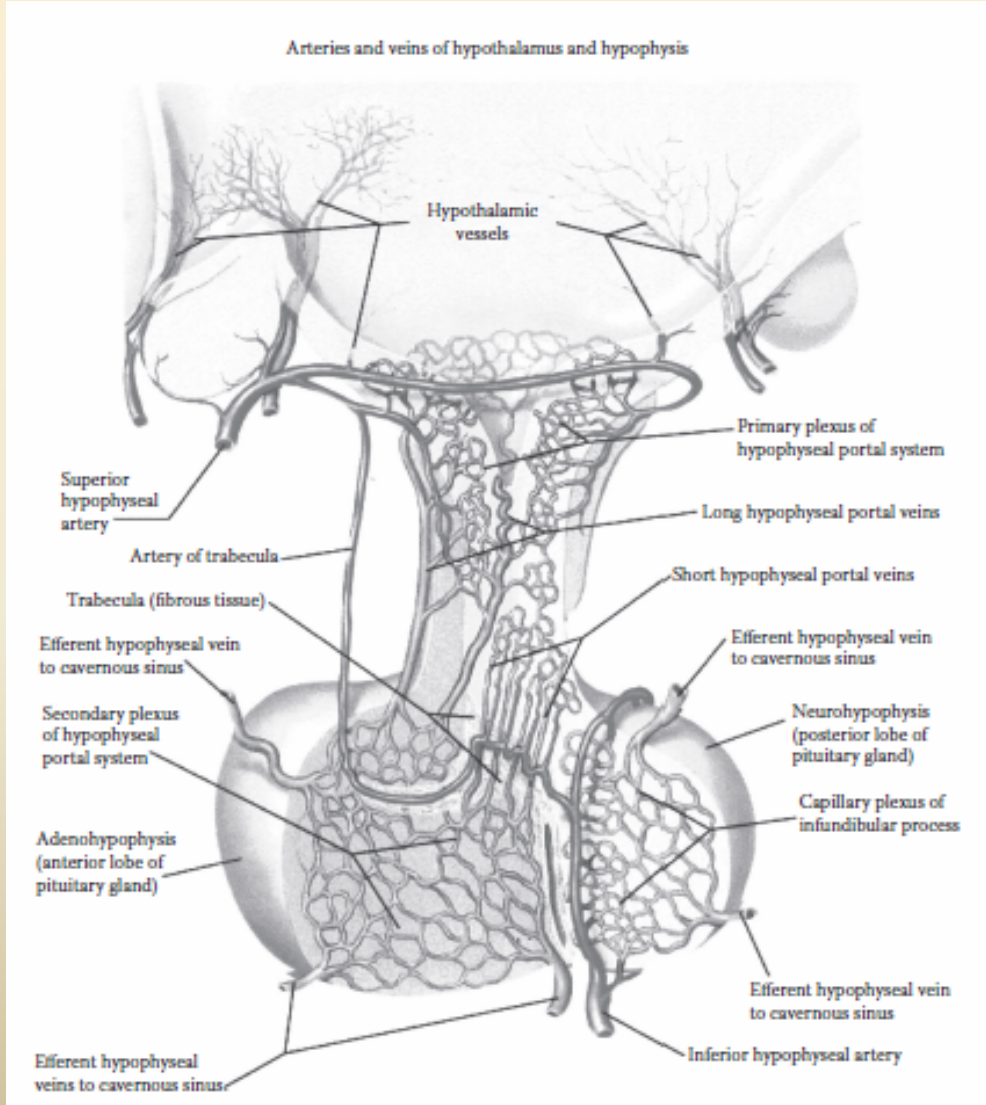
- Located deep inside the anterio-inferior region of the temporal lobe, the Amygdala connects with the hippocampus, the septal nuclei, the prefrontal area and the medial dorsal nucleus of the thalamus.
- These connections make it possible for the **amygdala to control the major affective activities** like friendship, love and affection, on the expression of mood and, mainly, on fear, rage, and aggression.
- TBI can lead to the loss of connectivity.

Amygdala.2

- The amygdala, is the center for the identification of danger, and is fundamental for self-preservation.
- **When triggered, it gives rise to fear and anxiety which lead to a heightened stage of alertness, getting ready to fight or for flight.**
- Experimental destruction of both amygdales tames the animal, which becomes **sexually non-discriminative**, deprived of affection and indifferent to danger.

Damage to blood supply to AP

- Compromised blood supply to the pituitary is seen in **Sheehan's, repetitive or prolonged surgery, stokes, and with increase intracranial pressure.**
- This can lead to selective anterior pituitary hormone deficiencies.

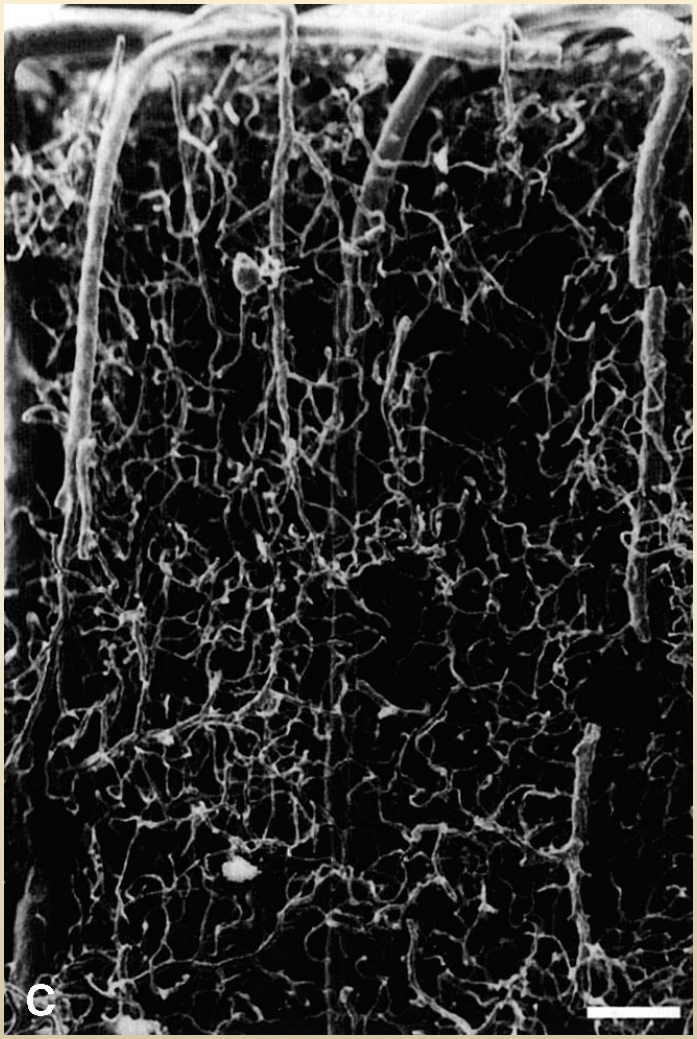


The lesion(s) in traumatic brain injury: implications for clinical neuropsychology

. Archives of Clinical Neuropsychology. 16 (2001) 95-131. Sept 2000.

Erin D. Bigler. Depts of Psychology and Neuroscience, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA

- Many times in TBI micro vessels permeating the gray to white matter are sheared along with neurons.
- The added insult of **free blood** in the brain augments the production of inflammation with free radical damage induced by the iron released from hemoglobin.



Diffuse Axonal Injury

- Diffuse axonal injury (DAI) is caused by acceleration–deceleration and rotational forces during the primary head injury.
- This injury causes a stretching and shearing of the neurons (white matter tracts) throughout the brain, disrupting neuronal transmission and connectivity.
- DAI is only visible on the MRI scan however, there is a high index of suspicion when multiple small cerebral contusions appear on CT scan.
- DAI can be clinically diagnosed when the patient has experienced a prolonged coma (> 6 hours) and does not have signs of a mass lesion or ischemia.

The lesion(s) in traumatic brain injury: implications for clinical Neuropsychology

. Archives of Clinical Neuropsychology 16 (2001) 95-131. Erin D. Bigler Departments of Psychology and Neuroscience, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA

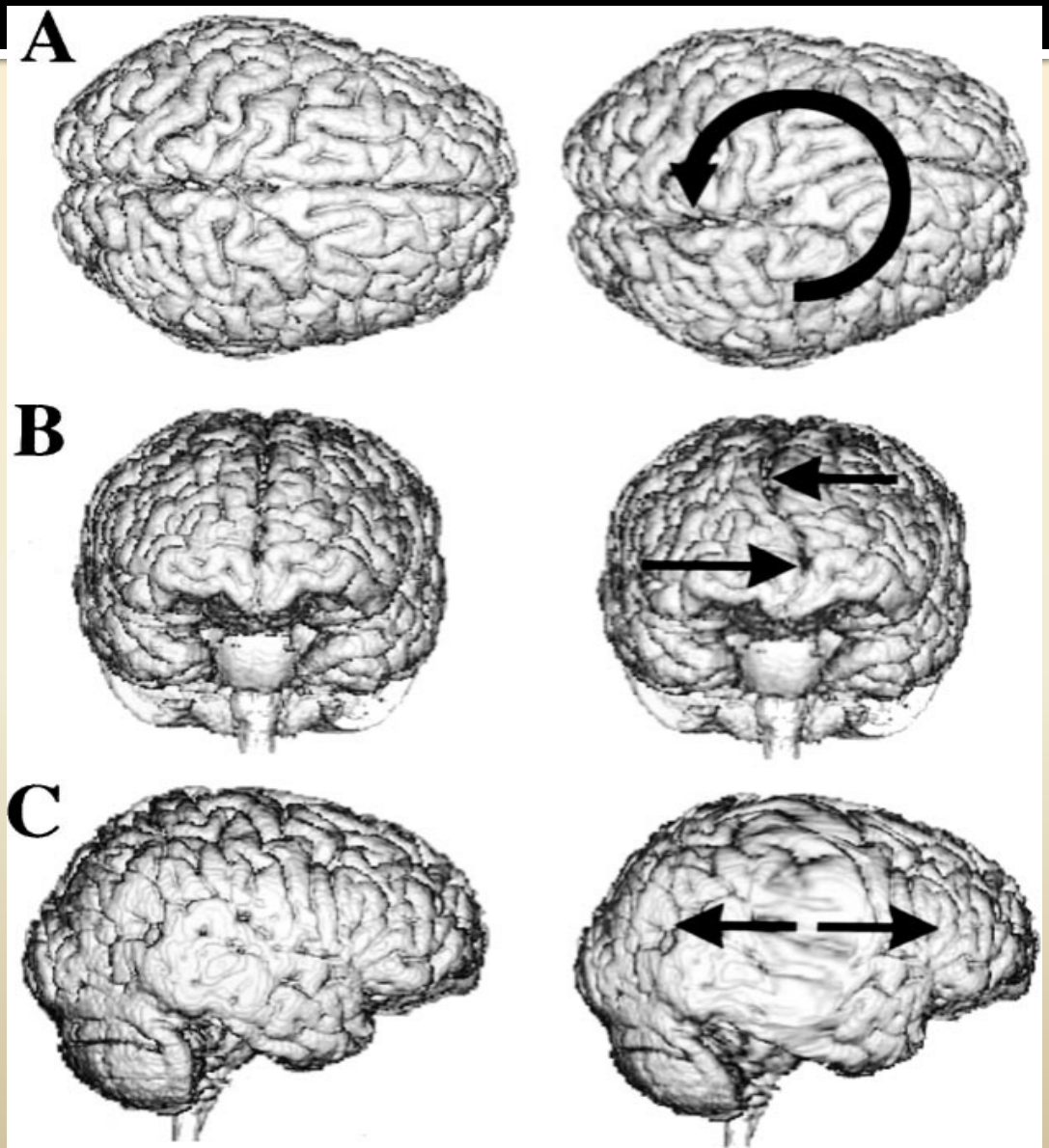
(A) Dorsal View of a high velocity side impact that is rotating the brain with twisting action.

Shearing actions

(B) Frontal View of a high velocity side impact that is twisting the brain.

Shearing actions

(C) Lateral View of a high velocity side impact that is stretching and twisting the brain.



Diffuse Axonal Injury

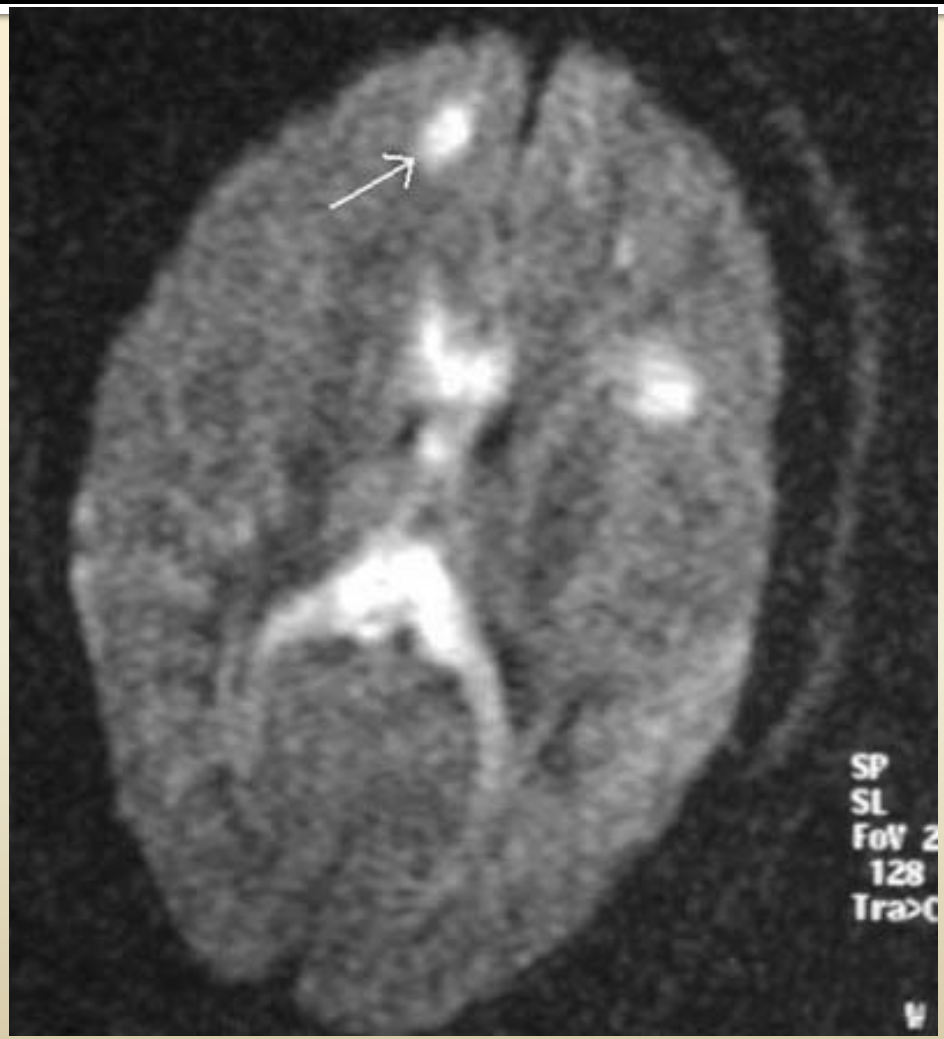
- Typically, diffuse and bilateral involving the lobar white matter (FL) at the gray-white matter interface.
- Most Common areas involved:
  - Frontal and Temporal White Matter
  - Corpus Callosum
  - Caudate Nuclei
  - Tegmentum
  - Thalamus
  - Hypothalamus
  - Internal Capsule

Mechanism of Head Injuries. Holbourn A., Lancet. **1943**;2:438-41

- Sudden acceleration-deceleration impact can produce shearing injury which is not found to be induced by linear or translational forces but only by rotational forces.
- Greater than 60% of the shearing injuries produced by rotational force is at the gray-white matter junction.
- When shearing forces occur in this area of greater density differential, the axons suffer trauma resulting in edema and axonal leakage which is most **severe in the 2 week post trauma period.**
- Loss of consciousness is associated with DAI.

Diffuse Axonal Injury. Jeffrey R Wasserman, DO, Diagnostic Radiologist, Manatee Memorial Hospital and Lakewood Ranch Medical Center Robert A Koenigsberg, DO, MSc, FAOCR, Professor, Director of Neuroradiology, Program Director, Diagnostic Radiology and Neuroradiology Training Programs, Department of Radiology, Hahnemann University Hospital, Drexel University College of Medicine. **2010**





Classification of DAI

DAI is classified as mild, moderate or sever:

- **Mild DAI**: Coma lasting 6-24 hours, mild to moderate memory impairment, and mild to moderate disabilities.
- **Moderate DAI**: Coma lasting > 24 hours, followed by confusion and long-lasting amnesia. Withdrawal to purposeful movements, and mild to severe memory, behavioral, cognitive, and intellectual deficits.
- **Severe DAI**: Deep prolonged coma lasting months with flexion and extension posturing. Dysautonomia can occur. Deficits are noted in cognition, memory, speech sensorimotor function and personality.

Summary

- TBI affects functioning at subcellular and cellular levels influencing the integration of the different lobes of the brain. Connectivity.
- At the subcellular level **neurotransmitters and neurosteroids** are affected along with their ability to modulate gated-ion channels and receptors, thereby altering both cognition and neurobehavior.
- On the cellular level, destruction of neurons and glial cells further flame the fires of inflammation with the progression and expansion of cell death and loss of cerebral tissue = Cavitation.

Summary

- Compromise of the hypophyseal blood supply can lead to the loss of anterior pituitary hormones (Sheehan's-like syndrome).
- Bleeding into the brain not only causes local ischemic, hypoxia, and hypoglycemia but deposits iron which initiates free radical production raising OS.
- All adverse reactions are modifiable with the use of NS, NAS and supplements that address inflammation and Oxidative Stress.

Traumatic Brain Injury:

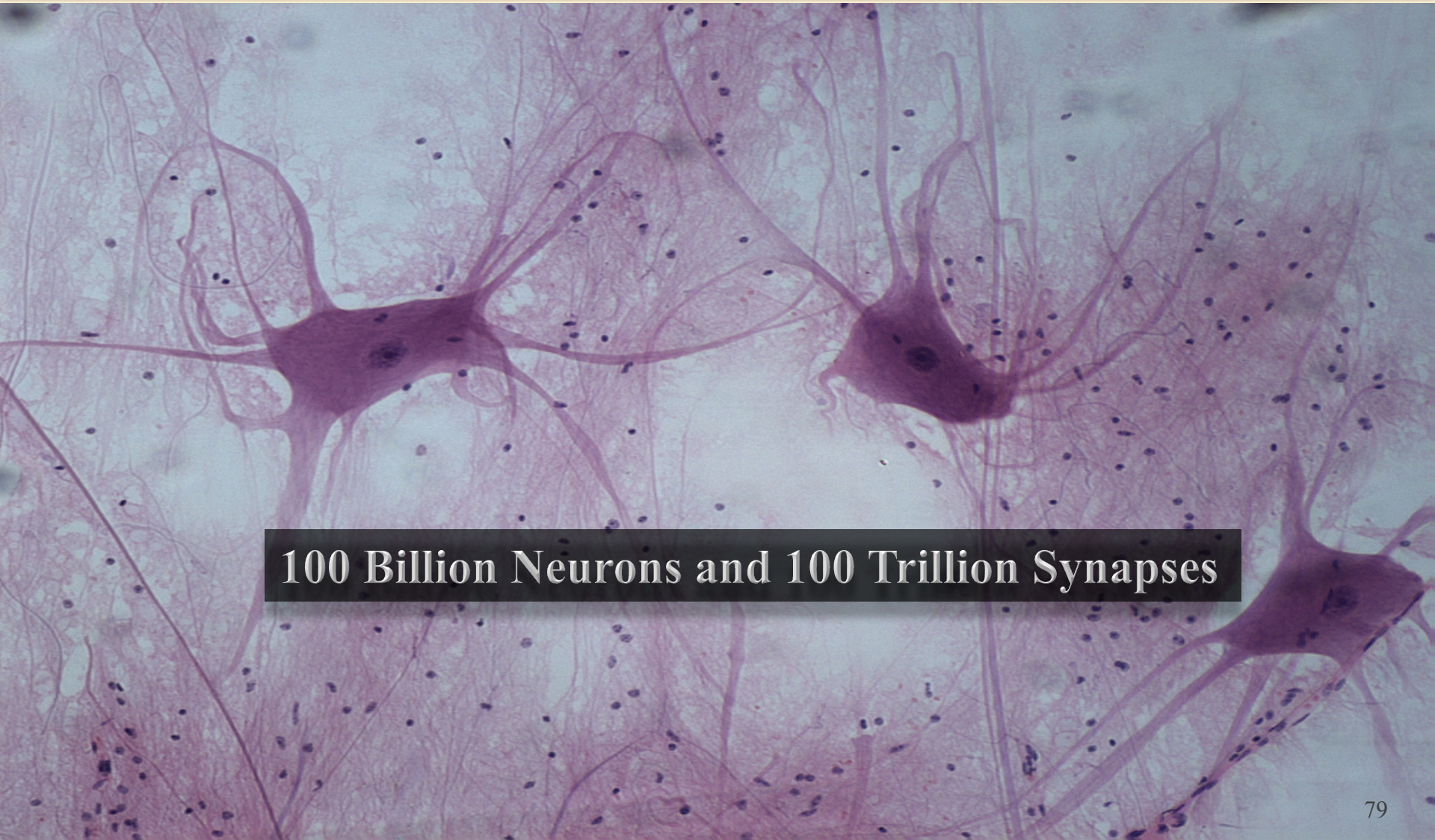
A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.

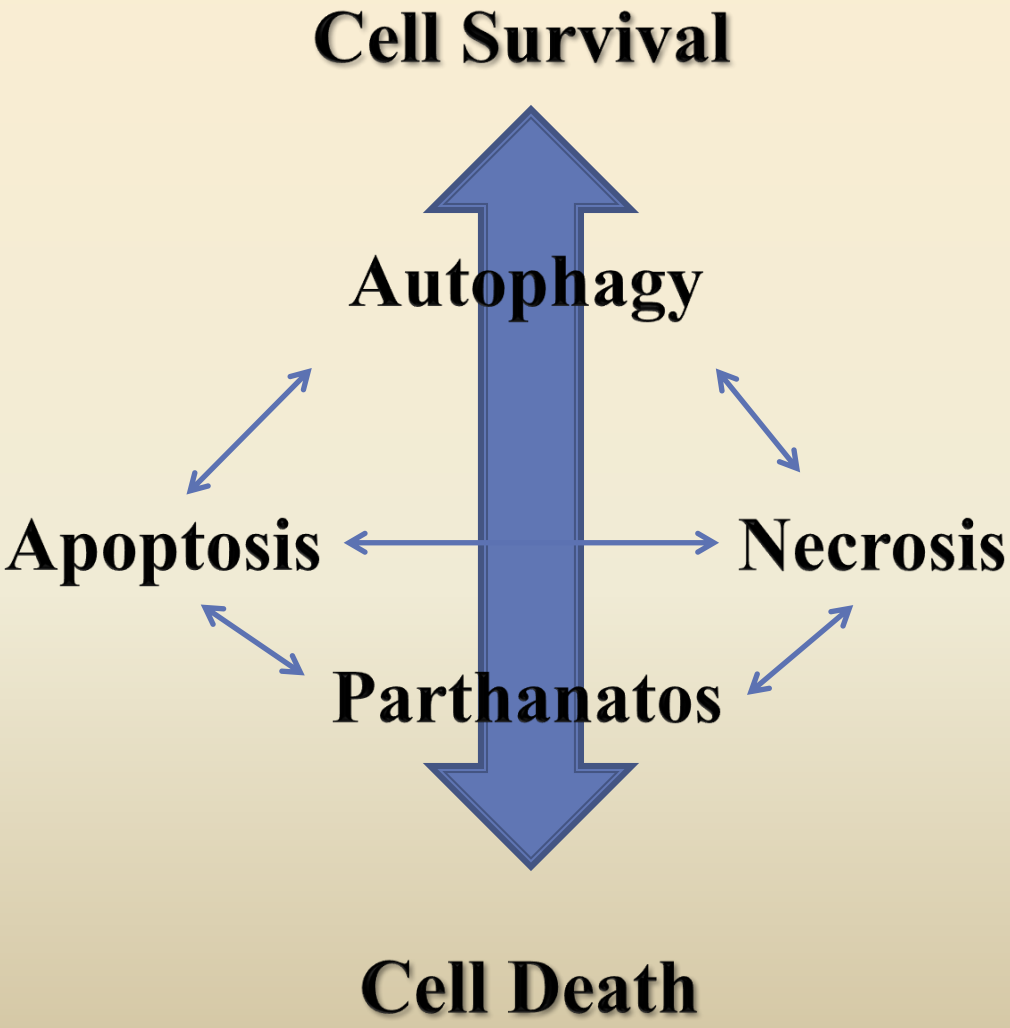


Chapter 3: Neuropathology

Neuropathology



A balance between life almost death and death



Cell Death Mechanisms Following Traumatic Brain Injury. Brain Pathology 2004;14:215-222. Ramesh Ragupathi, PhD. 2004

- Traumatic Brain Injury is a **complex neurodegenerative disease** resulting in preferential neuronal loss in the **Cortex**, **Hippocampus**, **Cerebellum**, and **Thalamus** **(Hypothalamus)**.
- The progressive increase in cortical lesion volume (cavitation), in the post-traumatic period suggests that delayed or chronic neuronal degeneration is a component of post-trauma pathology.
- **Cavitational lesions** expand over time due to the continued production of free radicals and heightened oxidative stress that induces further neuronal loss.

Cortical Functioning

- Loss of normal neocortical modulation may result in spasticity, tachycardia, gastrointestinal dysfunction, pyramidal patterns of muscle weakness, blood pressure changes, behavioral changes, changes in affect, and many other functional disorders.
- The associated muscle weakness patterns causing joint dyskinesia, may also result in primary musculoskeletal pain and dysfunction.

Hippocampal Functioning

- The hippocampus is critical for the formation of new autobiographical and fact memories. It may function as a memory "gateway" through which new memories must pass before entering permanent storage in the brain.
- Hippocampal damage can result in **anterograde amnesia**: loss of ability to form new memories, although older memories may be safe.

Cerebellar Functioning

- The cerebellum does not initiate movement, but it contributes to coordination, precision, and accurate timing of movement.
- It receives input from sensory systems of the spinal cord and from other parts of the brain, and integrates these inputs to fine tune motor activity.

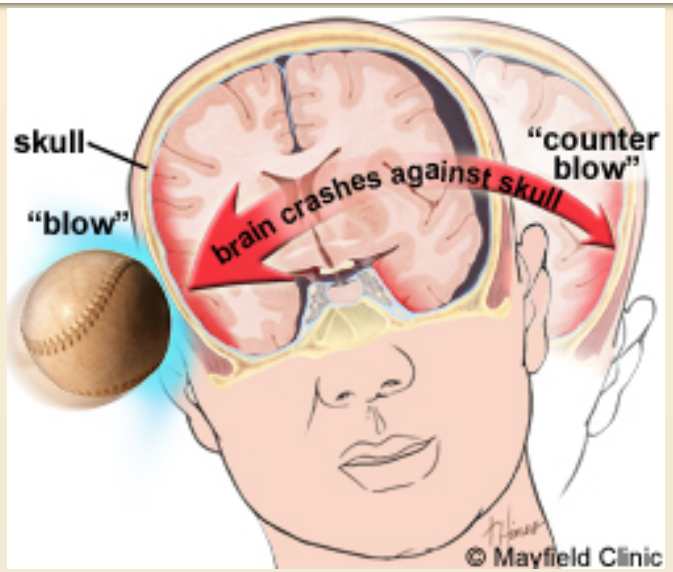
Thalamic Functioning

- Some of its functions are the relaying of sensory and motor signals to the cerebral cortex, and the regulation of consciousness, sleep, and alertness.

Hypothalamic Functioning

- The hypothalamus has a central neuroendocrine function, most notably by its control of the anterior pituitary trophic hormones (TSH, LH, FSH..ect).
- The hypothalamus controls body temperature, hunger, important aspects of parenting and attachment behaviors, thirst, fatigue, sleep, and circadian rhythms.

Primary Phase Injury









Macro-Damage: the Primary Phase of TBI

- Non-penetrating injures:
  - Contusions, micro-hemorrhages, Subdural Hematomas and Subarachnoid Hemorrhages.
  - Diffuse axonal injury.
  - Precipitation and Initiation of Secondary Cascades of injury.
- Penetrating injuries:
  - Fracture to the skull.
  - Loss of brain tissue.
  - Destruction or disruption of neuronal pathways.
  - Compromise of vasculature.
  - Precipitation and Initiation of Secondary Cascades of injury.

Micro-Damage: the Secondary Phase of TBI

- Cell death pathways; Necrosis, Apoptosis, Autophagy, and Parthanatos*.
- Free radicals and Oxidative stress*.
- Excitotoxicity*
- Hypoxia.
- Ischemia. Lactic Acidosis. Hypoglycemia*.
- Increased ICP with edema.
- Ionizing radiation (CT-Scan and plain x-rays)

Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases.

Acta Pharmacol Sin 2009 Apr; 30 (4): 379–387. Xiao-xia DONG, Yan WANG, Zheng-hong QIN* Department of Pharmacology and Laboratory of Aging and Nervous Diseases, Soochow University School of Medicine, Suzhou 215123, China.

- Excitotoxicity is defined as cell death resulting from the toxic actions of excitatory amino acids.
- Increased **extracellular Glutamate** levels leads to the activation of Ca^{2+} permeable NMDA receptors on myelin sheaths and oligodendrocytes, leaving oligodendrocytes susceptible to Ca^{2+} influxes and subsequent excitotoxicity by virtue of the elevated Ca^{2+}.
- Excessive activation of glutamate receptors by excitatory amino acids leads to impairment of calcium buffering, generation of free radicals, activation of the mitochondrial permeability transition and secondary excitotoxicity.

Neuronal Calcium Signaling Review

Neuron, Vol. 21, 13–26, July, 1998. Michael J. Berridge Siegesmund, 1968; Takahashi and Wood, 1970; Henkart The Babraham Institute et al.,1976). Babraham Laboratory of Molecular Signaling Cambridge CB2 4AT United Kingdom

Ionotropic

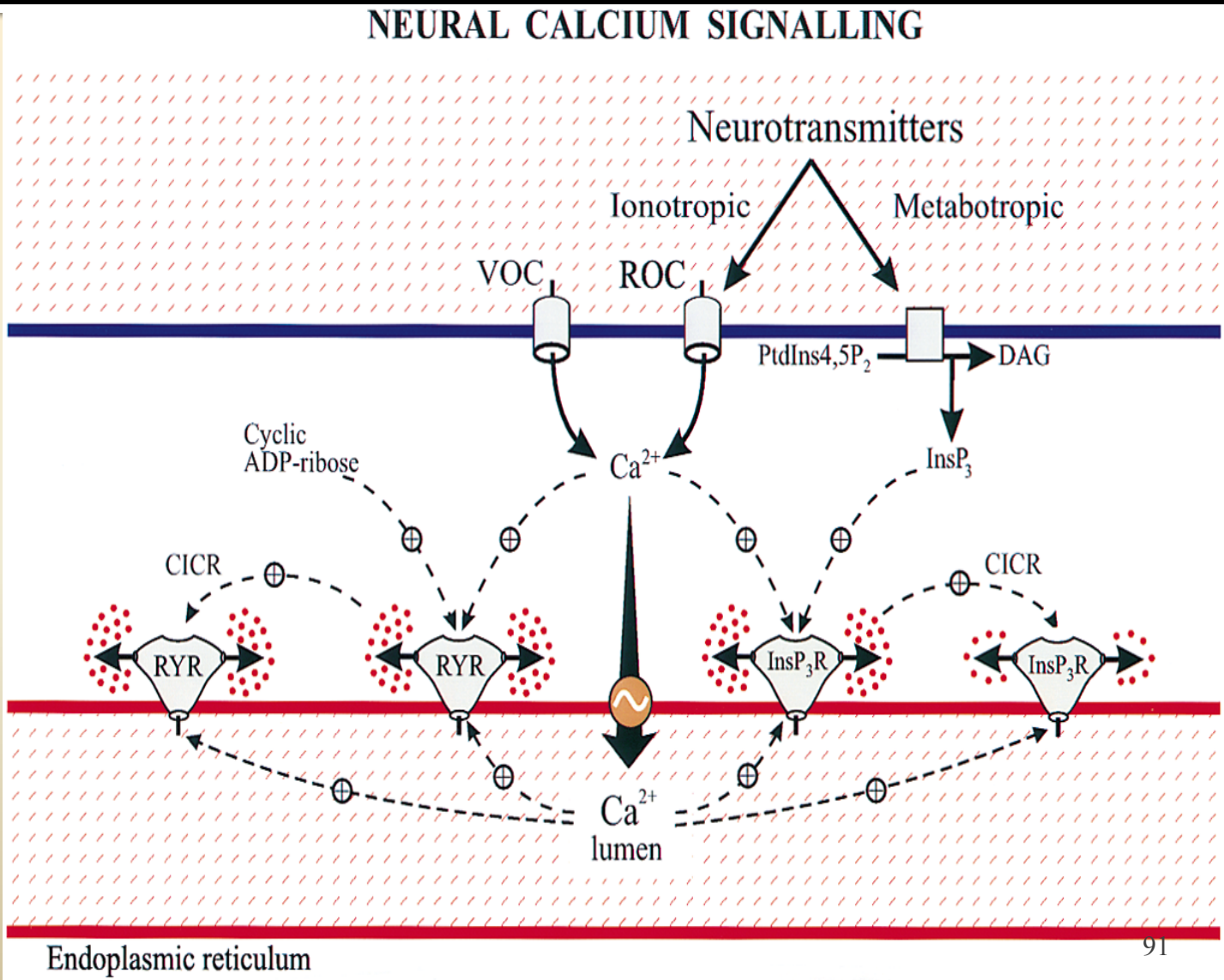
- Ion Channel

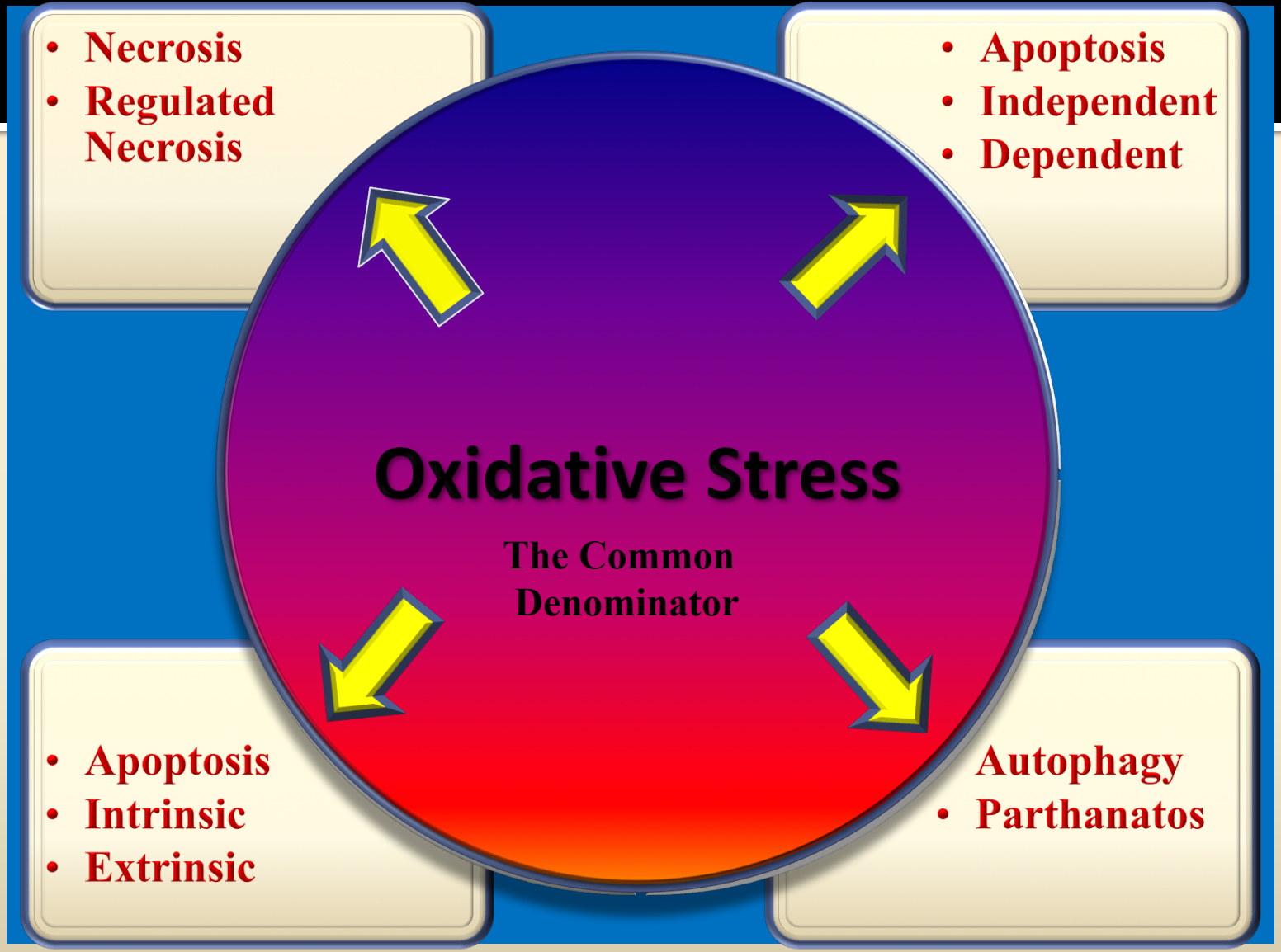
-Open allowing Ca+2 in.

Metabotropic

- G-Coupling

-Releases Ca+2 from ER.




• Necrosis
• Regulated Necrosis
• Apoptosis
• Independent
• Dependent
Oxidative Stress
The Common Denominator
• Apoptosis
• Intrinsic
• Extrinsic
Autophagy
• Parthanatos

Phase II: Oxidative Stress

Oxidative Stress
- Reactive Oxygen
- Reactive Nitrogen
- Lipid Peroxidase

Inflammation
- TH1
- Cytokines
- Chemokines

Disruption of BBB
- Hypoxia
- Ischemia
- Cerebral Edema

Neurosteroids
- Deficiencies
- Enzyme Inhibition
- Retarded production



Mitochondrial Dysfunction
BAX ► AIF, CytoC.

Excitotoxicity
- Glutamate
- Calcium

Disruption of Receptors
- NMDA, Sigma=1
- GABA-α and -β
- AMPA

Cell Death
- Necrosis
- Apoptosis
- Cavitation
- Loss of Brain

Traumatic Brain Injury: Oxidative Stress and Neuroprotection. Antioxidants & Redox Signaling Vol. 00, N0. 00, 2013.
Carolin Cornelius, Vittorio Calabrese, et al.

Ketones inhibit mitochondrial production of ROS following glutamate excitotoxicity by increasing NADH oxidation.

Neuroscience. 2007 March 2; 145(1): 256–264. Marwan Maalouf, Patrick G. Sullivan, Laurie Davis, Do Young Kim, and Jong M. Rho, Barrow Neurological Institute and St. Joseph's Hospital & Medical Center, Phoenix, Az. Spinal Cord and Brain Injury Research Center, Dept of Anatomy & Neurobiology, University of Kentucky, Lexington, Kentucky, USA

- Dietary protocols that increase serum levels of ketones, such as calorie restriction and the ketogenic diet, offer robust protection against a multitude of acute and chronic neurological diseases.
- Previous studies have suggested that the ketogenic diet **may reduce free radical levels in the brain**. Thus, one possibility is that ketones may mediate neuroprotection through antioxidant activity.
- Note: although caloric restriction will induce hypoglycemia which has been shown to increase apoptosis.

Mitochondrial Membrane Permeabilization in Cell Death. Physiol Rev 87: 99–163, 2007; Guido Kroemer, Lorenzo Galluzzi, and Catherine Brenner. Institut Gustave Roussy, Institut National de la Sante et de la Recherche Me dicale Unit "Apoptosis, Cancer and Immunity," Universite ´ de Paris-Sud XI, Villejuif; and Centre National de la Recherche Scientifique UMR 8159, Universite de Versailles/Saint-Quentin en Yvelines, Versailles, France.

- **Glucose**, favors the anti-apoptotic interaction between HKII and VDAC, exerts HK-mediated antioxidant effects, and promotes BAD inactivation* glucokinase.



- **Glucose**, at high concentrations, may have pro-apoptotic effects due to the local generation of ROS.

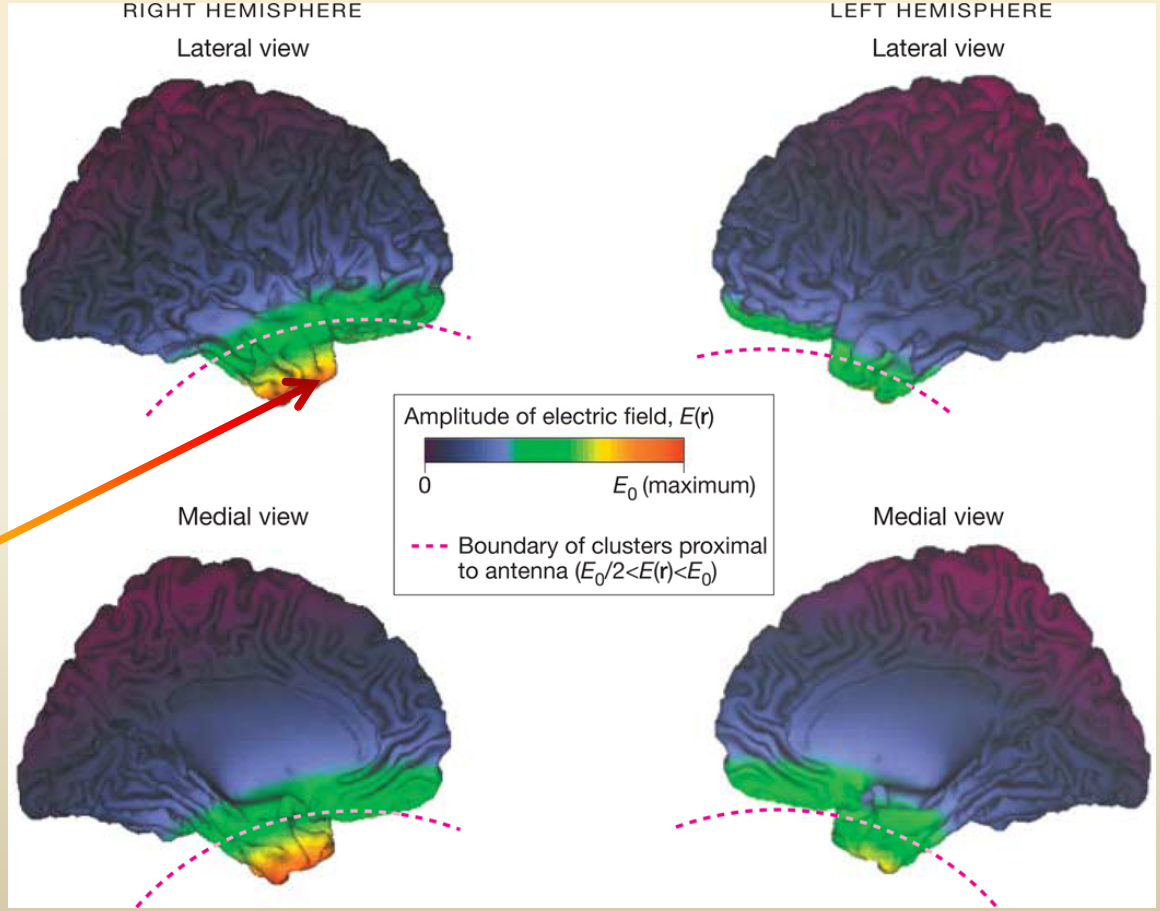
* BAD inactivation – stops opening of mitochondrial pores that allows for Cytochrome c and AIF to precipitate Apoptosis, Necrosis, and Autophagy.

Hypoglycemia

Effects of Cell Phone Radio-frequency Signal Exposure on Brain Glucose Metabolism

. JAMA. 2011 Feb. 23; 305(8): 808–813. Nora D. Volkow, MD, Dardo Tomasi, PhD, Gene-Jack Wang, MD, Paul Vaska, PhD, Joanna S. Fowler, PhD, Frank Telang, MD, Dave Alexoff, BSE, Jean Logan, PhD, and Christopher Wong, MS. National Institute on Drug Abuse, Bethesda, Maryland; National Institute on Alcohol Abuse and Alcoholism, Bethesda; and Medical Department, Brookhaven National Laboratory, Upton, New York.

Cell against Right Ear.



Necrosis-Apoptosis-Autophagy-Parthnatos

	Necrosis	Apoptosis	Autophagy	Parthanatos
Nucleus Fragmentation	NO	YES	NO	Yes
Chromatin Condensation	NO	YES	NO	Yes
Apoptotic Body Formation	NO	YES	NO	No
Cytoplasmic Vacuolation	YES	NO	YES	No
Organelle Degradation	YES	NO	YES	No
Mitochondrial Swelling	YES	Late	Variable	?
Cytoplasmic Swelling	YES	NO	NO	No
Caspase Activity	NO	**YES**	NO	No
PARP-1 (poly ADP ribose polymerase)	**YES**	Cleaved	NO	**YES**
Cathepsin B (Lysosomal)	NO	NO	YES	?
Bcl-2 Proteins/Cytochrome c	NO	YES	NO	No
Death Associated Protein	YES	YES	YES	?
PARP-1/AIF	?	YES	NO	YES

Caspases the “Messengers of Death”



- **Caspases**, are a family of cysteine proteases that play essential roles in necrosis, apoptosis, and inflammation.
- Caspases are essential in cells for apoptosis and have been termed "executioner" proteins for their roles in causing cell death.
- Some caspases are also required in the immune system for the maturation of lymphocytes.

Molecular mechanisms of "regulated" necrosis. Seminars in Cell & Developmental Biology. 2014 Nov;35:24-32. Galluzzi L, Kepp O, Krautwald S, Kroemer G, Linkermann A

- Up until 2005, cellular Necrosis was looked upon as an uncontrollable process leading to cell death and the precipitation of collateral damage by the release of inflammatory chemistry.
- Dr. Junying Yuan, discovered a protein called **Necrostatin** which could regulate the process of Necrosis.
- If Necrosis could be regulated then it was no longer a default mechanism lacking control, but one that is triggered by a chemical cascade that can now be influenced by pharmacology.



Cell Death by Necrosis: 1

- Necrosis is characterized morphologically by vacuolation of the cytoplasm, breakdown of the plasma membrane and an induction of inflammation around the dying cell attributable to the release of cellular contents and pro-inflammatory molecules.
- Cells that die by necrosis frequently exhibit changes in nuclear morphology but not the organized chromatin condensation and fragmentation of DNA that is characteristic of apoptotic cell death.
- It has become increasingly clear that Necrosis and Apoptosis share the same biochemical networks.

Cell Death by Necrosis: 2

- The final form of a cell's death is highly dependent on its physiologic context at the time when the death signal is received.
- Linking the term "programmed" or “regulated” to the word "necrosis" implies that cellular signaling pathways initiate necrosis in response to specific cues rather than "by accident".
- Programmed necrosis may not simply be a backup when apoptosis fails, but has a biological function under conditions where an immune reaction to the dying cell is desirable, such as in microbial infection.

Autophagy, Apoptosis, Mitoptosis and Necrosis: Interdependence Between Those Pathways and Effects on Cancer.

Arch. Immunol. Ther. Exp. (2013) 61:43–58. Wiem Chaabane, Sırma D. User, Mohamed El-Gazzah, Roman Jaksik, Elaheh Sajjadi, Joanna Rzeszowska-Wolny, Marek J.Łos



- 10 million cells per day undergo apoptosis in a healthy adult human.
- **During apoptosis**; chromatin condenses, cells lose their attachment to the surrounding tissue and shrink, becoming a part of a cell membrane bleb or Apoptotic Body.
- **Phosphatidylserine**, embedded in the plasma membrane, is exposed on the outer side of apoptotic bodies (ABs) and acts as an "eat me" signal, attracting macrophages to get efficiently phagocytized.

Apoptosis and autophagy: regulatory connections between two supposedly different processes

. Apoptosis (2008) 13:1–9. Department of Pharmacology, University of Colorado at Denver and Health Sciences Center, Aurora, CO 80045, USA. Andrew Thorburn. **APOPTOSIS**

- The loss of mitochondrial ATP production culminates in the cells inability to regulate intra-cellular metabolism and mechanisms for cell survival.
- The lack of energy allows Ca+ stores to rise, leakage of cytochromes from the inner membrane space, and release of AIF (apoptotic inducing factor).
- In a death rattle, the mitochondria try to make ATP only to generate more toxic forms of ROS. There is no alternative left other than to die by Apoptosis.

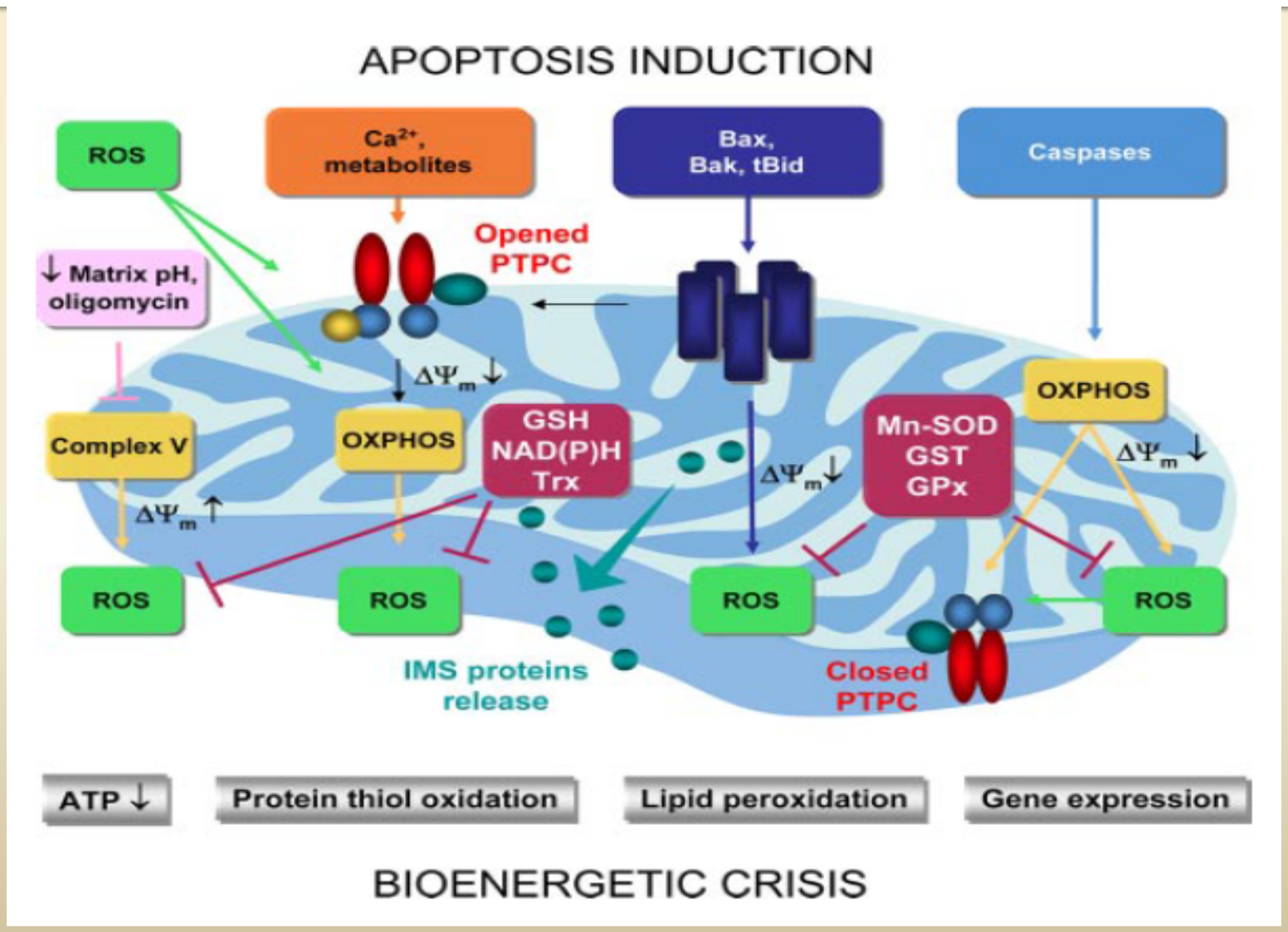
Mitochondrial Dysfunction and Reactive Oxygen Species in Excitotoxicity and Apoptosis : Implications for the Pathogenesis of Neurodegenerative Diseases.

Neurochemical Research, Vol. 28, No. 10, October 2003, pp. 1563–1574. A. Cristina Rego, and Catarina R. Oliveira.

- The role of mitochondria, not only as ATP producers through oxidative phosphorylation but also as regulators of intracellular Ca^{2+} homeostasis and endogenous producers of ROS.
- Mitochondrial Ca^{2+} overload resulting from excitotoxicity is associated with generation of superoxide radicles that induce the release of pro-apoptotic mitochondrial proteins, proceeding through DNA fragmentation, condensation and culminating in cell demise by apoptosis and/or necrosis.



Loss of ATP production



Androgens selectively protect against apoptosis in hippocampal neurons.

J Neuroendocrinol . 2010 Sept ; 22(9): 1013–1022. Thuy-Vi V. Nguyen, Anusha Jayaraman, Allison Quaglino, and **Christian J. Pike** Neuroscience Graduate Programme and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089

- Androgens directly activate a neuroprotective mechanism specific to inhibition of cell death involving apoptosis.





Apoptosis and **Autophagy**: regulatory connections between two supposedly different processes.

Apoptosis (2008) 13:1–9. Department of Pharmacology, University of Colorado at Denver and Health Sciences Center, Aurora, CO 80045, USA. Andrew Thorburn. **AUTOPHAGY**

- One suggested mechanism is the sequestration of damaged Mitochondria to avoid release of Apoptotic activating chemicals (AFIP, AIF, Cytochrome c).
- As long as energy can be generated (increased glycolysis caused by elevated GAPDH), cells can use autophagy to survive MOMP^ and the release of cytochrome c and other apoptogenic proteins and recover to continue to grow.

^ Mitochondrial outer membrane permeabilization (MOMP) is considered the 'point of no return' as this event is responsible for engaging the apoptotic cascade in numerous cell death pathways.

Poly(ADP-ribose) Signals to Mitochondrial AIF: A Key Event in Parthanatos

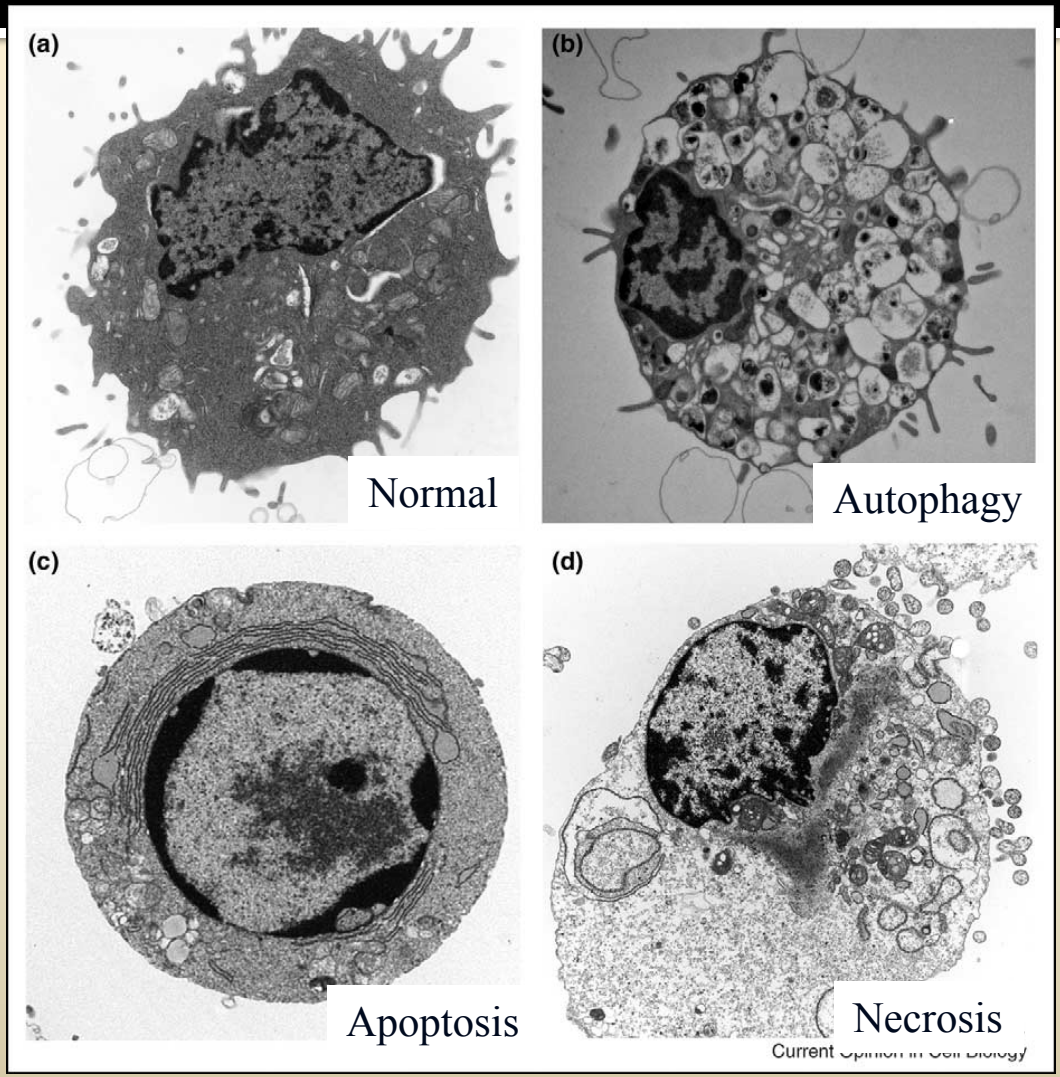
. Experimental Neurology. 2009 August ; 218(2): 193–202. Yingfei Wang, Valina L. Dawson, and Ted M. Dawson, Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins. University School of Medicine, Baltimore, MD, USA Departments of Neurology, Neuroscience, and Physiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

- Poly(ADP-ribose) polymerase-1 (PARP-1) plays a role in a number of neurologic diseases by mediating caspase-independent cell death. (Apoptosis)
- Mitochondrial apoptosis-inducing factor (AIF) release and translocation into the nucleus is the commitment point for Parthanatos.
- Intra-nuclear activation of PARP-1 then translocates to the mitochondria to mediate the release of AIF.
- In Parthanatos, the PARP signaling to mitochondrial AIF is the key event initiating the deadly crosstalk between the nucleus and the mitochondria.

Death by design: apoptosis, necrosis and autophagy. Current Opinion in Cell Biology 2004, 16:663–669Aimee L Edinger and Craig B Thompson. University of Pennsylvania, Abramson Family Cancer Research Institute, 450 BRB II/III, 421 Curie Blvd, Philadelphia, Pennsylvania 19104, USA

Morphological features of autophagic, apoptotic and necrotic cells. (a) Normal, (b) autophagic, (c) apoptotic (d) and necrotic cells. Whereas the morphologic features of apoptosis are well defined, the distinction between necrotic and autophagic death is less clear.

The bioenergetic catastrophe that culminates in cellular necrosis also stimulates autophagy as the cell tries to correct the decline in **ATP levels by catabolizing its constituent molecules**. Thus, vacuolation of the cytoplasm is observed in both autophagic cells (b) and in cells stimulated to undergo **programmed necrosis** (d). By contrast, ATP levels are maintained in normal (a) and apoptotic cells (c) consistent with the limited number of autophagic vacuoles in their cytoplasm.



Summary

- The primary trauma initiates a secondary processes which leads to disruption of regulatory communication between cells and regions of the CNS.
- It is the accumulation of the secondary traumas that allow for continuation and expansion of the primary trauma and prevents repair and regeneration.
- Cell death by any programmed or unprogrammed means is used to remove non-viable or potentially damaging cells and their contents from the brain.
- **Therefore, the key for optimal treatment is to diminish the secondary phase of Traumatic Brain Injury via limitation of inflammation and the production of free radicals.**

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.

The JAMA Network

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.

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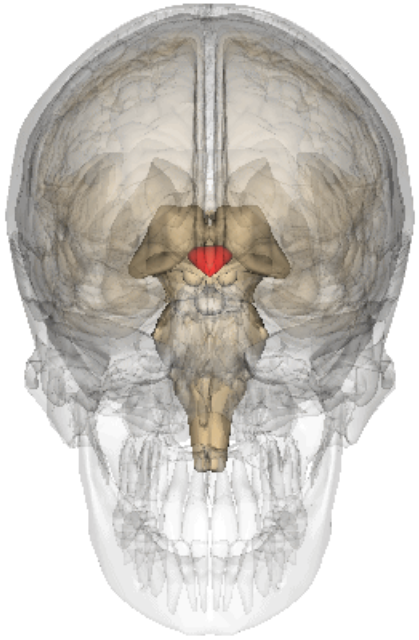
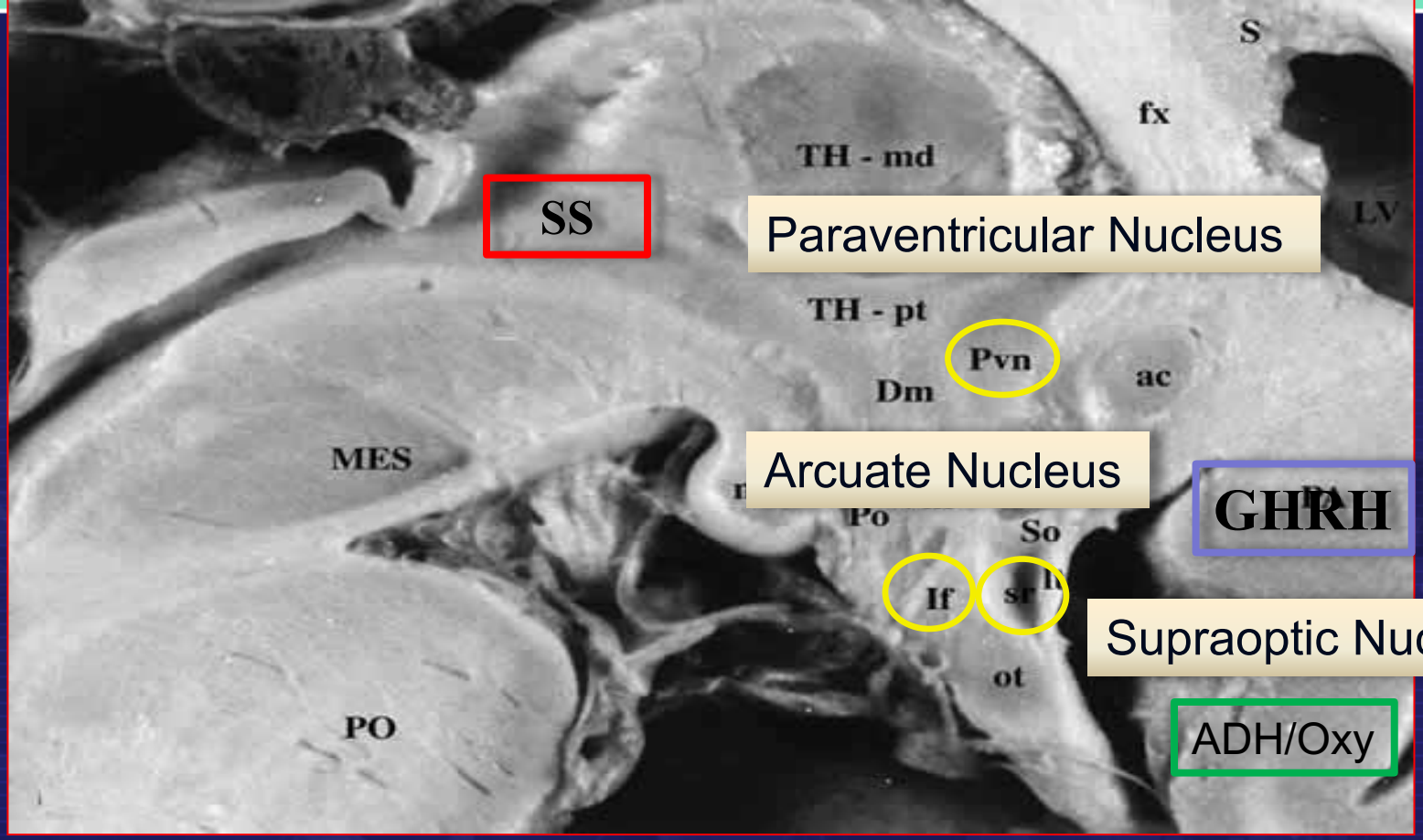
The Hypothalamus



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.

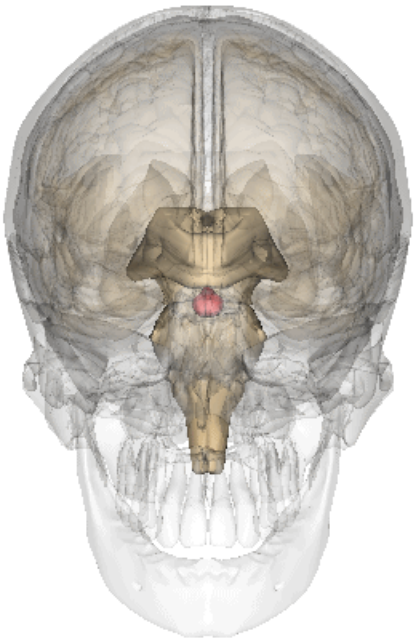
Table 4.1: Hypothalamic nuclei responsible for integration of hormonal homeostasis and the nervous system.

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



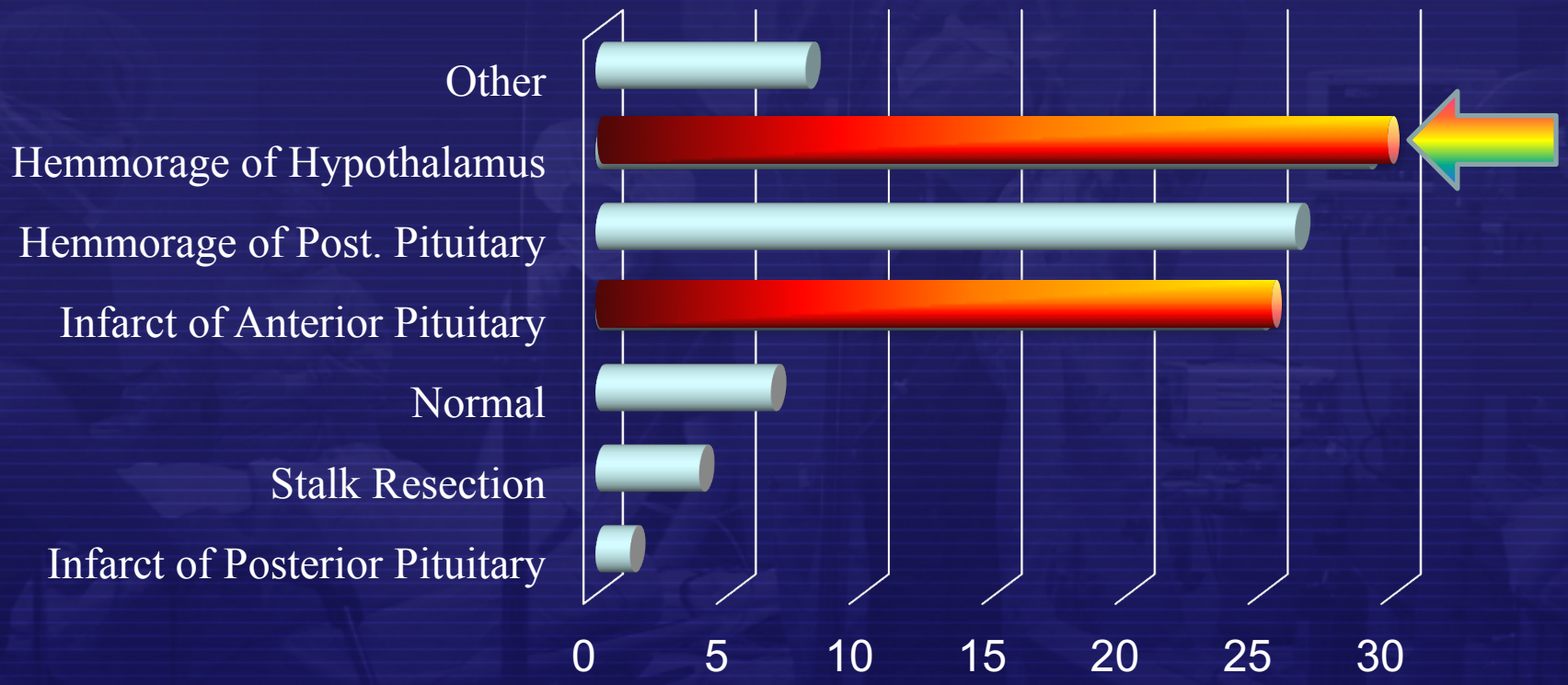
Anatomy of the Pituitary Gland

- 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)

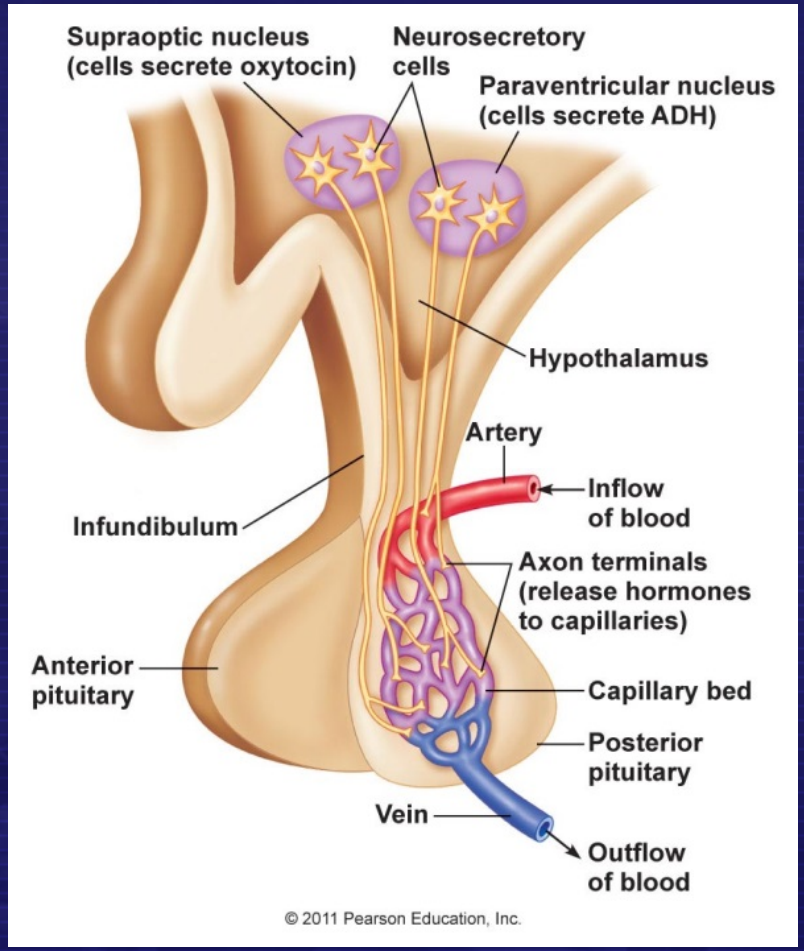
Posterior Pituitary

(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

The JAMA Network

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.

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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

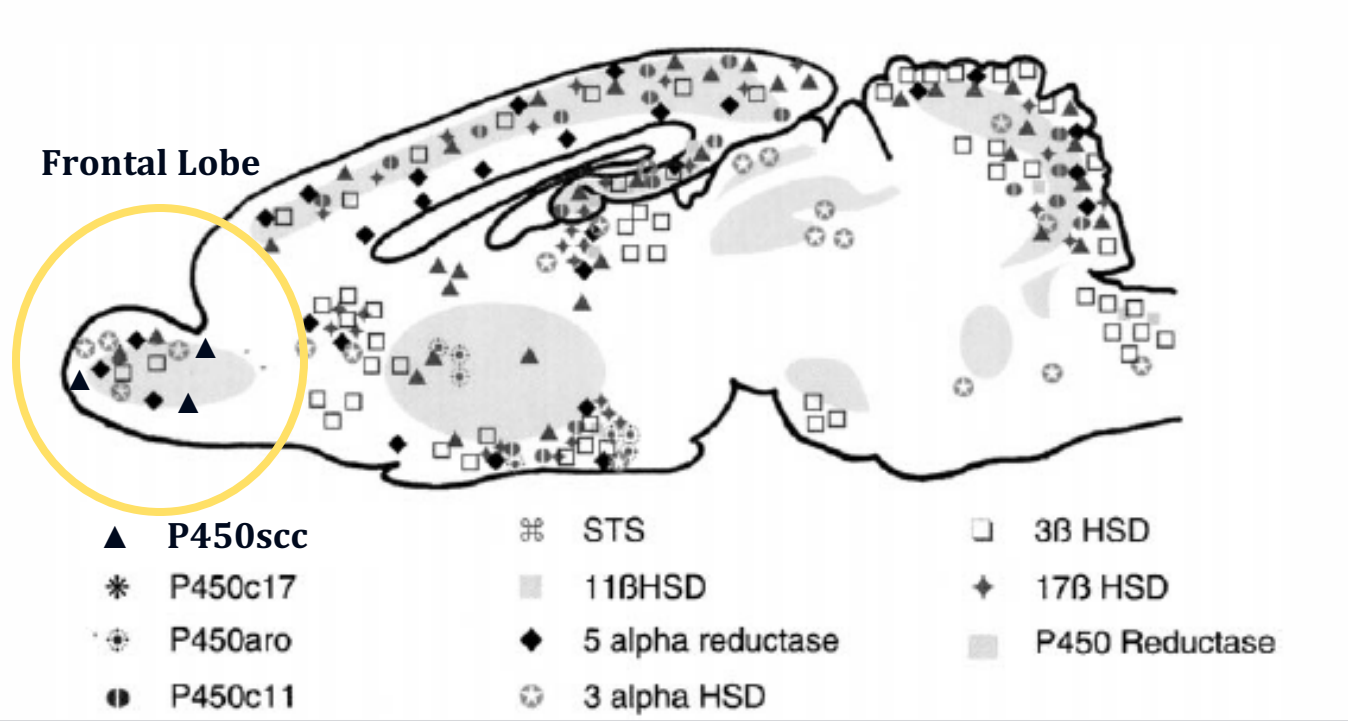
- NeuroActive Steroids (NAS) are the body's hormones that are produced in the periphery and pass through the BBB into the brain.
- Neurosteroids (NS) are those that are produced de nova in the brain by the glial cells like astrocytes, oligodendrocytes and microglia.
- Enzymes responsible for the production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

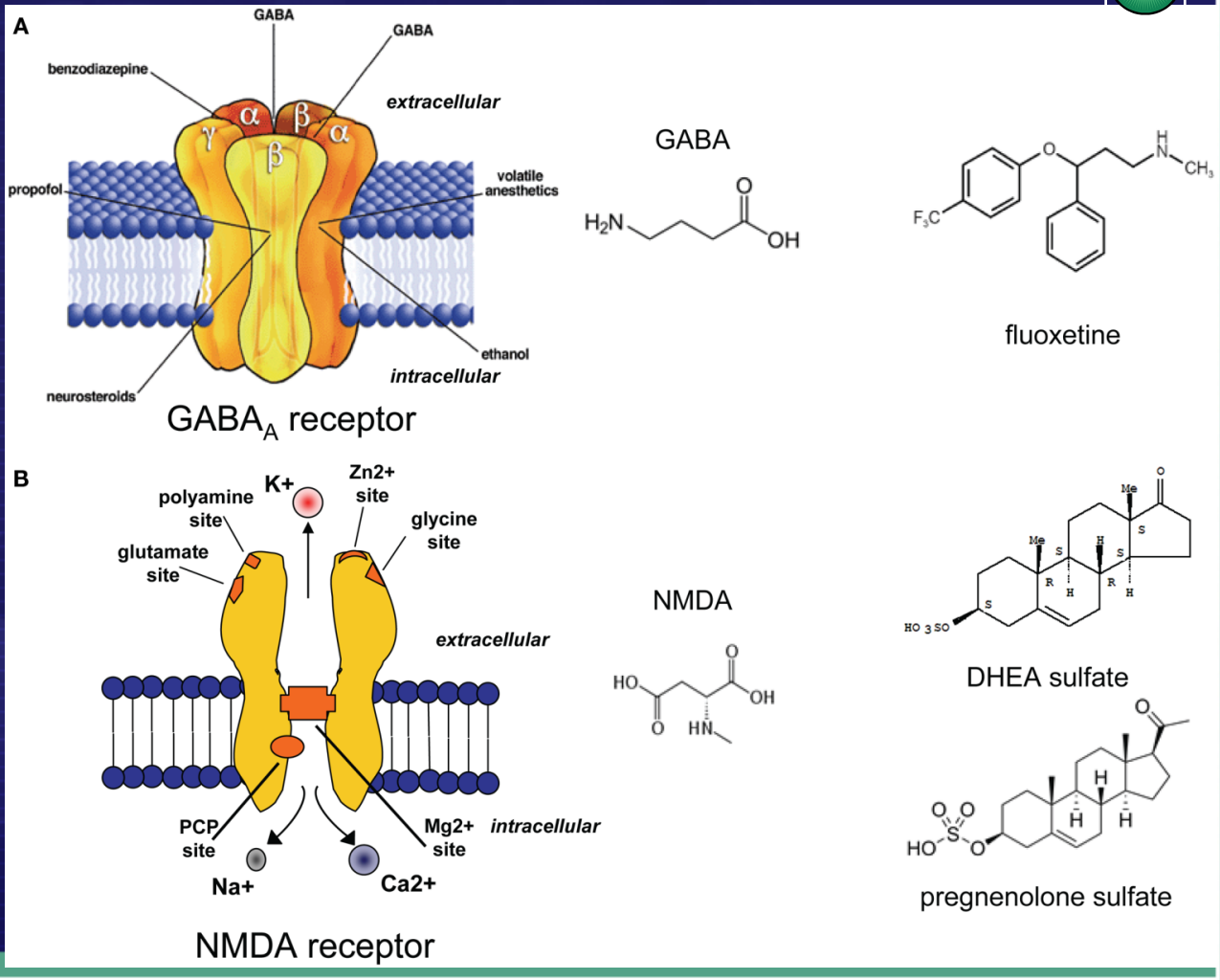
Pharmacological Reviews. Vol. 51, No. 1. (1999). Ayikoe G. Mensah-nyagan, Hubert Vaudry. Et al Institut Fédératif de Recherches Multidisciplinaires sur Les Peptides No. 23, Laboratoire de Neuroendocrinologie Cellulaire et Moléculaire, Institut National de la Sante et de la Recherche Medicale , UA Centre 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.

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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.

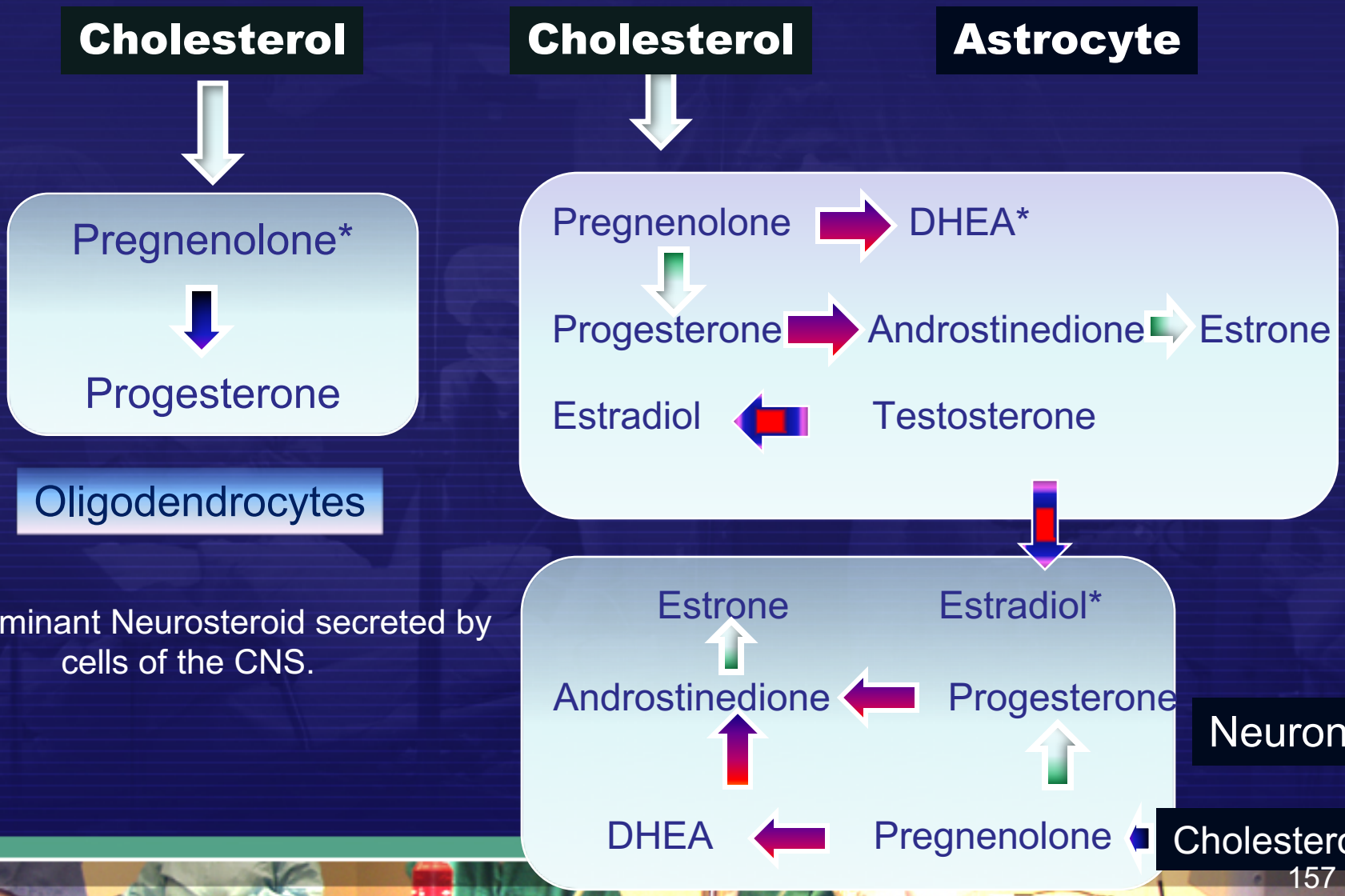


Astrocytes and Neurosteroids: Metabolism of Pregnenolone and Dehydroepiandrosterone. Regulation by Cell Density The Journal of Cell Biology, Volume 121, Number 1, April 1993 135-143 Yvette Akwa, Nicole Sanan~s, Monique Gou6zou, Paul Robel, Etienne-Emile Baulieu, and Claude Le Goascogne. INSERM U33, Lab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

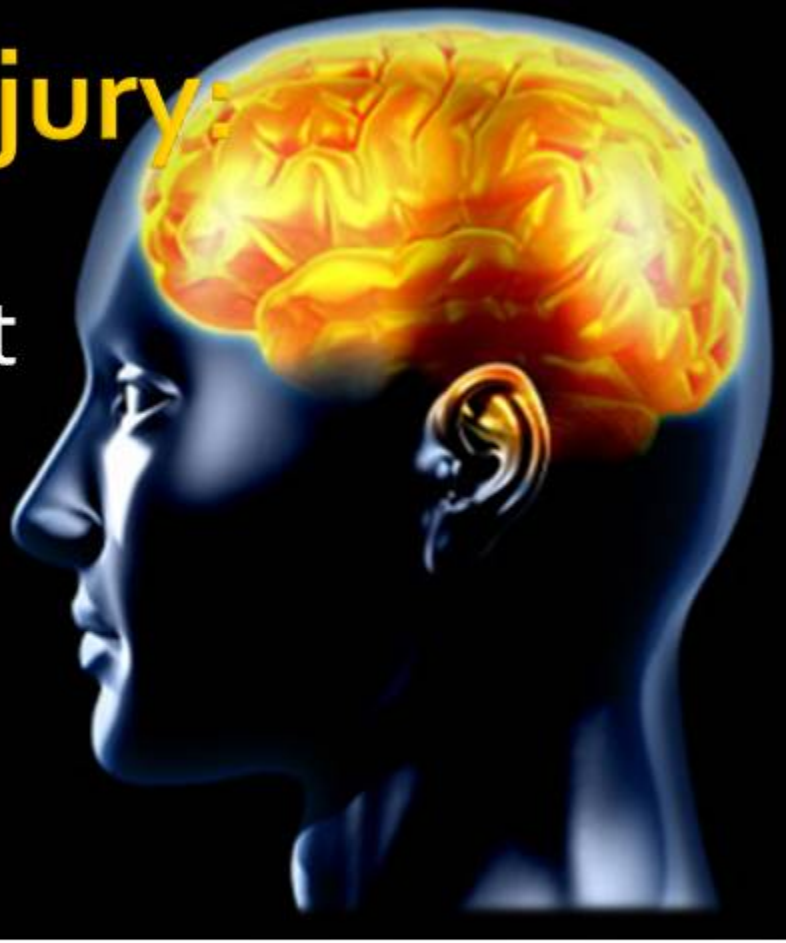
- **"Fill all the tires…. not just the ones in front."**



Traumatic Brain Injury:

A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.



Chapter 6: The Laboratory of TBI

There is no such thing as "**Anti-Aging Medicine**", there is only good medicine.

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.

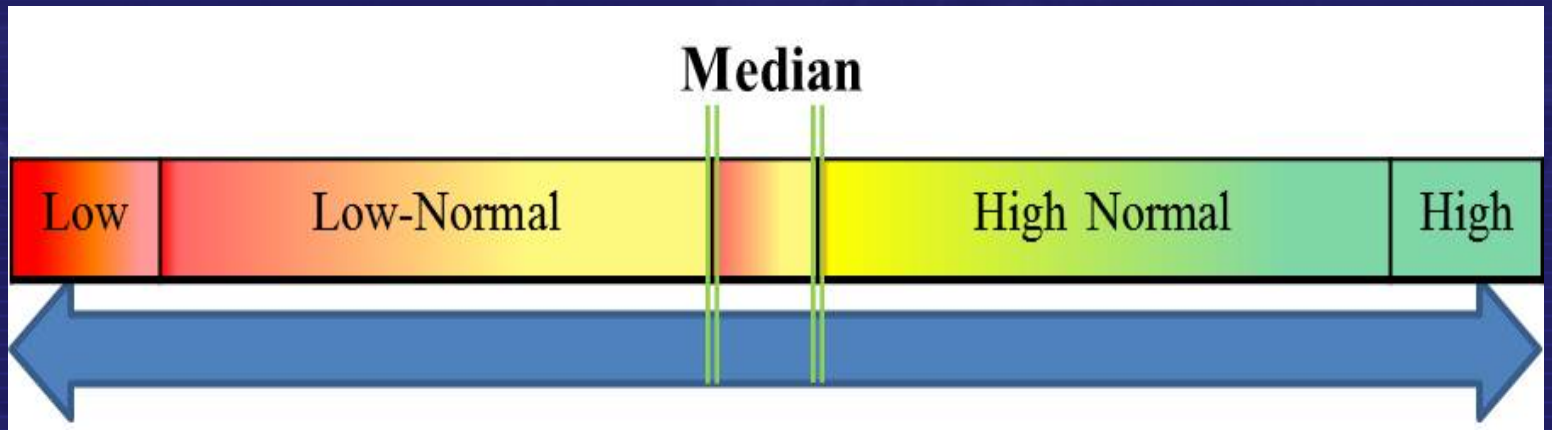


Figure 6.1 Optimal results with optimal treatment. Using treatment protocols to achieve a homeostatic balance so that each hormone hovers around its median range. Although this might be viewed as arbitrary, the concept of Homeostasis, a dynamic process, would place each hormone with points of its median 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

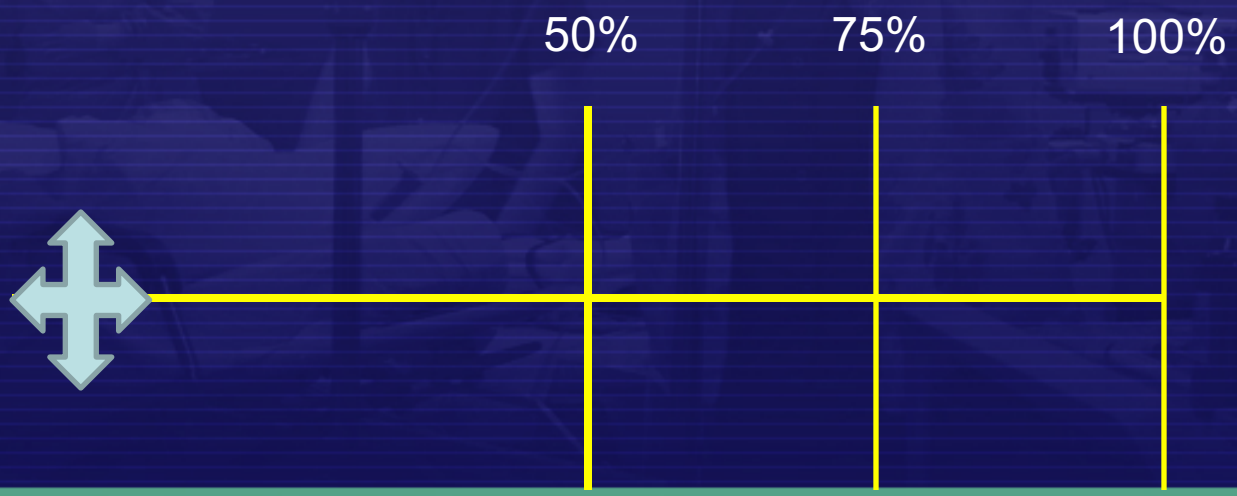
Hormone	Median M	Median F	Hormone	Median M	Median F
DHEA-s	200 ug/dL	277 ug/dL	Growth Hormone	5.0 ng/ml	5.0 ng/ml
T-Testosterone	690 ng/ml	44 ng/ml	IGF-1	>200 ng/ml	>200 ng/ml
F-Testosterone	14 pg/ml	2-4 pg/ml	IGFBP-3	4000 ng/ml	4000 ng/ml
DHT	< 52 ng/dl	< 30 ng/ml	TSH	2.5 mcu/ml	2.5 mcu/ml
SHBG	45 pg/ml	<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.

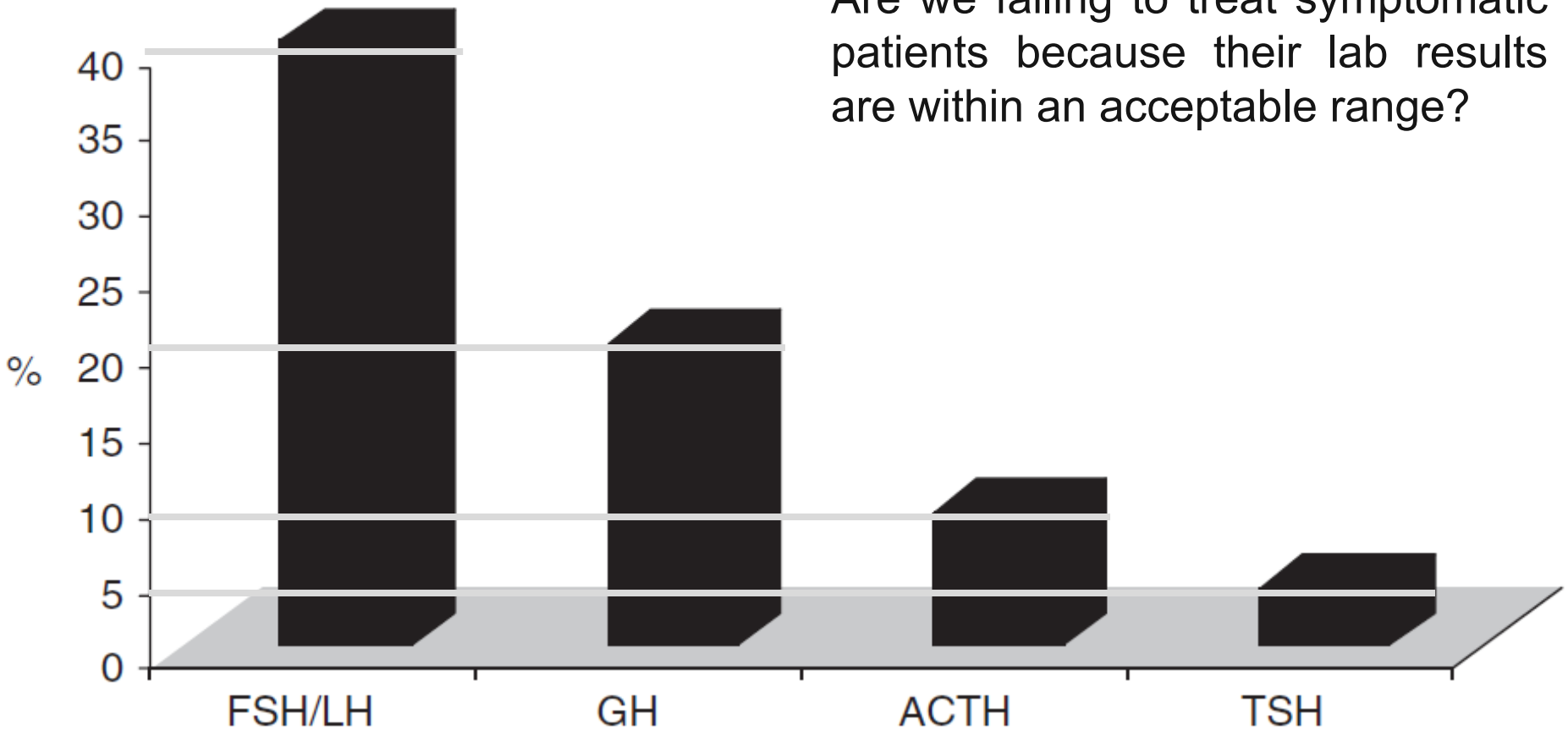


Pituitary functions in the acute phase of traumatic brain injury: Are they related to severity of the injury or mortality?

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.

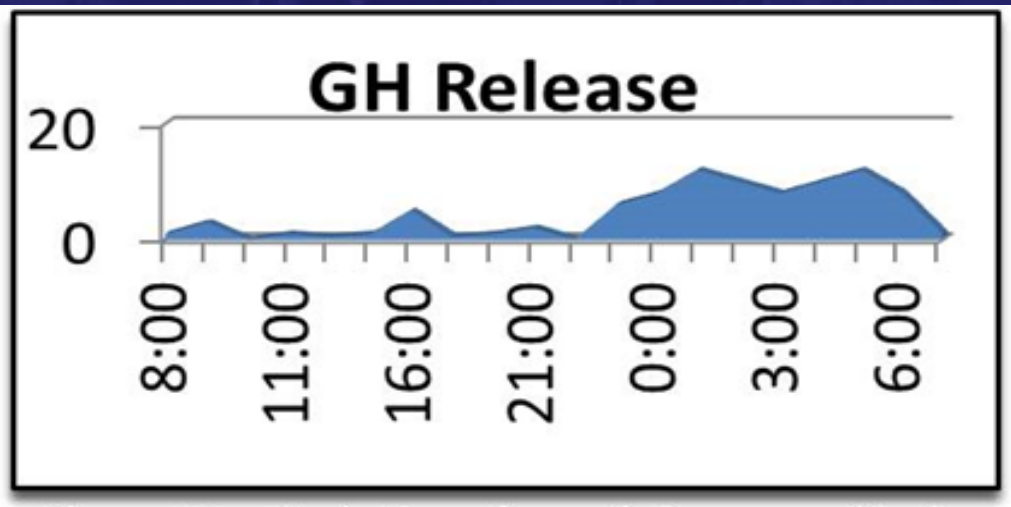
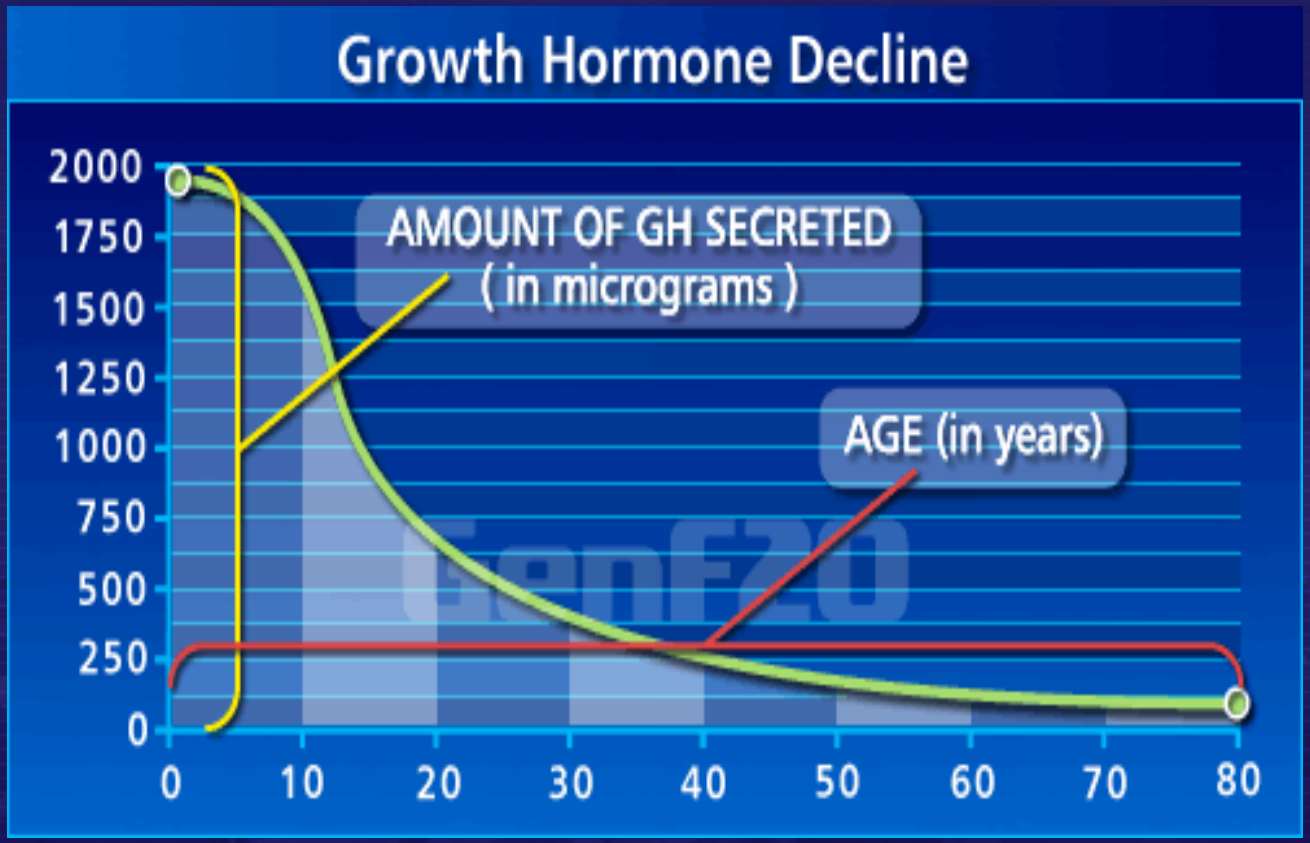


Figure 6.1: Production of growth hormone with the majority of GH released from 8pm to 4am with minor pulses throughout the day.

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.

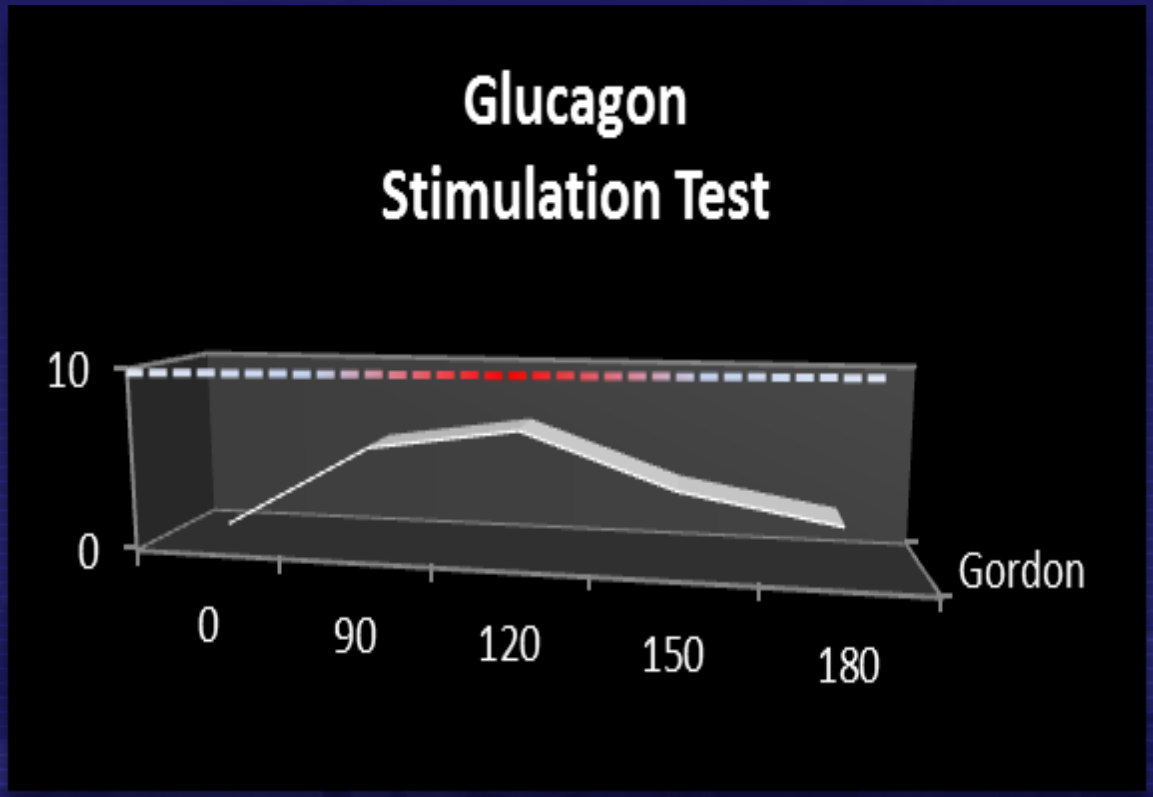
Case 1c

- 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

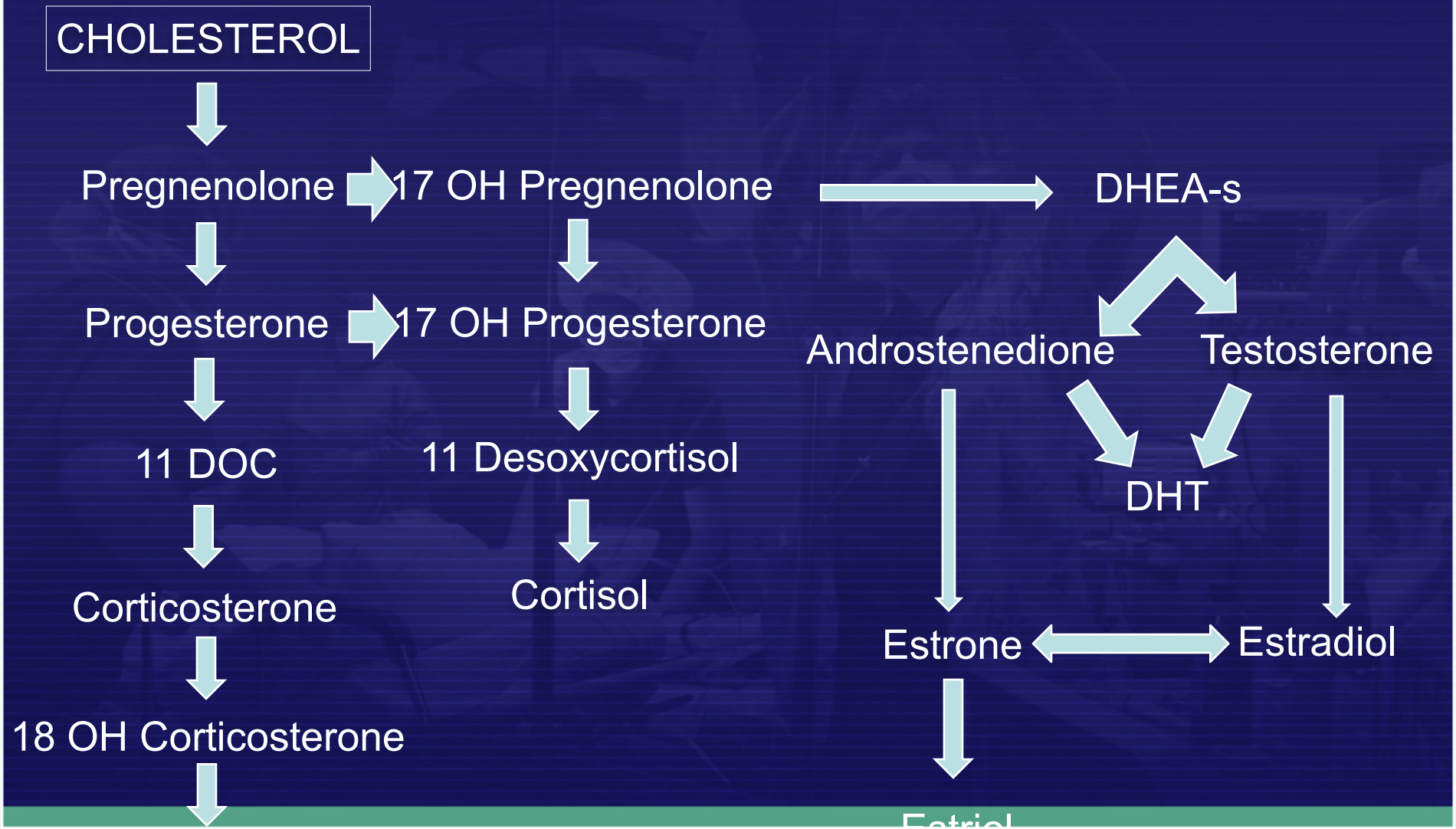


Testosterone

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

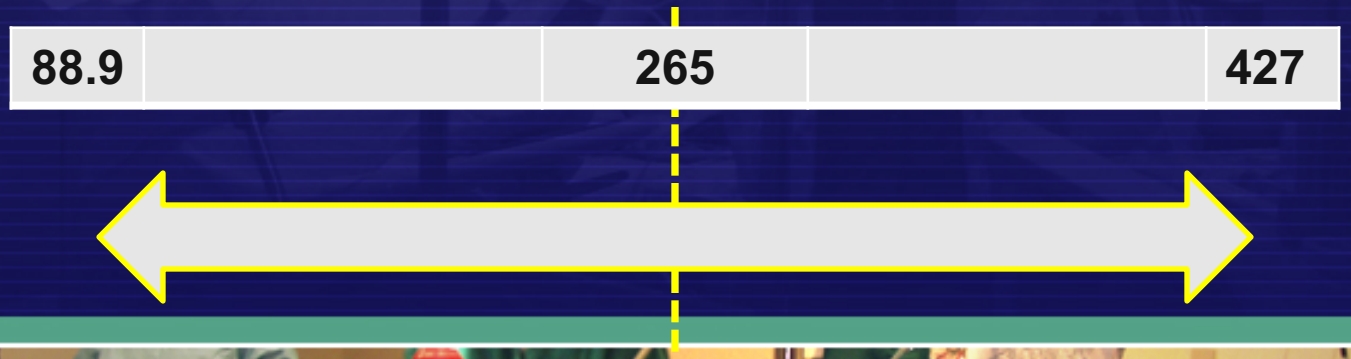
Hormone Cascade



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

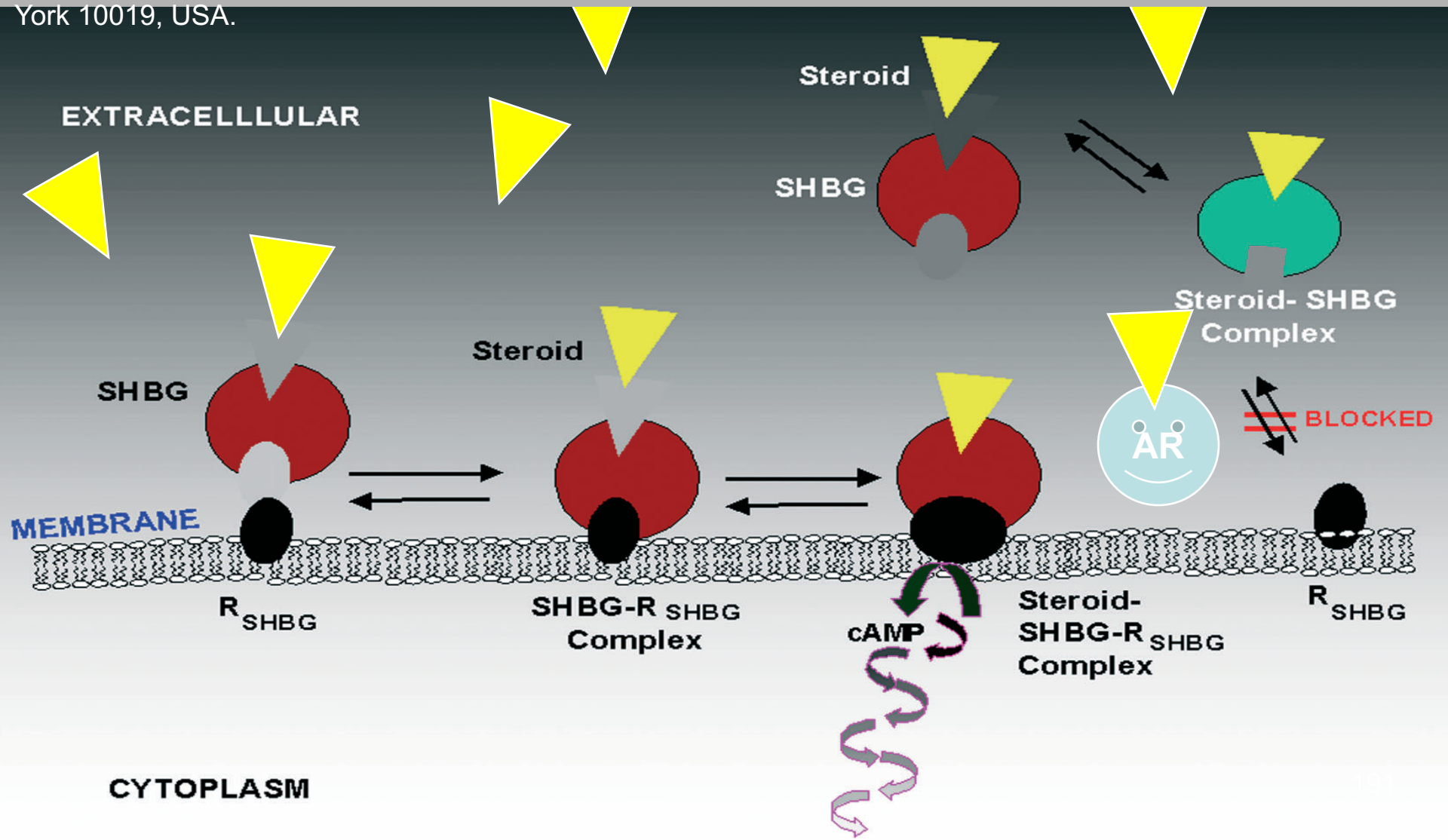
Table 2. Conditions and Medications Associated With Alterations in SHBG*[4]

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.

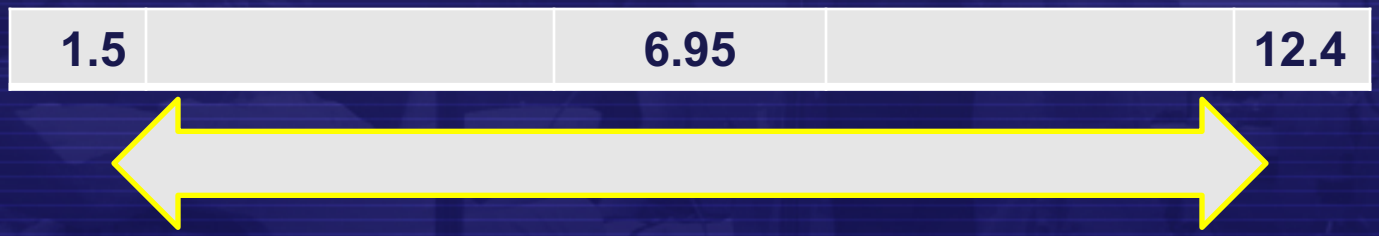
Luteinizing Hormone

- **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)

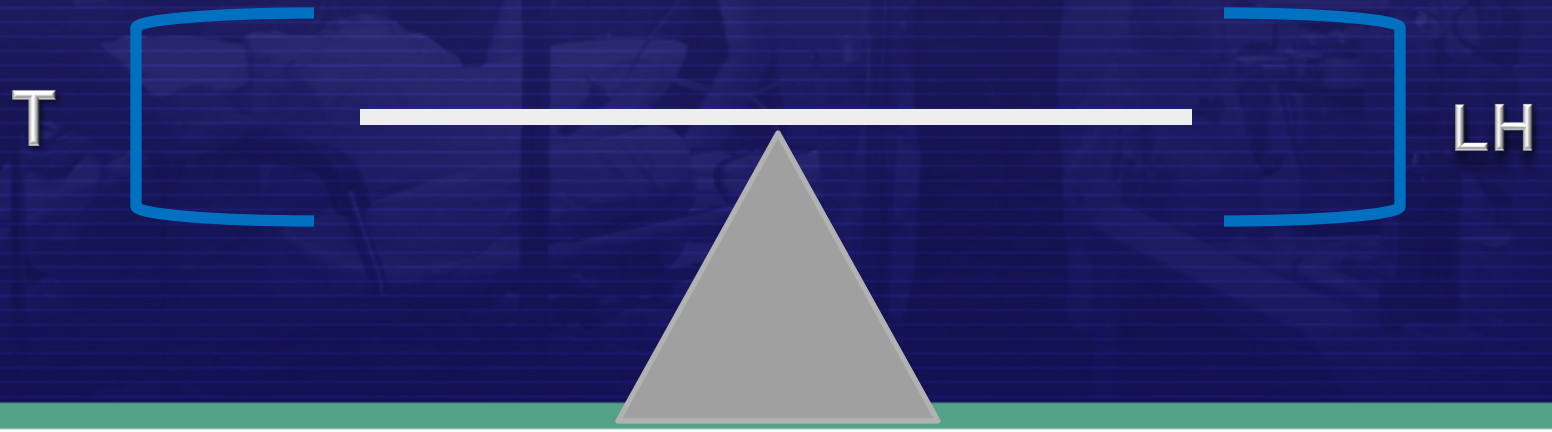


Testosterone Summary-1

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.

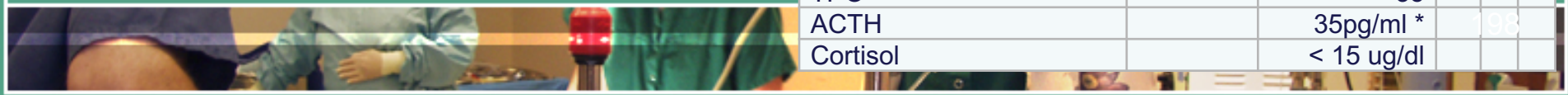
Male Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	23 L	245 ug/dl*
Estrone (E1)	2.37 N	< 60 pg/ml*
Estradiol (E2)	5.60 N	<25 pg/ml*
Progesterone	0.65 LN	0.8 ng/ml*
Pregnenolone	27 LN	110 ng/dl*
EP Ratio		< 250
Testosterone Free	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.

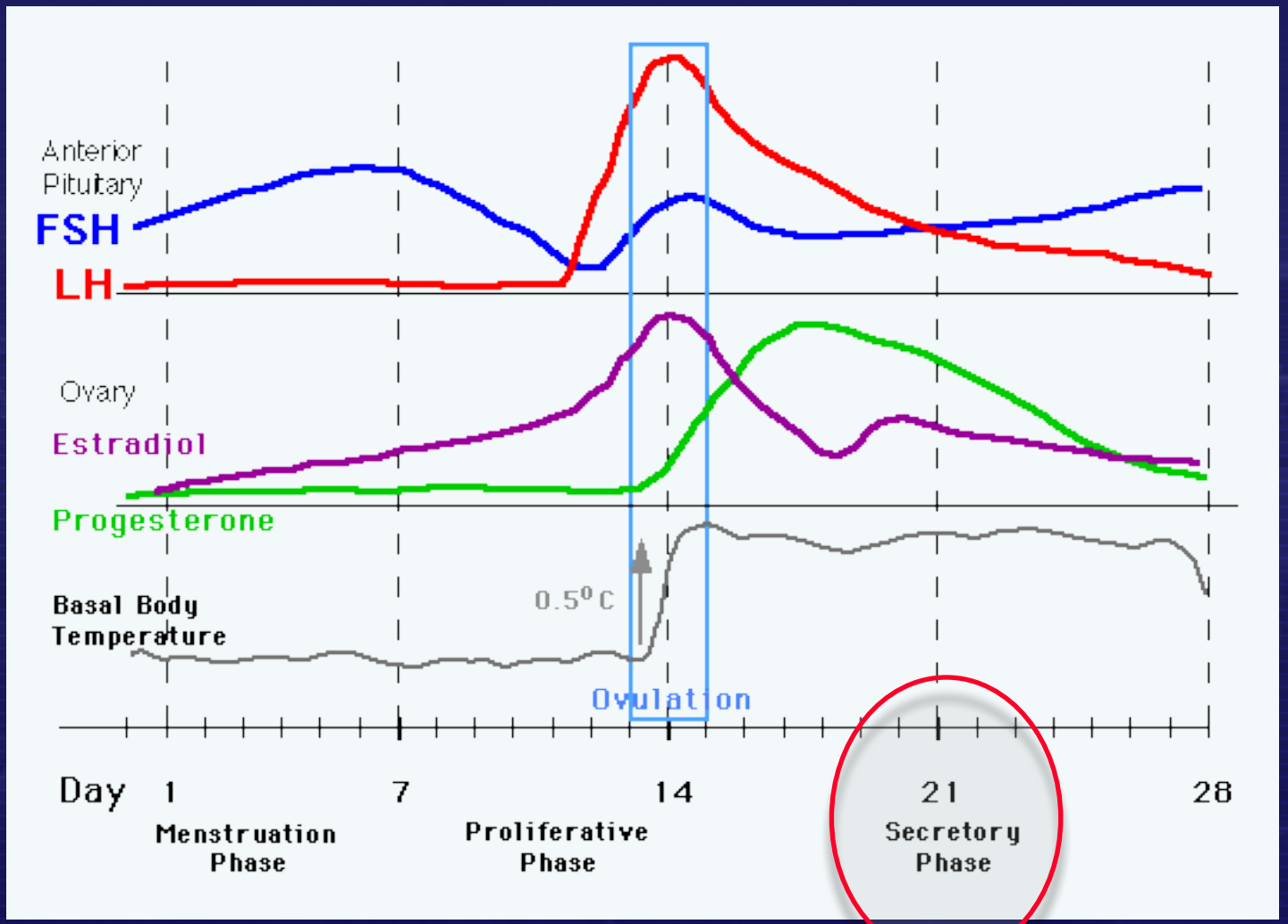
Estradiol (E2)

- 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.

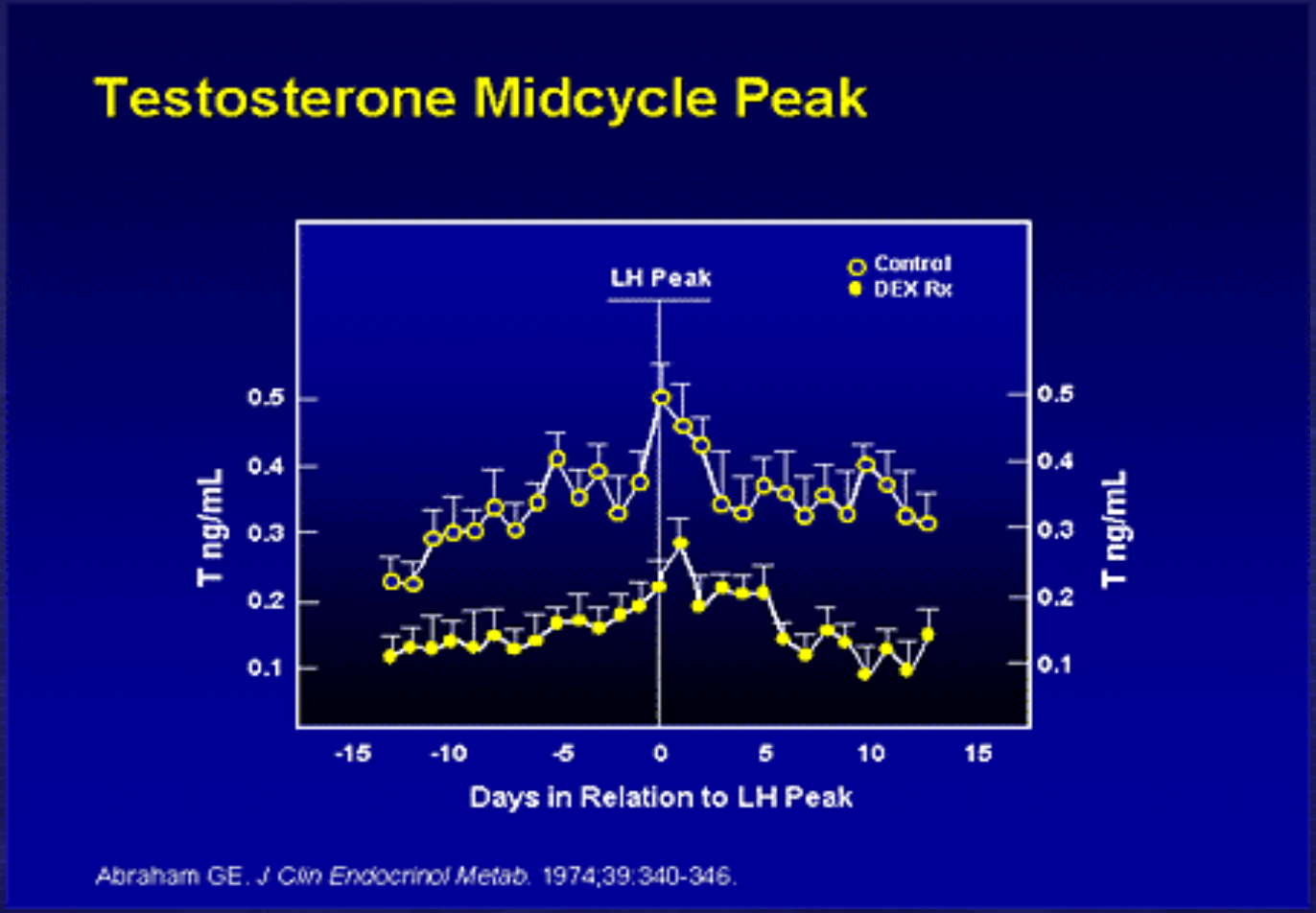
Summary for Estrogens

- 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

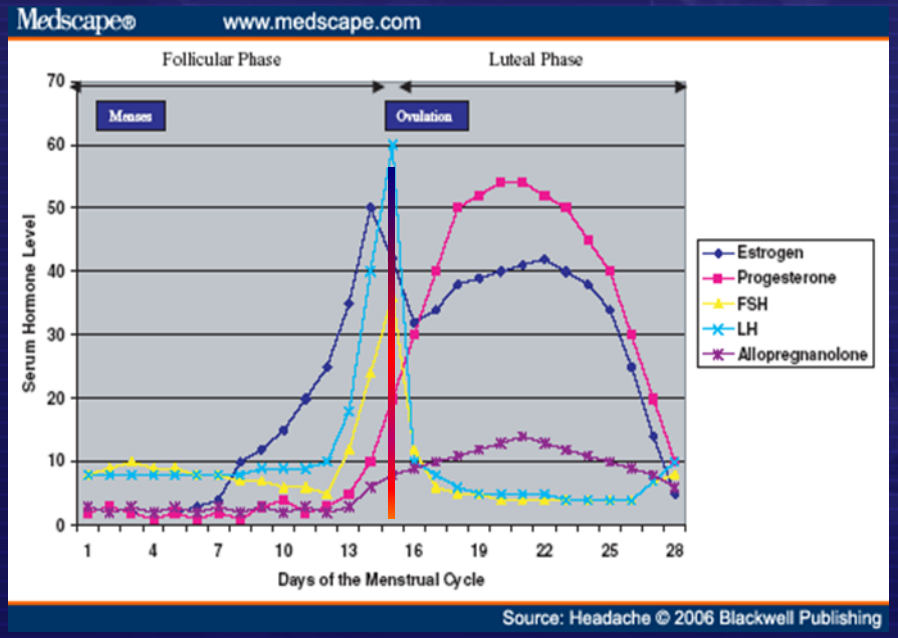
The Millennium Health Group started looking at the relationship between estrogens and progesterone in 2005 based upon the recognition that those female patients that had symptoms were on an Estrogen-Only replacement regimen as provided by their HCP. Knowing the relationship between progesterone and GABA(up-regulation) 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**

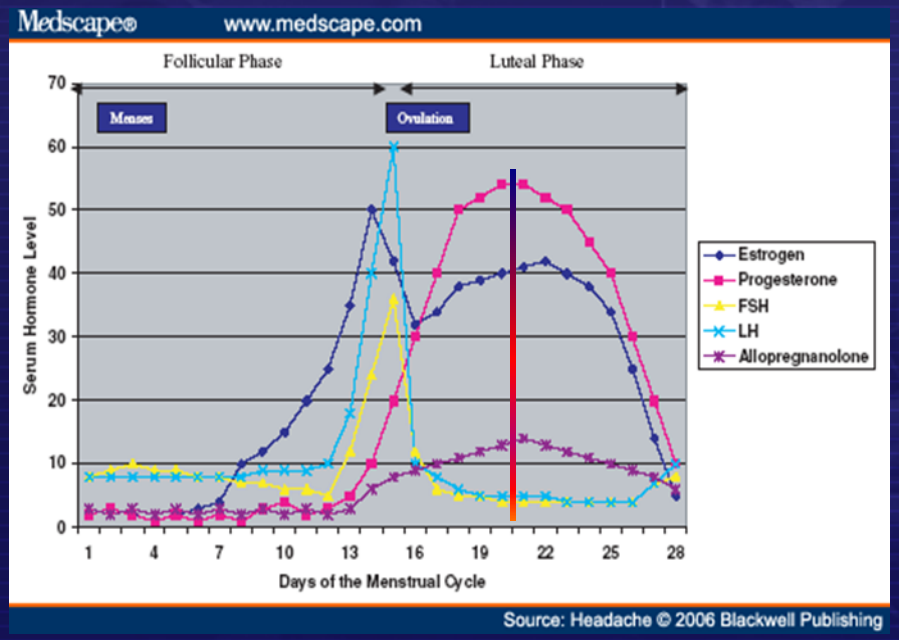


Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	143 L	195 ug/dl*
Estrone (E1)*	36 N	< 200 pg/ml*
Estradiol (E2)*	187.3 HN	90 pg/ml*
Progesterone*	1.17 LN	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio*	190 N	< 250
Testosterone 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**



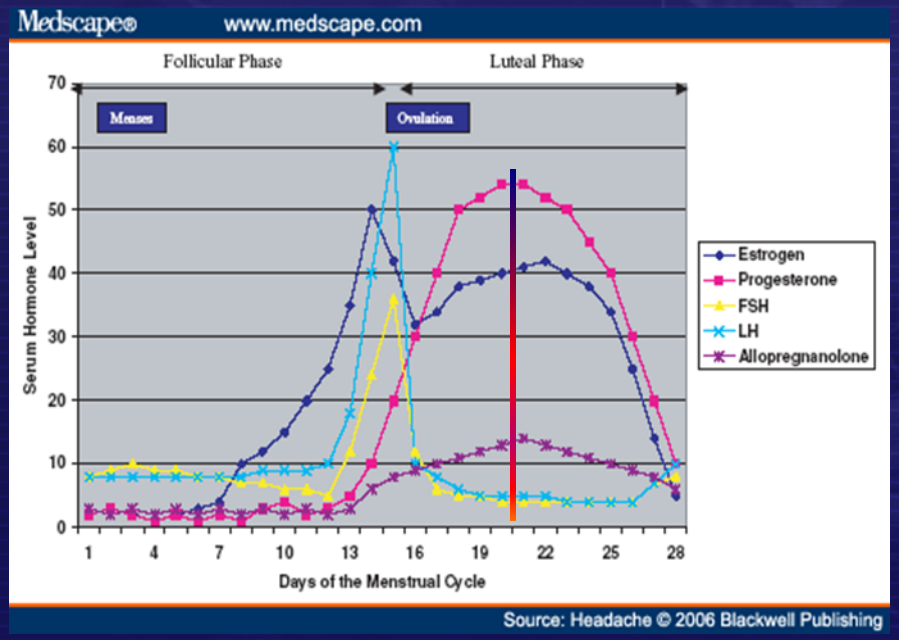
Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	121 LN	195 ug/dl*
Estrone (E1)*	8 N	< 200 pg/ml*
Estradiol (E2)*	68 LN	90 pg/ml*
Progesterone*	9.7 HN	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio*	6.6 N	< 250
Testosterone Free*	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

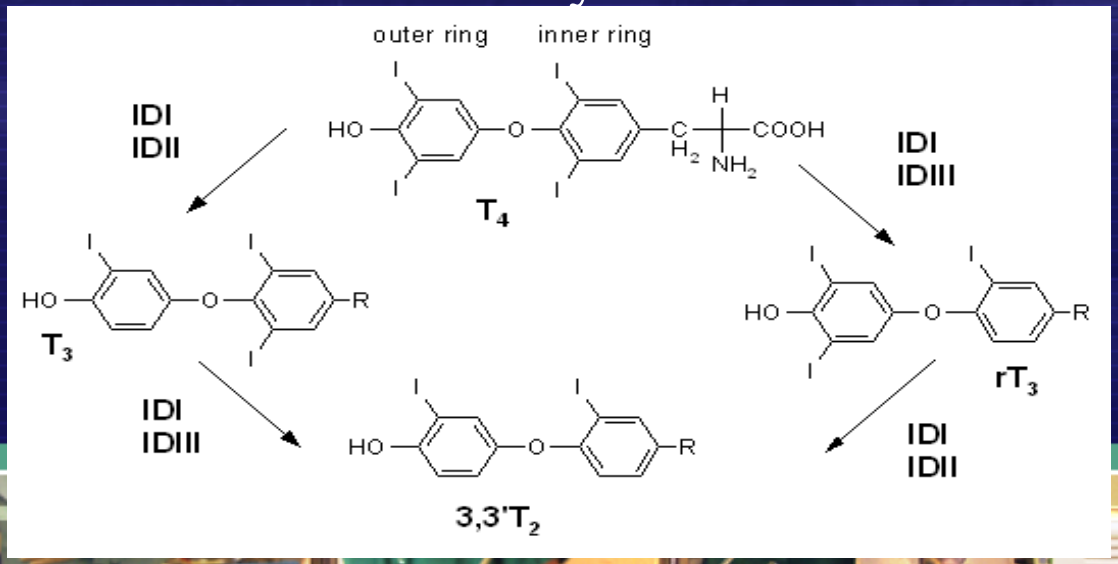
- Reference range: 1.3 – 4.6 pg/ml
- Median: 2.95 pg/ml

- 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

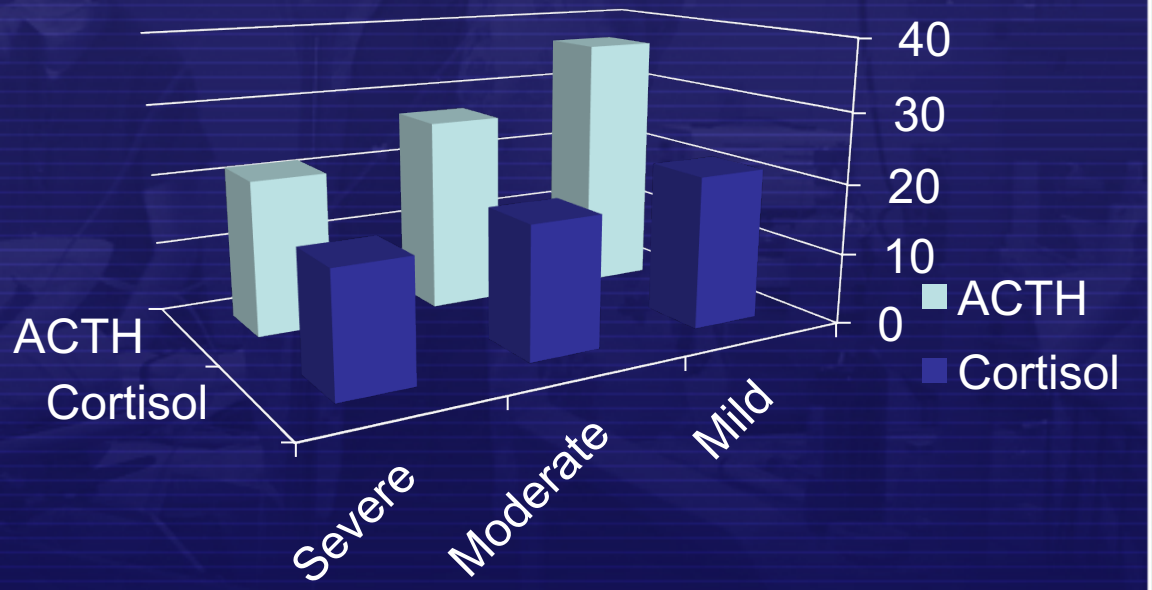
Cortisol

- 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:

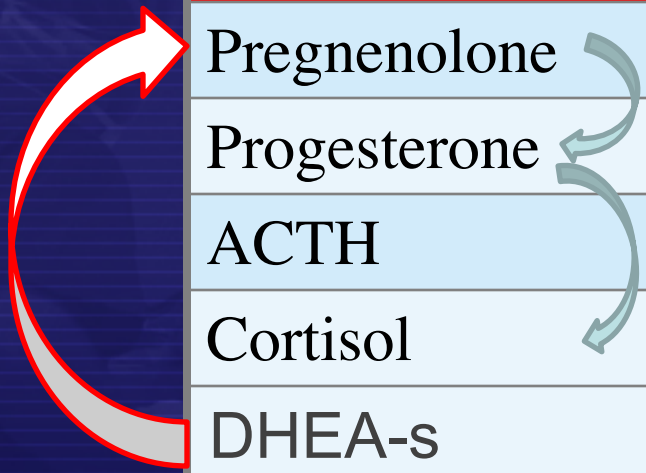
1. **Traditional**: CRH from the hypothalamus, inducing ACTH released from the pituitary causing an increase in adrenal cortical production and release of Cortisol.
2. **Non-Traditional**: Catecholamines stored in the splanchnic nerves can induce Cortisol production by release of dopamine, epinephrine, 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. -

Traumatic Brain Injury:

A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.



Chapter 7: Neuropsychiatry

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.

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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

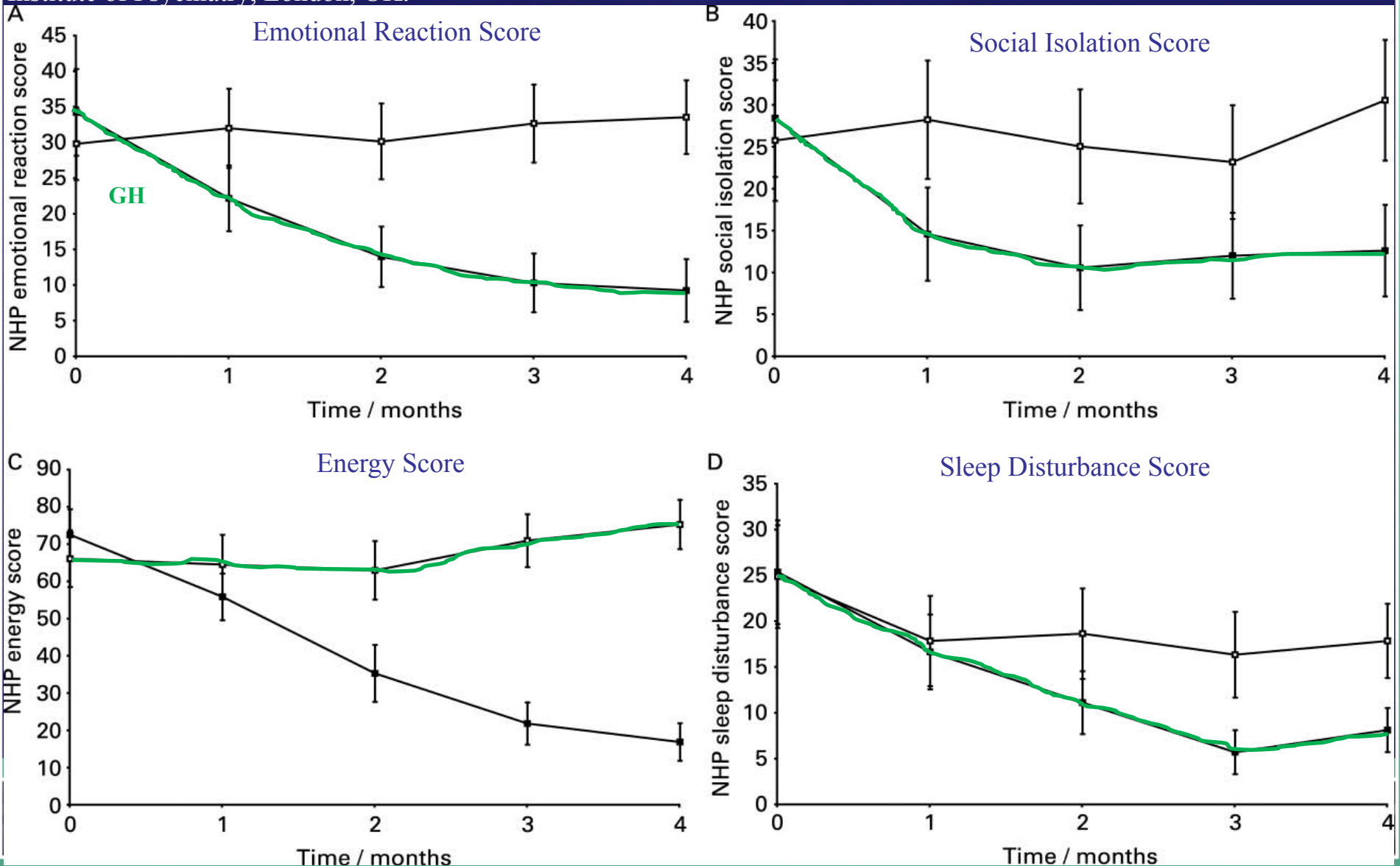
- 61% of the patients with Adult Onset Growth Hormone Deficiency were found to have atypical depression at baseline.
- There were significant improvements in the depression rating scale scores after 2 months of GH therapy, with significant improvements in emotional reaction and social isolation scores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

2009 Elsevier Ltd 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.

Traumatic Brain Injury:

A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.



Chapter 8: Supplements

Phase I - Neurotrauma

- Damage to the brain includes not only white and gray matters and their cellular constituents, but also an extensive vascular supply.
- Ischemia causing hypoxia/anoxia and hypoglycemia can initiate inflammatory pathways and further neuronal and glial death.
- Cavitation of the brain with the loss of brain tissue, is a progressive mechanism where areas of initial injury can continue to expand due to these underlying processes, led by all aspects of Oxidative Stress.



Cellular and Molecular Mechanisms of Glial Scarring and Progressive Cavitation: *In Vivo* and *In Vitro* Analysis of Inflammation-Induced Secondary Injury after CNS Trauma

. The Journal of Neuroscience, October 1, 1999, 19(19):8182–8198 Michael T. Fitch, Catherine Doller, Colin K. Combs, Gary E. Landreth, and Jerry Silver. Dept of Neurosciences and 2Alzheimer Research Lab, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106

- Post-traumatic cystic cavitation, in which the size and severity of a CNS injury progress from a small area of direct trauma to a greatly enlarged secondary injury surrounded by glial scar tissue, is a poorly understood complication of damage to the brain.
- Persistent inflammation in the absence of significant physical damage within CNS white matter can result in an expanding astrocyte-free cavity surrounded by glial scarring and extracellular matrix proteoglycans and the secondary destruction of axons. A NPE condition.

Phase II - Neurotrauma

- mTBI represents 85% of the cases of head trauma.
- The injured is usually highly functioning with a slow progression of neuropsychiatric and physical complaints.
- Identification of hormonal deficiencies is simple as is the treatment, but the insidious and underlying "stealth" processes of **oxidative damage** can be missed or ignored.
- A number of impressive studies give us the support to venture on….

Mitochondrial Biogenesis

- Oxidative stress and cellular injury that damage mitochondria may impair the cell's capacity to generate sufficient ATP for homeostasis, ultimately leading to apoptosis or necrosis.
- The cell's energy supply is protected from conditions that damage mitochondria by an inducible transcriptional program of mitochondrial biogenesis that operates in large part through redox signals involving nitric oxide synthase, heme oxygenase-1 and CO systems.

Redox Regulation of Mitochondrial Biogenesis. Free Radic Biol Med. 2012 December 1; 53(11): 2043–2053. Claude A. Piantadosi, MD and Hagir B. Suliman, PhD, DVM. Depts of Medicine, Anesthesiology, and Pathology Duke University Medical Center and the Durham VA Medical Center Durham, NC 27710 USA

Mitochondrial Biogenesis

Initiators of Mitochondrial Biogenesis

- Embryonic development
- Cell division and repair
- Changes in physiological state
  - Exercise
  - Energy limitation
  - Cold stress
  - Calorie restriction (Hypoglycemia)
  - Hypoxia(?)
  - Sympathetic stimulation
  - Hormones
    - Erythropoietin
    - Leptin
    - Thyroid hormone

Inhibitors of Mitochondrial Biogenesis

- Oxidative/Nitrosative stress
- Hypoxia/ischemia
- Inflammation
- Apoptosis (AIF)
- Necrosis
- Parthanatos (PARP-1)
- BAX, Bcl2….. Cytochrome c



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Mitochondrial and the Theory of Aging

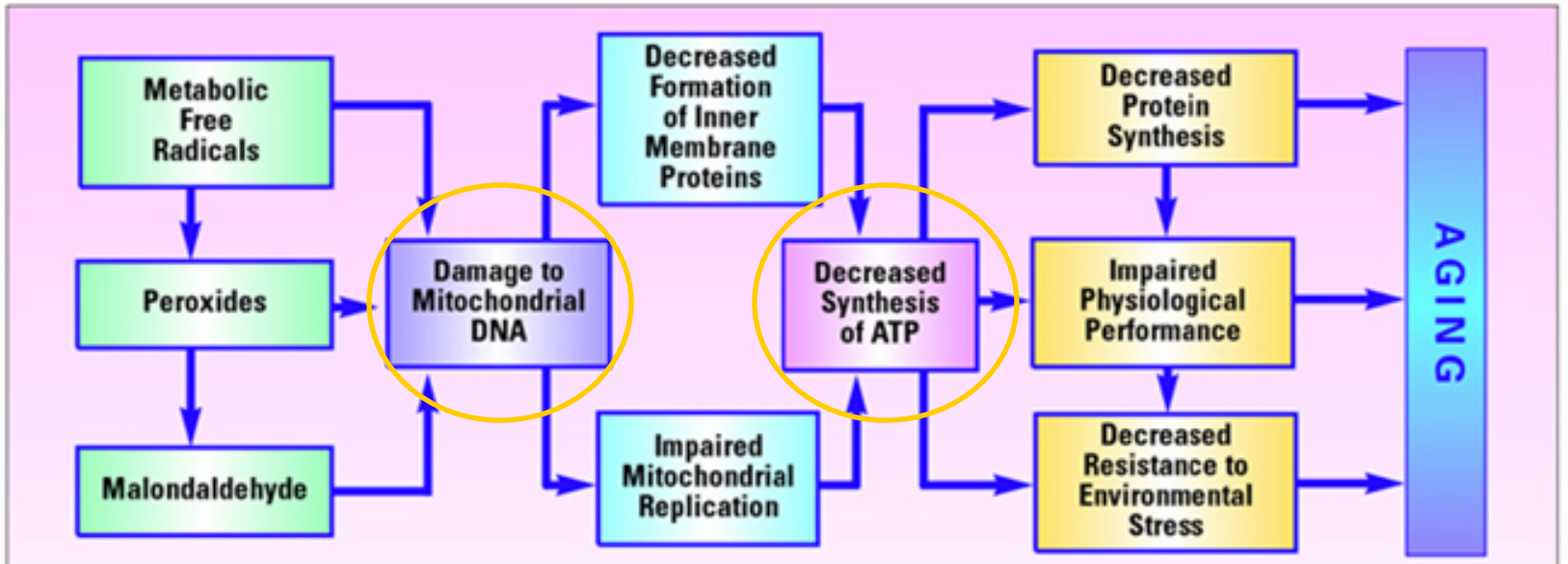


Fig. 1. Miquel's proposed model of aging, based on free radical-induced damage to mitochondrial DNA. This concept is consistent with the finding that free radicals, peroxides and malonaldehyde (which are injurious to DNA) are generated in the mitochondrial inner membrane. Accumulation of unrepaired damage to mitochondrial DNA leads to inadequate formation of inner membrane proteins, which interferes with mitochondrial replication. The resulting decline in ATP synthesis sets up a vicious cycle of mitochondrial loss, decline in energy production, decreased protein synthesis and impaired physiological performance. (Adapted from Fleming, J.E., Miquel, J., and Bensch, K.G. Age-dependent changes in mitochondria. *Molecular Biology of Aging*, 1985, Plenum, New York, 143-155.)

Reducing Agents

- Substances that have the ability to reduce other substances (gain electrons) are said to be reductive or reducing and are known as reducing agents, reductants, or reducers.
- The reducing agent transfers electrons to another substance, and is thus itself oxidized.
- And, because it "donates" electrons, the reducing agent is also called an electron donor.
- **Reduction is the *gain* of electrons**.

Oxidative Agents

- Substances that have the ability to oxidize other substances are said to be oxidative, oxidizers, or oxidizing agents.
- The oxidizing agent removes electrons from another substance, and is thus itself reduced.
- Because it "accepts" electrons, the oxidizing agent is also called an electron acceptor.
- Oxygen is the classical and quintessential oxidizer.
- Oxidation is the *loss* of electrons.

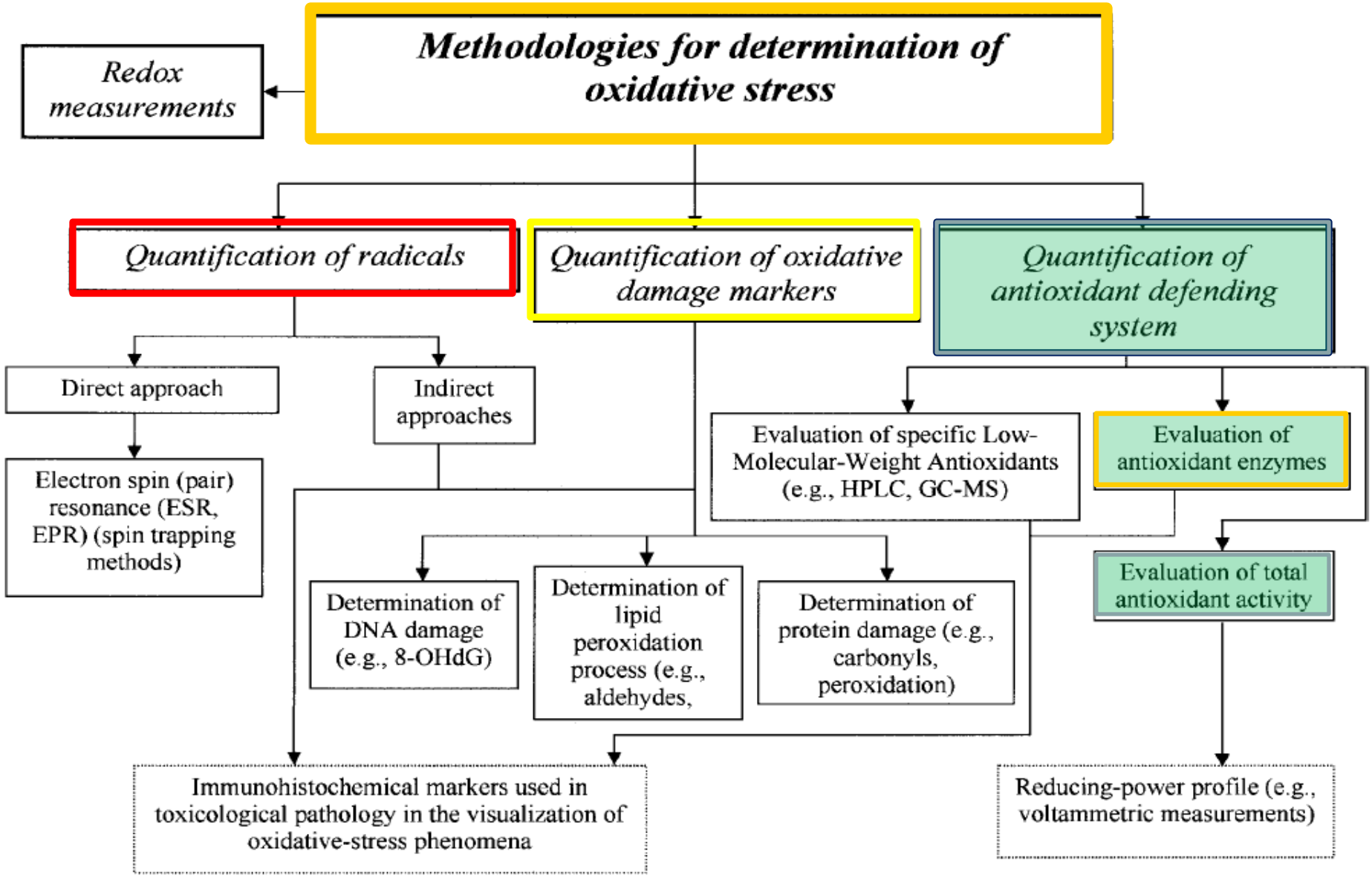
Free Radical & Oxidation

- Free radicals are highly reactive compounds which are mostly generated during cellular respiration and normal metabolism .
- Their possession of unpaired electrons in their outer shell causes them to be more reactive than their corresponding non-radicals.
- This is because they act as electron acceptors, and essentially "steal" electrons from other molecules and thereby modify their chemical structures – an action which is referred to as oxidation.

Disruption of the Balance

- Normally, a state of equilibrium exists between tissue oxidant and anti-oxidant activities.
- This balance can, however, be upset as a result of excessive free radical generation, depletion of endogenous antioxidants or failure to repair oxidative injury induced by reactive oxygen species.
- The resultant condition is referred to as **oxidative stress** and has been implicated in the disruption of neuronal homeostasis induced by traumatic brain injury.

Oxidative Stress Following Traumatic Brain Injury: Enhancement of Endogenous Antioxidant Defense Systems and the Promise of Improved Outcome. Eghwrudjakpor P O, *MBBS, DMS, FICS* Allison A B, *MBBS, FRCS, FICS* Department of Surgery University of Port Harcourt Teaching Hospital, Port Harcourt Nigeria

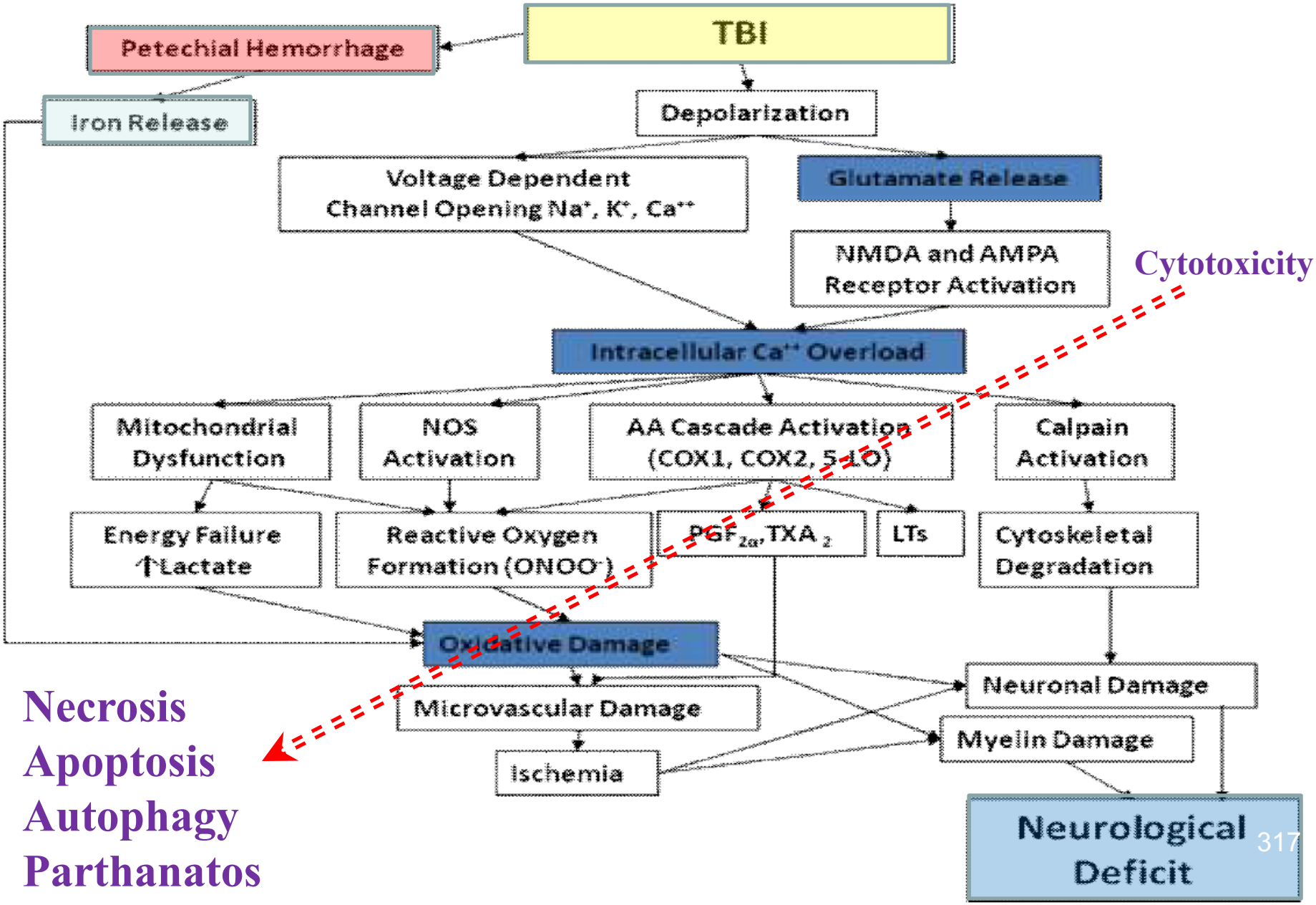

Methodologies for determination of oxidative stress
Redox measurements
Quantification of radicals
Quantification of oxidative damage markers
Quantification of antioxidant defending system
Direct approach
Indirect approaches
Electron spin (pair) resonance (ESR, EPR) (spin trapping methods)
Evaluation of specific Low-Molecular-Weight Antioxidants (e.g., HPLC, GC-MS)
Evaluation of antioxidant enzymes
Evaluation of total antioxidant activity
Determination of DNA damage (e.g., 8-OHdG)
Determination of lipid peroxidation process (e.g., aldehydes,
Determination of protein damage (e.g., carbonyls, peroxidation)
Immunohistochemical markers used in toxicological pathology in the visualization of oxidative-stress phenomena
Reducing-power profile (e.g., voltammetric measurements)

Antioxidant Therapies for Traumatic Brain Injury. Neurotherapeutics. 2010 January ; 7(1): 51. Edward D. Hall, Radhika A. Vaishnav, and Ayman G. Mustafa Spinal Cord & Brain Injury Research Center, University of Kentucky Medical Center

- Free radical-induced oxidative damage and membrane lipid peroxidation (LP) are one of the best validated secondary injury mechanisms in preclinical traumatic brain injury models.
- The disruption of the membrane phospholipid architecture, LP results in the formation of cytotoxic aldehyde-containing products that bind to cellular proteins on the cell membrane and impair their normal functions .

Gated-Ion Channels are impaired with LP of the cell membrane.

The full IMPACT of TBI



Oxidation of Biological Systems: Oxidative Stress Phenomena, Antioxidants, Redox Reactions, and Methods for Their Quantification.

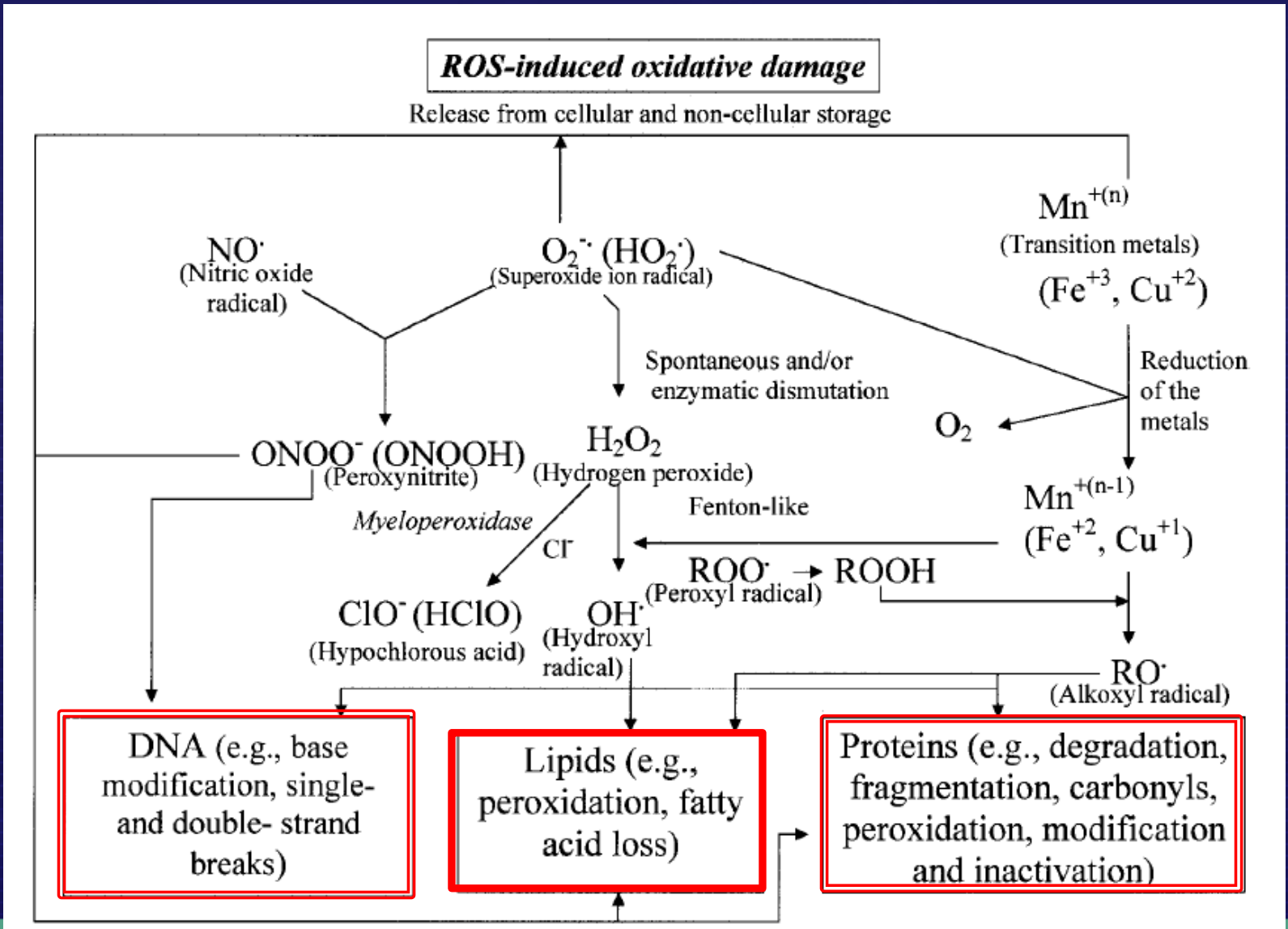
Toxicol Pathol 2002 30: 620. Ron Kohen and Abraham Nyska

TABLE 1.—Radical and nonradical oxygen metabolites.

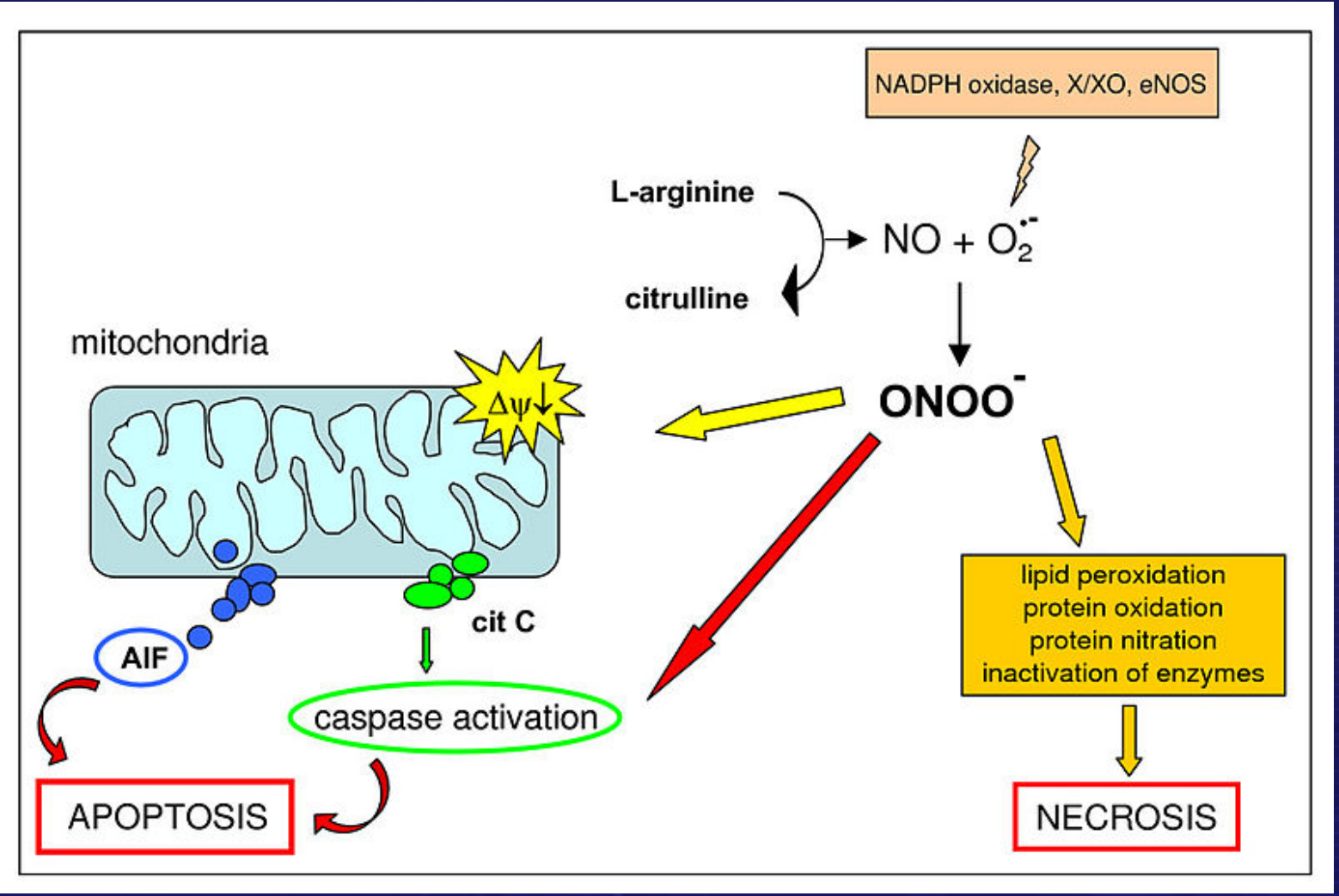
Name	Symbol
Oxygen radicals	
Oxygen (bi-radical)	$O_2^{\cdot\cdot}$
Superoxide ion	$O_2^{\cdot -}$
Hydroxyl	$OH^{\cdot}$
Peroxyl	$ROO^{\cdot}$
Alkoxyl	$RO^{\cdot}$
Nitric oxide	$NO^{\cdot}$
Nonradical oxygen derivatives	
Hydrogen peroxide	H_2O_2
(Organic peroxide)	ROOH
Hypochlorous acid	HOCL
Ozone	O_3
Aldehydes	HCOR
Singlet oxygen	$^1O_2$
Peroxynitrite	ONOOH

om by guest on June 28, 2014

Reactive oxygen species (ROS)



Peroxynitrite



Melatonin

- *N-Acetyl-5-methoxytryptamine* (Melatonin) is produced in the pineal gland and readily crosses the blood brain barrier to enter neurons and glial cells.
- A potent scavenger of peroxyl and hydroxyl radicals, shown to prevent both initiation and propagation of lipid peroxidation and stimulate ***brain glutathione peroxidase***.
- Melatonin acts as an antioxidant in both ***lipophilic*** and ***hydrophilic*** environments because of its solubility properties.
- Recently it was shown that melatonin inhibits nitric oxide synthase (*NOS*), thus preventing the toxic effect obtained after its interaction with ***superoxide radicals***.

Melatonin: A Multitasking Molecule. Progress in Brain Research Volume 181, 2010, Pages 127–151. Russel J. Reiter, Dun-Xian Tan, Lorena Fuentes-Broto

- Melatonin has revealed itself as a ubiquitously distributed and functionally diverse molecule.
- Its ability to detoxify free radicals and related oxygen derivatives, melatonin influences the molecular physiology of cells via receptor-independent means.

Carnosine

- Carnosine (beta-alanyl-L-histidine) is a naturally-occurring, pluripotent, homeostatic agent – in both muscles and brain of humans.
- Carnosine is a dipeptide found at high concentrations in **glial and neuronal cells** throughout the brain.
- Because of its enrichment in histidine residues, carnosine has also been proposed as a chelator for divalent cations like Cu^{2+} and Zn^{2+}
- Carnosine can suppress amyloid-beta peptide toxicity, inhibit production of oxygen free-radicals, scavenge hydroxyl radicals and reactive aldehydes, and suppresses protein glycation.

Antioxidant activity of carnosine, homocarnosine, and anserine present in muscle and brain. Proc. Nat. Acad. Sci. USA Vol. 85, pp. 3175-3179, May 1988. Ron Kohen, Yorihiro Yamamoto, Ken C. Cundy, and Bruce N. Ames Department of Biochemistry, University of California, Berkeley, CA 94720

- Carnosine, anserine, and histidine protect phage against gamma-irradiation, which gives rise to oxidative DNA damage.
- Roles of carnosine, include chelation of metal ions, quenching of singlet oxygen, and binding of hydroperoxides.

Vitamin C

- Ascorbic acid is considered a powerful hydrophilic scavenger in biological fluids and tissues.
- Humans and primates have lost the ability to synthesize ascorbic acid and therefore rely on dietary sources.
- Vitamin C is distributed throughout the brain, and its concentration in the cerebrospinal fluid is about **tenfold higher than in the plasma.**
- The vitamin serves as a strong reducing agent by donating electron(s), thus directly neutralizing ROS.
- Vitamin C also acts to **recycle the Tocopherol radical** to its active reduced form.

Ascorbate and glutathione: the heart of the redox hub. Plant Physiology, January 2011, Vol. 155, pp. 2–18. Christine H. Foyer and Graham Noctor. Centre for Plant Sciences, Faculty of Biology, University of Leeds, Leeds LS2 9JT, United Kingdom (C.H.F.); and Institut de Biologie des Plantes, UMR CNRS 8618, Universite de Paris Sud 11, 91405 Orsay cedex, France (G.N.)

Ascorbate-Glutathione Cycle:

(1) H_2O_2 + Ascorbate $\xrightarrow{APX}$ H_2O + Monodehydroascrobate (MDA)

(2) MDA + NAD(P)H $\xrightarrow{MDAR}$ Ascorbate + $NAD(P)^+$

(3) Dehydroascorbate + GSH $\xrightarrow{DHAR}$ Ascorbate + GSSG

(4) GSSG + NAD(P)H $\xrightarrow{GR}$ GSH + $NAD(P)^+$

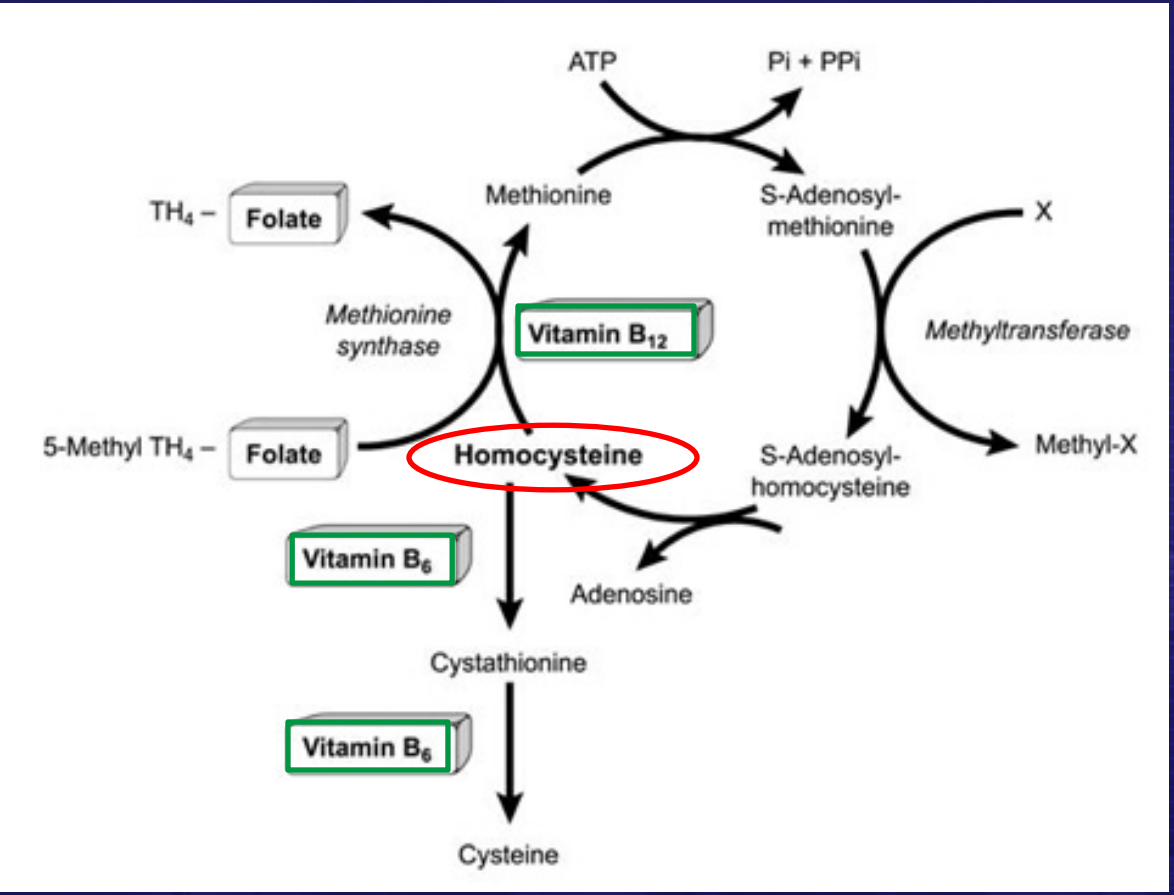
Vitamin B-12

- Vitamin B_{12}, also called cobalamin, is a water-soluble vitamin with a key role in the normal functioning of the brain and nervous system, and for the formation of blood cells.
- It is one of the eight B vitamins.
- It is normally involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation, but also fatty acid metabolism and amino acid metabolism.

Homocysteine Elicits a DNA Damage Response in Neurons That Promotes Apoptosis and Hypersensitivity to Excitotoxicity. The Journal of Neuroscience, Sept 15, 2000, 20(18):6920–6926. Inna I. Kruman, Carsten Culmsee, Sic L. Chan, Yuri Kruman, Zhihong Guo, LaRoy Penix, and Mark P. Mattson. Laboratory of Neurosciences, NIA, Baltimore, Maryland, and Sanders-Brown Research Center on Aging and Dept of Anatomy and Neurobiology, University of Kentucky, Lexington, Kentucky

- Homocysteine can induce neuronal apoptosis and can increase neuronal vulnerability to excitotoxicity by a mechanism involving DNA damage, PARP activation, and p53 induction.
- B-12 as well as B6 and Folate have been found to reduce the serum levels of HCY by increasing its conversion to cysteine.

Homocysteine Removal



Nicotinamide

- Nicotinamide (Vitamin B-3) is the amide form of nicotinic acid (niacin) and is currently used in the treatment of pellagra, a vitamin deficiency.
- It has been identified as a neuroprotective agent and has been shown to increase growth factors in Huntington's disease, reduce excitotoxicity in vitro, prevent cell death from oxidative damage both in vitro and in vivo, and improve behavioral outcomes following TBI and stroke.

The effects of nicotinamide on apoptosis and blood-brain barrier breakdown following traumatic brain injury. Brain Research. 2006 Dec 13;1125(1):185-93. Hoane MR, Kaplan SA, Ellis AL

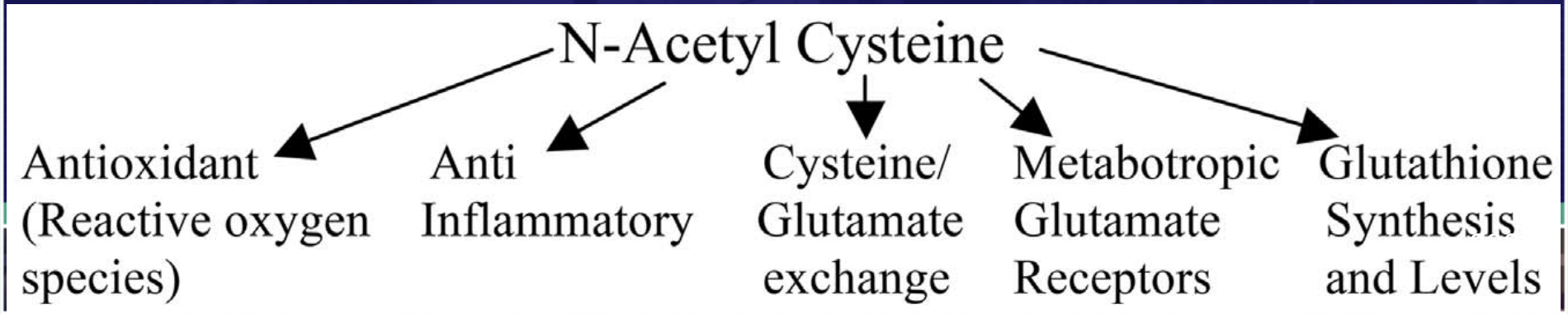
- Nicotinamide has been shown to protect against many of the pathophysiological factors associated with both ischemic and traumatic brain injuries.
- Nicotinamide reduced lesion cavity expansion 72 h following Cortical Contusion Injury.
- These findings suggest that nicotinamide reduces BBB breach and neuronal cell loss acutely following injury and that these reductions may account for the beneficial behavioral effects seen in previous studies.

N-Acetyl Cysteine

- A thiol acetylated cysteine that is a component of the tri-peptide Glutathione.
- NAC has anti-oxidant and free radical capabilities against Superoxides and Hydrogen peroxide, as well as hydroxyl radicals.

Efficacy of N-Acetyl Cysteine in Traumatic Brain Injury. PLOS ONE,April **2014**,Vol 9,4 , Katharine Eakin1, Renana Baratz-Goldstein, Chiam G. Pick, Ofra Zindel, Carey D. Balaban, Michael E. Hoffer, Megan Lockwood1, Jonathan Miller1, Barry J. Hoffer1, Dept of Neurosurgery, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA, Dept of Anatomy and Anthropology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel, Dept of ENT, Neurobiology, Communication Sciences and Disorders, and Bioengineering, UofP, PA, USA, Dept of ENT, Spatial Orientation Center, Naval Medical Center San Diego, San Diego, Ca, USA, Graduate Program in Neuroregeneration, Taipei Medical University, Taipei City, Taiwan

- NAC has been shown to have antioxidant and neurovascular-protective effects after TBI.
- The researchers found that early post-injury treatment with NAC reversed the behavioral deficits associated with mTBI.



Amelioration of acute sequelae of blast induced mild traumatic brain injury by N-acetyl cysteine: a double-blind, placebo controlled study.

Michael E. Hoffer, Carey Balaban, Martin D. Slade, Jack W. Tsao, Barry Hoffer. Spatial Orientation Center, Dept of Otolaryngology, Naval Medical Center San Diego, California, USA, Depts of Otolaryngology, Neurobiology, Communication Sciences and Disorders, and Bioengineering, University of Pittsburgh, Pennsylvania, USA, Dept of Internal Medicine, Yale University, New Haven, Connecticut, USA, Wounded, Ill and Injured Directorate (M9), US Navy Bureau of Medicine and Surgery, Washington, D.C., USA, Dept of Neurosurgery, Case Western University, Cleveland, Ohio, USA.

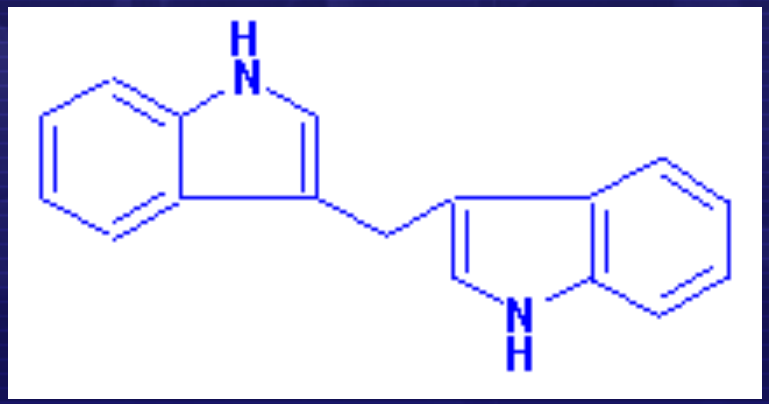
- A 4 gram loading dose was given followed by 2grams twice a day, then reduced to 1.5grams BID after 4 days.
- Early treatment with NAC resulted in a seven day symptom resolution rate of 86% as compared to 11% in those receiving placebo and began therapy between 24–72 hours after blast exposure.

Modulation of inflammation in brain: a matter of fat. Journal of Neurochemistry, 2007, 101, 577–599. Akhlaq A. Farooqui, Lloyd A. Horrocks, and Tahira Farooqui, *Depts of Molecular and Cellular Biochemistry, The Ohio State University, Columbus, Ohio,

- Cytokines are major effectors of the Neuroinflammatory cascade. They play an important role in neural cell response to infection and brain injury.
- Docosahexaenoic acid (DHA) is metabolized to resolvins and neuroprotectins. These lipid mediators inhibit the generation of prostaglandins, leukotrienes, and thromboxanes.
- A combination of NAC and Vitamin E (a,d,g) reduce the production of Nf Kappa B

Di-Indole-Methane

- A metabolite of indole–3–carbinol (I3C) found naturally in cruciferous vegetables like broccoli, kale and Brussels sprouts.
- Indole-3-carbinol (C9H9NO) is the subject of on-going biomedical research into its anti-carcinogenic, anti-oxidant, and anti atherogenic effects.



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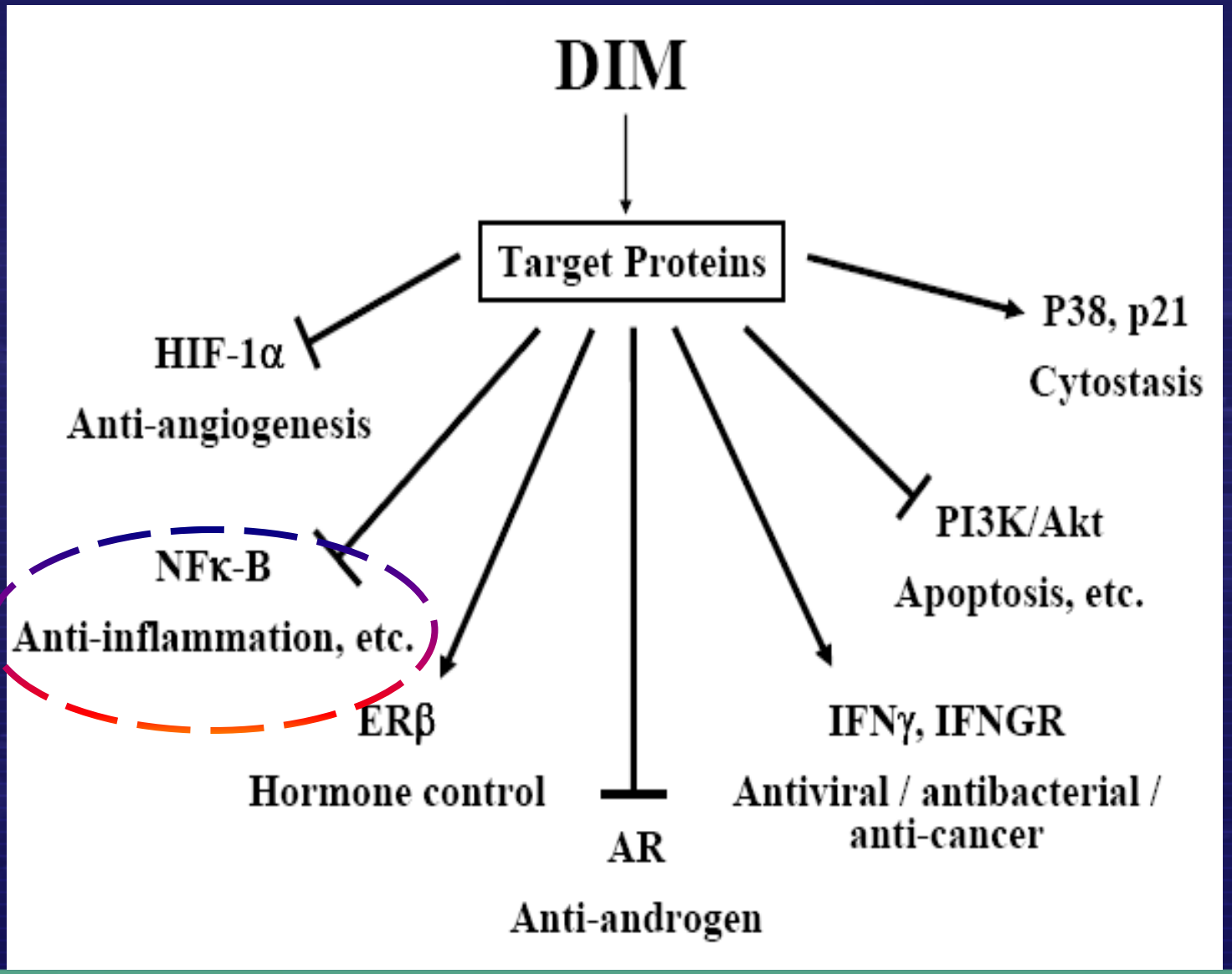
3,3'-Diindolylmethane Inhibits Lipopolysaccharide-Induced Microglial Hyperactivation and Attenuates Brain Inflammation.

Toxicological sciences 137(1), 158–167 2014. Hyo Won Kim, et al. WCU Biomodulation Major, Dept of Agricultural Biotechnology, Seoul National University, Korea; Center for Food and Bioconvergence, Seoul National University, Korea; Advanced Institutes of Convergence Technology, Seoul National University, Suwon Korea; Dept of Biological Sciences, Konkuk University, Seoul, Korea; and Research Institute of Bio Food Industry, Institute of Green Bio Science and Technology, Seoul National University, Pyeongchang ,Korea.

- Science indicates that microglial hyperactivation and neuro-inflammation are implicated in neurodegenerative diseases.
- DIM suppressed LPS-induced brain inflammation through the negative regulation (down-regulation) of the Nf-κappa-B signal pathway in microglia.

Article


DIM
Target Proteins
HIF-1α
Anti-angiogenesis
P38, p21
Cytostasis
NFκ-B
Anti-inflammation, etc.
PI3K/Akt
Apoptosis, etc.
ERβ
Hormone control
AR
Anti-androgen
IFNγ, IFNGR
Antiviral / antibacterial / anti-cancer

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Quercetin

- Quercetin, a natural polyphenolic flavonoid, is present in plants, including onions, apples, and berries.
- Similarity in the structure of quercetin to resveratrol and other flavonoid derivatives that have been shown to increase Mitochondrial Biogenesis (Mt-biogenesis).
- Quercetin increased mRNA expression of PGC-1α and SIRT1, mtDNA, and cytochrome c concentrations.
- An increase in Mt-biogenesis increases production of ATP.
- Quercetin contributes significantly to the protective effects of **neuronal cells from oxidative stress-induced neurotoxicity**.

Quercetin increases brain and muscle Mitochondrial biogenesis and exercise tolerance.

Am J Physiol Regul Integr Comp Physiol 296: R1071–R1077, 2009. J. Mark Davis, E. Angela Murphy, Martin D. Carmichael, and Ben Davis. Div. of Applied Physiology, Dept of Exercise Science and Dept of Com. Science and Disorders, Arnold School of Public Health, U. of South Carolina, Columbia, South Carolina. USA.

- Cerebral metabolism has important consequences on motivation, mood, fatigue, anxiety, depression, and central motor drive from the cortex; **ATP dependent.**
- Within 7 days of introduction of Quercetin, mitochondrial biogenesis with increased oxidative phosphorylation by facilitating transcription, translation, and replication are recorded. (Energy!!)

Protective Effect of Quercetin in Primary Neurons Against Aβ (1-42): Relevance to Alzheimer's Disease

Mubeen Ahmad Ansari, Hafiz Mohammad Abdul, Gururaj Joshi, Wycliffe O. Opii, and D. Allan Butterfield, Dept of Chemistry, Center of Membrane Sciences, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

- Quercetin increases glutathione (GSH) levels and antioxidant enzyme function.
- Considerable attention has been focused on increasing the intracellular GSH levels in many diseases, including Alzheimer's disease (AD).
  - Amyloid beta-peptide, elevated in AD brain, is associated with oxidative stress and neurotoxicity.

Coenzyme Q10

- ***CoQ10*** is an essential co-factor of the electron transport chain as well as a potent free radical scavenger in lipid and mitochondrial membranes.
- Supplementation with CoQ10 increased cerebral cortex concentrations which resulted in a significant increase in cerebral cortex mitochondrial concentrations of CoQ10.
- Co-Q10 has been shown to exert neuroprotective effects useful in the treatment of neurodegenerative diseases and the sequelae associated with TBI.

Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc. Natl. Acad. Sci. USA Vol. 95, pp.8892–8897, July 1998 Medical Sciences Coenzyme. Russell T Matthews, L. Yang, S. Browne, M. Baik, F. Beal., Neurochemistry Laboratory, Neurology Service, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114

- Lipid peroxidation leads to a decrease in coenzyme Q10 content and inactivation of respiratory chain enzymes, whereas administration of coenzyme Q10 preserves mitochondrial respiratory function.
- If defects in energy metabolism and oxidative damage play a role in the pathogenesis of neurodegenerative diseases then treatment with coenzyme Q10 could exert beneficial therapeutic effects. (A major component of TBI!)
- This study was able to show that oral administration of CQ10 increases both brain and brain mitochondrial concentrations.

Pyrroloquinoline Quinone (PQQ)

- Pyrroloquinoline Quinone (**PQQ**) is a micronutrient that is found in **soybeans, parsley and green pepper**.
- **PQQ as an antioxidant influences nerves and neurological health, as well as cognitive function.**
- PQQ supports several signal transduction pathways that are important in maintaining mitochondrial homeostasis and oxidative metabolism.
- When CoQ10 and PQQ used together there is a synergistic enhancement of functions for each

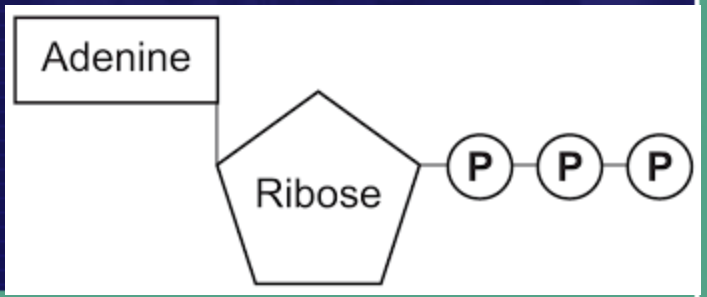
The Neuroprotective effect of Pyrroloquinoline Quinone (PQQ) on Traumatic Brain Injury. Journal of Neurotrauma 29:851–864. March 20, 2012. Lili Zhang, Jie Liu, Chun Cheng, Ying Yuan, Biyun Yu, Aiguo Shen, and Meijuan Yan

- PQQ has been classified as a new B vitamin.
- PQQ is an effective antioxidant in protecting mitochondrial lipid and protein, and it has been shown to protect mitochondrial functions against oxidative damage.
- PQQ has additional beneficial effects; anti-inflammatory, hepatoprotective, cardioprotective, and antioxidative properties.

Ribose

Ribose is a 5 carbon sugar that participates in a number of biological systems:

- Phosphorylated to become ATP, in fact the back bone of all energy molecules. (Energy)
- The core of RNA, mRNA, tRNA and DNA.
- Transport of inorganic phosphate into Oxidative Phosphorylation. (Energy - R-5-P)
- Poly (ADP-ribose) polymerase-1 (PARP-1), the DNA repair enzyme.



The use of D-ribose in Chronic Fatigue Syndrome and Fibromyalgia: a pilot study. Journal of alternative and complementary medicine. Volume 12 number 9. pages 857-862. 2006.

- Approximately 66% of patients experienced significant improvement while on D-ribose, with an average increase in energy on the VAS¥ of 45% and an average improvement in overall well-being of 30% ($p < 0.0001$).

❖ ¥VAS Testing for Pain evaluation in Adults.

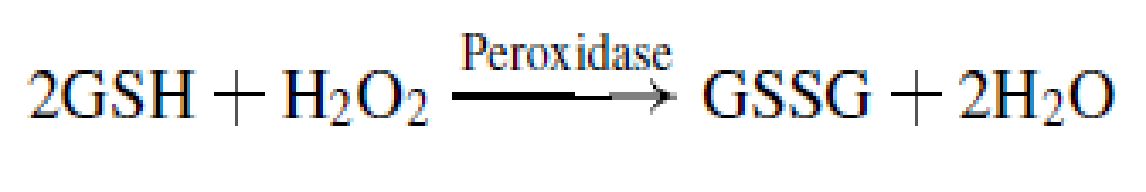
The NO/ONOO- Vicious Cycle Mechanism as the Cause of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis.

Martin L. Pall, Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University and Research Director, The Tenth Paradigm Research Group. 2009

- Cases of chronic fatigue syndrome(CFS) are reported to be initiated by nine different short-term stressors, each of which increase levels of nitric oxide(NO) in the body.
- Elevated nitric oxide, acting through its oxidant product, Peroxynitrite, initiates a local biochemical vicious cycle, the NO/ONOO-cycle, which is proposed to be the cause of CFS and related diseases.

Glutathione

- This tripeptide (glu-cys-gly) is the most abundant non-protein thiol found in the brain.
- Glutathione acts as an antioxidant via its capacity to serve as a substrate for the enzyme glutathione peroxidase and seems to mainly be found in **Astrocytes**.



Glutathione Efflux and Cell Death

. Antioxidants & Redox Signaling Volume 17, Number 12, 2012. Rodrigo Franco and John A. Cidlowski. Redox Biology Center and School of Veterinary Medicine and Biomedical Sciences, University of Nebraska-Lincoln, Lincoln, Nebraska. 3Laboratory of Signal Transduction, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina.

- Glutathione (GSH) depletion is a central signaling event that regulates the activation of cell death pathways.
- Glutathione (GSH) depletion is a marker of **oxidative stress** and is a key event in the secondary phase of Traumatic Brain Injury.

Synthesis of the Antioxidant Glutathione in Neurons: Supply by Astrocytes of CysGly as Precursor for Neuronal Glutathione. The Journal of Neuroscience, January 15, 1999, *19*(1):562–569. Ralf Dringen, Brigitte Pfeiffer, and Bernd Hamprecht *Physiologisch-chemisches Institut der Universita, Germany*

- Deficiency of Brain Glutathione is associated with several diseases characterized by Neuronal Loss.
- Astrocytes release glutathione into the extracellular space to generate the dipeptide CysGly that is subsequently picked up and used by neurons as precursor for glutathione synthesis.
- Functional impairment of this process is directly associated with Inflammation.

Alpha Lipoic acid

- The lipid-soluble dithiol a-lipoate is absorbed from the diet, crosses the BBB, and is taken up by cells. It possesses a wide spectrum of activities as a metabolic antioxidant, and its reduced form, dihydrolipoate, exits the cells to act as an extracellular antioxidant.
- Alpha-lipoate scavenges a large variety of species including hydroxyl radicals, hypochlorous acid, NO, peroxynitrite, hydrogen peroxide, and singlet oxygen.
- Thus, α-lipoate and its reduced product act as potent antioxidants in both intra- and extracellular environments and shows **neuroprotective properties in traumatic brain injury**.

Antioxidant Therapies for Traumatic Brain Injury. Neurotherapeutics. **2010** January ; 7(1): 51. Edward D. Hall, Radhika A. Vaishnav, and Ayman G. Mustafa Spinal Cord & Brain Injury Research Center, University of Kentucky Medical Center

- α-Lipoic acid has lipid peroxyl radical (LOO•) scavenging effects, but functions indirectly via the regeneration of other endogenous electron-donating antioxidants including; **Vitamin E**, **Glutathione** and **Vitamin C**.

- Brain Cocktail: ALA, Qu, Vit E(a,d,g), NAC.

Pregnenolone

A. The MOTHER of ALL HORMONES
B. Precursor to DHEA/DHEA-s
C. Produced in adrenals **and brain.**
D. Can raise levels of steroids lower down or they can remain the same.
E. Neurosteroid for peak brain function!
    A. Found in highest concentrations in the brain!

Pregnenolone

A. Initiates the memory storage process by stimulating neuronal Adenylate Cyclase (**AC**).*
B. Regulates the timed-sequential flow of calcium ions through the cell membrane.
C. Calcium ion exchange may determine how memory is encoded by neurons.

*(T) → (DHT) → (3AAD) → (AC)

Neurosteroids in the Hippocampus: Neuronal Plasticity and Memory.

Stress 1997 Oct;2(1):65-78 Schumacher M, et al.

- There is accumulating evidence that Pregnenolone sulfate (Preg-s), has a strong influence on learning and memory processes, most likely by regulating neurotransmission in the hippocampus (CA1 cells).

Analysis of Neurosteroid levels in attention deficit hyperactivity disorder.

International Journal of Neuropsychopharmacol 2001 Sep;4(3):259-64. Strous RD et al.

- Inverse correlation between clinical symptoms and levels of DHEA-s and Pregnenolone in young male subjects aged 7-15 years with DSM-IV criteria of ADHD.

Pregnenolone Sulfate and Aging of Cognitive Functions: Behavioral, Neurochemical and Morphological Investigations. Hormones and Behavior 40, 215-217 (2001), Mayo M et al.

- Cerebral Pregnenolone correlated with cognitive performance and is improved with replacement in deficient older adults.
- Pregnenolone increases Acetylcholine in the amygdala, cerebral cortex and hippocampus.

Progesterone(P4) and Allopregnanolone(Allo) reduce inflammatory cytokines after traumatic brain injury. Exp Neurol **2004** Oct;189(2):404-12. He J; et al. Department of Psychology, Emory University, Atlanta, GA 30322, USA

- The excessive release of **IL-1β and TNF-α** is a major cause of cerebral edema, which in turn, can cause permanent neuronal loss and cognitive deficits.
- **Progesterone** attenuates the production of IL-1β and TNF-α, and this may be one mechanism by which P4/Allo reduces cerebral edema and promotes functional recovery from **Traumatic Brain Injury**.

The Neurosteroid Allopregnanolone is reduced in prefrontal cortex in Alzheimer's disease.

Biol Psychiatry. 2006; 60(12):1287-94. Marx CE; Trost WT; Shampine LJ; et. Al. Duke University Medical Center, Department of Psychiatry and Behavioral Sciences, Durham, North Carolina 27705, USA

- Postmortem AD subjects when compared to controls were found to have significantly diminished levels of Pre-frontal cortex (PFC) Allopregnanolone levels.
- Neurosteroids may have utility as candidate biomarkers in AD. (They now are!)

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**.

- Low Pregnenolone-s is associated with Social Phobia, and has been correlated in male patients who suffer from generalized anxiety disorder (GAD).

- MHC Note: The combination of a low to low-normal Pregnenolone and Prolactin appears to exacerbate all forms of anxiety secondary to an elevation in Dopamine.

Dehydroepiandrosterone

- DHEA is a steroid hormone secreted primarily by the adrenal glands and to a lesser extent by the **brain**, **skin**, **testes**, and **ovaries**.
- DHEA is classified as an adrenal androgen and is rapidly sulfated to DHEA-s, the predominant form found circulating in the plasma. (**Test for DHEA-s**).
- DHEA serves as precursor to androgens and estrogens and is low with anorexia, end-stage kidney disease, Diabetes, AIDS, adrenal insufficiency, auto-immune diseases, and in the critically ill.
- DHEA's secretion decreases from the age of 30 years and is already decreased by 60% at time of menopause

Dehydroepiandrosterone Sulphate: Action and Mechanism in the Brain,

Journal of Neuroendocrinology 24, 215–224. 2011. Y. Dong and P. Zheng. State Key Laboratory of Medical Neurobiology, Shanghai Medical College and Institutes of Brain Science, Fudan University, Shanghai, China.

- DHEA-s is one of the most important Neurosteroids in the brain having a concentration higher than peripheral system.
- DHEA-s has been shown to modulate a variety of synaptic transmission, including cholinergic, GABAergic, dopaminergic, and glutamatergic synaptic transmission.
- DHEA-s has memory enhancing, antidepressant and anxiolytic effects.
- Enhances myelin production from Oligodendrocytes.
- Reduction of Glia production of IL-6.

- MHC Note: The sole use of Testosterone will shut off DHEA production.

DHEA Stimulates Growth of Brain Cells. UCSF Researchers Conclude , Proceedings of the National Academy of Sciences, *Jeffrey Norris April 1998*

- In the April 14, 1998 issue of the Proceedings of the National Academy of Sciences, researchers at the University of California San Francisco report that in the brains of mice -- and very likely in the brains of humans as well:
- "DHEA and DHEA-s, **can stimulate the growth of nerve cell fibers needed to form electrical connections in the brain**. "

Oral DHEA supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women. Fertil Steril 2001 Aug;76(2):241-8., Genazzani AD University of Pisa, Italy. 2001.

- DHEA significantly affects several endocrine parameters in early and late postmenopausal women.
- Our data support the hypothesis that DHEA treatment acts similarly to estrogen-progestin replacement therapy on the GHRH-GH-IGF-1 axis. *
- This suggests that DHEA is more than a simple "diet supplement" or "anti-aging product"; rather it should be considered an effective hormonal replacement treatment.

* High-Normal levels of DHEA-s increase GH release from the AP.

Diffuse Muscoskeletal Pain and Proximal Myopathy; Do Not Forget Hypovitaminosis D. Journal of Clinical Rheumatology • Volume 16, Number 1, January 2010. G.i Fabbriciani, MD, M. Pirro, MD, PhD, C. Leli, MD, A. Cecchetti, MD, L Callarelli, MD, Giuseppe Rinonapoli, MD, PhD Anna Maria Scarponi,MD, and E. Mannarino, MD

- Without VitD, only 10% to 15% of dietary calcium and about 60% of phosphorus is absorbed.
- Lack of VitD decreases muscular strength. Interaction of VitD with muscle VitD receptors (VID-r) exerts a positive influence on muscle mass and strength by promoting protein synthesis (Actin and Myosin).
- In addition VitD stimulates muscle cell uptake of inorganic phosphate, which is important for the production of energy-rich phosphate compounds such as ATP and creatine phosphate, vital for muscle contraction.

Effect of Vitamin D supplementation on testosterone levels in men.

Horm. Metab. Res. **43** (3): 223–5. **2011**. Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, Obermayer-Pietsch B, Wehr E, Zittermann A

- The male reproductive tract has been identified as a target tissue for Vitamin D, and previous data suggest an association of 25-hydroxyvitamin D [25(OH)D] with testosterone levels in men.
- The hormone vitamin D in levels of 400-1000 IU (10-25 mcg) can raise the testosterone level.

DL-Phenylalanine

- **As** an essential amino acid DLP is a precursor to the synthesis of neurotransmitters such as dopamine, norepinephrine, epinephrine, and serotonin.
- Researchers have concluded that L-phenylalanine can increase mental alertness, help control addictive substance abuse, promote sexual arousal, and release hormones that can curb appetite.
- D-phenylalanine is a non-nutrient amino acid that breaks down opiate-like substances known as enkephalins in the brain. Consequently, D-phenylalanine is able to modulate chronic pain.

dl-Phenylalanine versus imipramine: A double-blind controlled study. European achieves for psychiatry and clinical neuroscience **1979**, Vol. 227, #1, pp 49-58. Helmut Beckmann, Dieter Athen, Margit Olteanu, Reinhild Zimmer.

- In this double-blind, cross-over, wash-out study comparing the efficacy of dl-P against the tricyclic anti-depressant **Imipramine**,
- both patient groups using the Hamilton Depression Scale and the Bf-S self rating questionnaire, documented improvement on both portions of the study but without the side-effects on dl-P that were experienced with Imipramine.

Tocopherols and Tocotrienols

- **Vitamin E** is a collective term for eight naturally occurring compounds, four tocopherols (alpha-, beta-, gamma-, and delta-) and four tocotrienols (alpha-, beta-, gamma-, and delta-).
- Vitamin E is a potent, lipid-soluble, anti-oxidant with neuroprotective benefits.
- Pre-traumatic supplementation with alpha-tocopherol reduces TBI-induced lipid peroxidation, oxidative injury, and impairment in spatial memory.
- Gamma-tocopherol is the main anti-inflammatory component found to be more effective then alpha-tocopherol in scavenging free radicals and nitrogen oxygen species causing inflammation (RNS).

Modulation of inflammation in brain: a matter of fat. Journal of Neurochemistry, 2007, 101, 577–599. Akhlaq A. Farooqui, Lloyd A. Horrocks and Tahira Farooqui. Dept of Molecular and Cellular Biochemistry, and Entomology, The Ohio State University, Columbus, Ohio, USA

- Inhibiting transcription factor NFkB, preventing cytokine secretion, blocking the synthesis of prostaglandins, leukotrienes, and thromboxane, and modulating leukocyte trafficking.
- N-Acetyl Cysteine
- Quercetin
- PQQ
- Vitamin E (alpha, delta and gamma)

Vitamin E Protects Against Oxidative Damage and Learning Disability After Mild Traumatic Brain Injury in Rats.

Neurorehabil Neural Repair. 2010 March ; 24(3): 290–298 . Aiguo Wu, PhD1, Zhe Ying, BS, and Fernando Gomez-Pinilla, PhD, UCLA Brain Injury Research Center, Los Angeles, California, USA.

- Mixed Tocopherols (Vitamin E) can protect the brain against the effects of mild TBI on synaptic plasticity and cognition.
- The elevation of **superoxide dismutase** (SOD) and **Sir2** (silent information regulator 2) play an important role in resistance to oxidative stress and protection of neurosynaptic plasticity.

Eicosanoids (Omega 3 and 6)

- Omega-3 FAs are the major constituents of the cell membrane phospholipids, which suggest that supplementation of PUFAs, could help in reducing the irregular phospholipid metabolism that occurs during neuronal damage, as in TBI.
- There are three important physiological omega-3 FAs available, including alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).

Therapeutic use of omega-3 fatty acids in severe head trauma. Am J Emerg Med. 2013 January ; 31(1): 273.e5–273.e8. Michael Lewis, MD, et al, Brain Health Education and Research Foundation Arlington, VA.

- Arachidonic Acid, the primary N-6FA in the brain, is metabolized by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes to pro-inflammatory eicosanoids that increase vascular permeability, local blood flow, infiltration of leukocytes, and production of proinflammatory cytokines.
- N-3FA attenuate release of these proinflammatory cytokines, decrease COX activity, inhibit formation of proinflammatory eicosanoids and cytokines, and increases levels of anti-inflammatory DHA.
- DHA (N-3FA), in particular, promotes neuronal survival, neurogenesis, neurite development, neuronal cell migration1, synaptogenesis, and modulation of inflammatory cascade.

Mucuna Pruriens

- Mucuna Pruriens (MP), also known as the Velvet Bean, contains L-DOPA, a precursor to the neurotransmitter *dopamine* in a 30% W/V.
- Dopamine seems to be an important neurotransmitter for pre-frontal functioning which is expressed by the term "*Executive Functions*" that is meant to represent a wide range of cognitive abilities.
- Patients with damage to the prefrontal cortex show impaired judgment, organization, planning and decision-making, as well as behavioral disinhibition and impaired intellectual abilities.

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Neuroprotective effects of the Anti-Parkinson drug Mucuna pruriens.

Phytotherapy Research. 2004 Sep;18(9):706-12. Manyam BV, Dhanasekaran M, Hare TA. Department of Neurology, Health Science Center College of Medicine, Temple, TX 76508, USA

- Mucuna pruriens significantly increased the brain's mitochondrial complex-I activity but did not affect the total monoamine oxidase (MAO) activity.
- Unlike synthetic levodopa treatment, **Mucuna Pruriens** treatment significantly restored the endogenous levodopa, dopamine, norepinephrine and serotonin content in the substantia nigra.
- This additional finding of a neurorestorative benefit by Mucuna pruriens on degenerating dopaminergic neurons in the substantia nigra may be due to increased complex-I activity and the presence of NADH and CoQ-10.

Mucuna pruriens in Parkinson's disease: a double blind clinical and pharmacological study. J Neurol Neurosurg Psychiatry 2004;75:1672–1677.
R Katzenschlager, A Evans, A Manson, P N Patsalos, N Ratnaraj, H Watt, L Timmermann, R Van der Giessen, A J Lees

- The rapid onset of action and longer effectiveness without concomitant increase in dyskinesia on Mucuna (seed powder) suggests that this natural source of L-dopa might possess advantages over conventional L-dopa preparations in the long term management of Parkinson's disease.

You Think?

Amantadine

- Amantadine affects the synthesis, accumulation, release, and reuptake of catecholamines in the central nervous system with a peak plasma level within 1-4 hours.
- Amantadine is rapidly absorbed, but it is not metabolized so that 90% is excreted unchanged in the urine.
- Amantadine causes release of dopamine from central neurons, facilitates dopamine release by nerve impulses, and delays the re-uptake of dopamine by neural cells.
- **Amantadine has profound NMDA receptor antagonistic effects, which may contribute to its neuroprotective effects early after injury.

Effects of dopaminergic combination therapy for frontal lobe dysfunction in traumatic brain injury rehabilitation

. BRAIN INJURY, 1999, VOL. 13, NO. 1, 63-68. David T. Burke, MD, et al. Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, 125 Nashua Street, Boston, MA 02114, USA

- This trial demonstrated Amantadine's ability to positively affect frontal lobe dysfunction.
- Patients experienced decreases in agitation, fatigue, distractibility, rigidity and bradykinesia, and increases in general arousal, orientation, initiation, purposeful movement, attention & concentration, sequencing skills and processing/ response time.

Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury. N Engl J Med 2012;366:819-26. Joseph T. Giacino, Ph.D., John Whyte, M.D et al.

- Amantadine promotes dopaminergic activity by facilitating presynaptic release and blocking reuptake postsynaptically.
- Amantadine has the potential to restore an interrupted balance between glutamatergic and dopaminergic neurotransmitter systems, via its role as an NMDA antagonist-receptor inhibitor.

Statins: The bad and the very bad

- Statins are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver, which produces about 70 percent of total cholesterol in the body.
- Coenzyme Q10 (ubiquinone) levels are decreased in statin use. (WP)
- Statins may increase the risk of diabetes by 9%.
- Statins reduce the production of Cholesterol in the brain lowering Neurosteroid production.
- Peripheral production of all hormones from cholesterol; testosterones, progesterone, estrogens, vitamin D, cortisol, DHEA, and DHEA-s are all affected by statins.



Statins in Traumatic Brain Injury

. The Journal of the American Society for Experimental NeuroTherapeutics. Vol. 7, 62–73, Jan 2010. Elissa F. Wible* and Daniel T. Laskowitz. Depts of Medicine (Neurology), Anesthesiology, and Neurobiology, Duke University School of Medicine, Durham, North Carolina 27710

- The therapeutic effects of statins in brain injury may be divided according to mechanism from most acute to more chronic: acute lesional effects, anti-inflammatory and anti-excitotoxic effects, vascular and endothelial effects, anti-apoptotic effects, and effects on neurogenesis and angiogenesis.

Table 8.1: Statins Effects in Traumatic Brain Injury

ACUTE		SUBACUTE	CHRONIC
Cerebral Blood Flow	Neuroinflammation	Apoptosis	Angiogenesis
▼Microthrombosis	▼Inflammatory cytokines	▼Bax/Bcl-2	▲VEGF, VEGFR2
▼Platelet Activity	▲BBB Integrity	▼Caspase 3	▲Akt/eNOS
▼Von Willebrand Factor	▼Cerebral Edema	Neuronal Injury	Neurogenesis & Plasticity
▲Endothelial Integrity	▼Microglial Activation	▼Excitotoxicity Death	▲BDNF, VEGF
▲eNOS	▼Oxidative Stress		▲PI3K/Akt

Summary Statement

- Everyone has a degree of active cerebral inflammation due to free radicals.
- Selecting an initial starting point with supplements at the same time as starting a neurosteroid and neuroactive steroid replenishment protocol will enhance the process of recovery.
- As long as the Non-Permissive Environment exists there is little hope for improvement.

Traumatic Brain Injury:

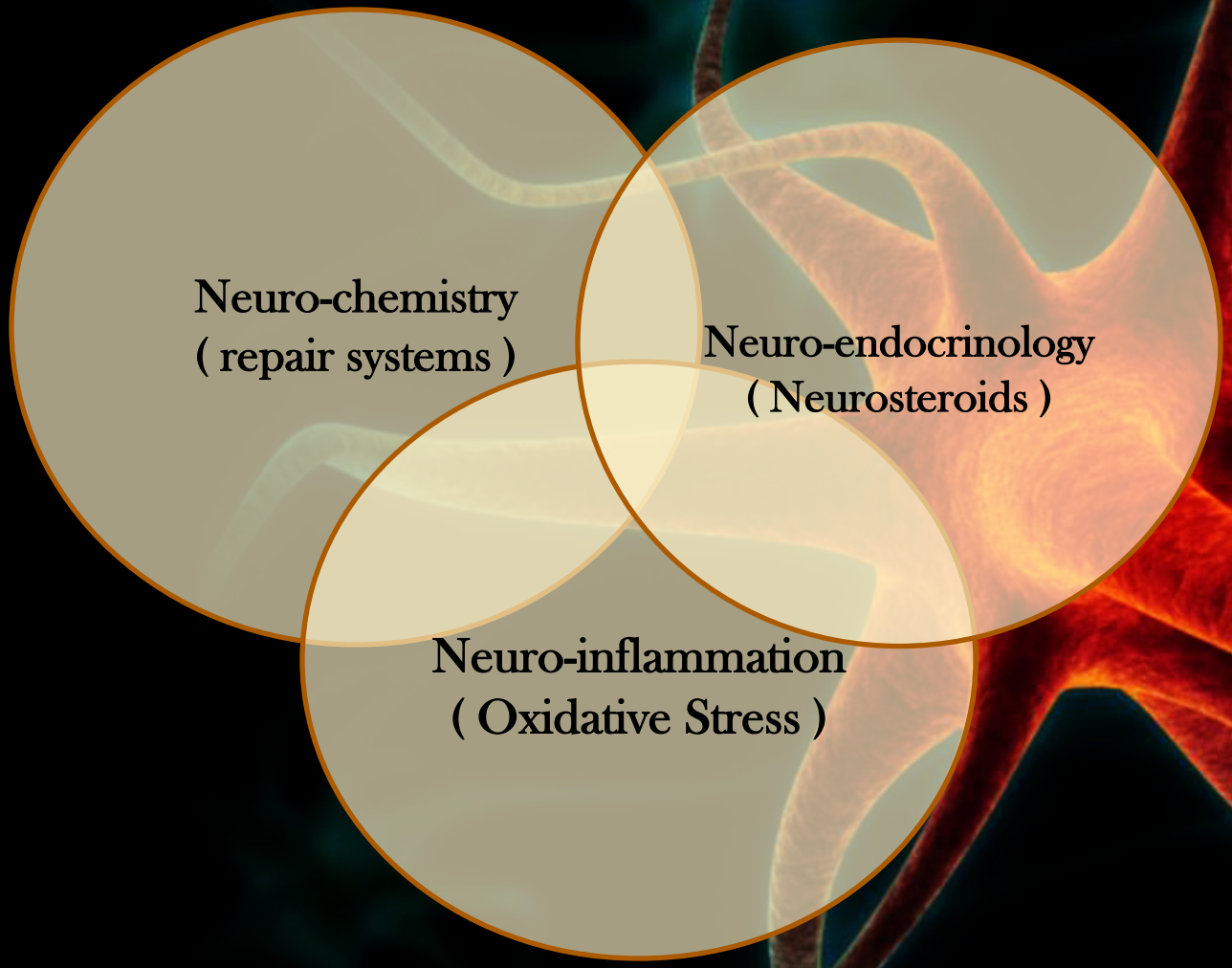
A Clinical Approach to Diagnosis and Treatment

by Mark L. Gordon, M.D.



Chapter 9: Treatment

Over-Lapping Concepts



Outcome Measures for Clinical Trials in Neuro-Trauma

M. Ross Bullock, M.D. Ph.D., Randall E. Merchant, Ph.D., Sung C. Choi, Ph.D., Charlotte B. Gilman, B.S.N., Jeffrey S. Kreutzer, Ph.D., Anthony Marmarou, Ph.D., And Graham M. Teasdale, F.R.C.P., F.R.C.S. Neurosurg Focus 13(1), 2002.

- Many large and expensive trials seeking treatment for TBI were terminated prematurely; based upon futility analyses where they failed to provide any conclusive result, either positive or negative.
- Animal studies when translated into Human studies failed to provide the same benefits.
- The **wholly grail** has been about looking for a Monotherapeutic approach.



Outcome Trials

Authors & Year	Agent	Patients/Country	Outcome/Comments
Ward. 1950	atropine	940, US	uncontrolled, no benefit
Schwartz, 1985	mannitol vs pentobarbital	59, Canada	randomized crossover permitted, mannitol group had better outcome
Ward, 1984	barbiturates	53, US	DBPRPCT, no benefit (prophylaxis)
Eisenberg, 1988	barbiturates	73, US	DBPRPCT, no benefit (prophylaxis)
Teasdale, 1992	nimodipine (HIT I)	255, UK & Finland	DBPRPCT, no benefit
Muizelaar,1993	PEG-SOD	94, US	DBPRPCT, ICP lower, outcome better ($p < 0.01$)
Wolf, 1993	tromethamine	149, US	DBPRPCT, no benefit
Muizelaar, 1994	PEG-SOD (Phase III),	463, US	DBPRPCT, outcome 9% better in drug vs. placebo ($p = 0.15$)
Clifton, 1995	moderate hypothermia	~360, US	DBPRPCT, terminated after interim analysis.
Harders, 1996	nimodipine Phase II	123, Germany	DBPRPCT, 55% relative reduction in bad outcome at 6 mos.
Bolland, 1998	Synthelabo eliprodil, Phase II	453, France	DBPRPCT, better outcome in "brain swelling" patients (p 0.01)
Marshall, 1998	tirilizad	1128, EU & Australia	DBPRPCT, no benefit (reports awaited)
Marmarou, 1999	Bradycor	133, US	DBPRPCT, no benefit but 10% trend toward better outcome
Morris, et al., 1999	Selfotel (CGS-19755) Phase III	266, US & Israel, 426, EU & Australia	DBPRPCT, both terminated due to excess mortality in concomitant stroke trials; no benefit.
Stewart, 1999	CGS 19755	113, US & UK	DBPRPCT, ICP lower. **GLUTAMATE ANTAGONIST**

Outcome Trials

Authors & Year	Agent	Patients/Country	Outcome/Comments
Ward. 1950	atropine	940, US	uncontrolled, no benefit
Schwartz, 1985	mannitol	ra	annitol group had better outcome
Ward, 1984	barbitu	DBPR	prophylaxis)
Eisenberg, 1988	barbiturates	DB	efit (prophylaxis)
Teasdale, 1992	nimodipine (HIT I)		benefit
Muizelaar,1993	PEG-SOD		, ICP lower, outcome better (p <0.01)
Wolf, 1993	tromethamine	14	T, no benefit
Muizelaar, 1994	PEG-SOD (Phase III),	463, U	utcome 9% better in drug vs. placebo (p = 0.15)
Clifton, 1995	moderate hypothermia	~360, I	ated after interim analysis.
Harders, 1996	nimodipine Phase II	1	reduction in bad outcome at 6 mos.
Bolland, 1998	Synthelabo eliprodil, Phase II		n "brain swelling" patients (p 0.01)
Marshall, 1998	tirilizad	& Australia	ited)
Marmarou, 1999	Bra		ard better outcome
Morris, et al., 1999	Selt	ael, 426, & Australia	ess mortality in concomitant
Stewart, 1999	CGS 19755	113, US & UK	DBPRPCT, ICP lower. **GLUTAMATE ANTAGONIST**

Use of Methylphenidate in Traumatic Brain Injury, Ann Pharmacother July/August **2005** vol. 39 no. 7/8 1309-1313 O'Rita M Siddall PharmD Drug Information Specialist, College of Pharmacy, Xavier University, New Orleans, LA; Drug Information Center at Tulane University Hospital and Clinic,

- Ten clinical trials evaluating the efficacy and safety of methylphenidate in patients with TBI were reviewed (1966-2004). The end-point was an improvement in cognition with results stating "..likely to improve memory, attention, concentration, and mental processing."

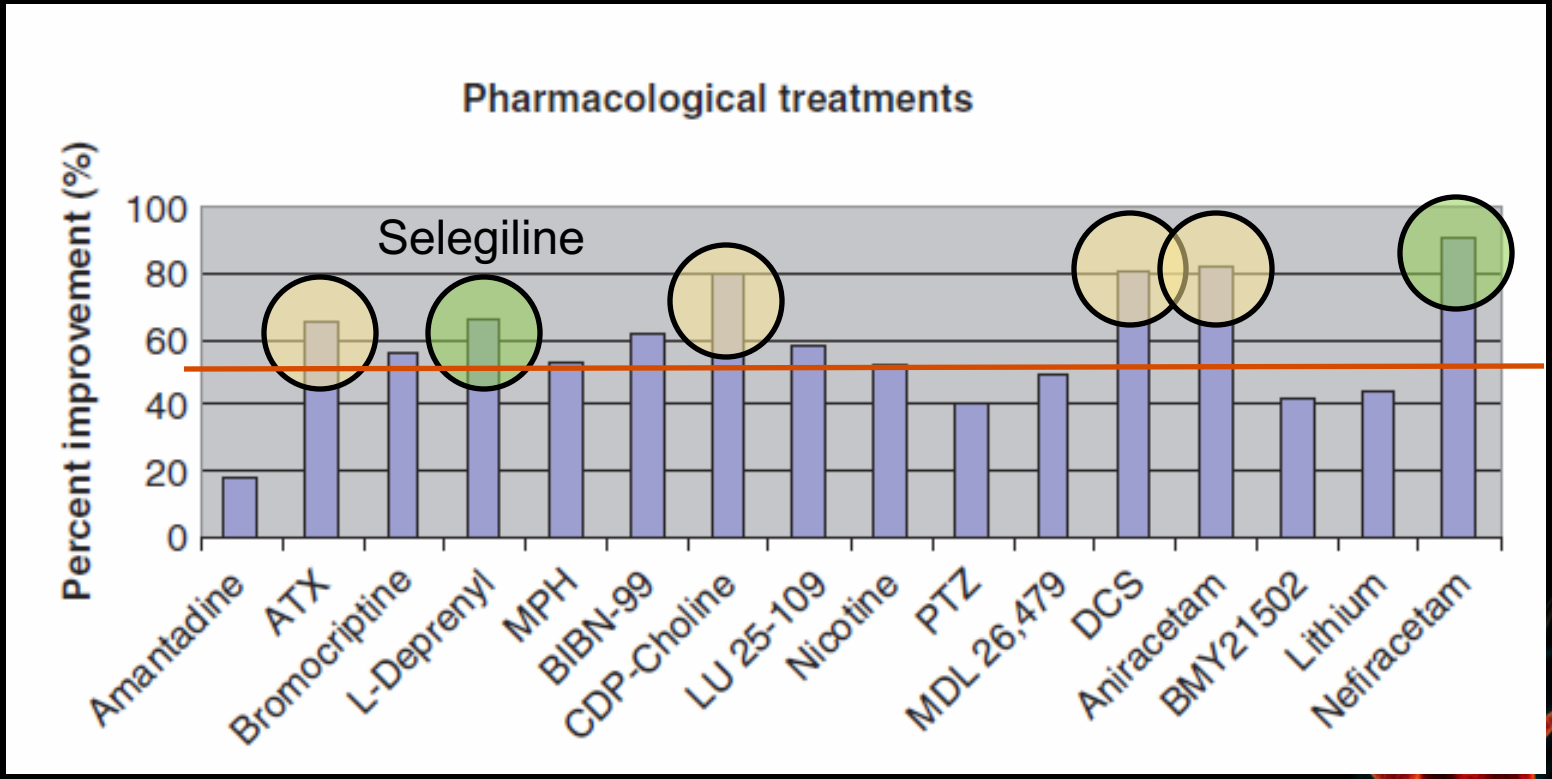
- Comment: What the F- does it mean "likely to improve…", it did not clearly state any benefits to its use.

Active cooling in Traumatic Brain Injured patients: a questionable therapy? Acta Anaesthesiol Scand. 2009 Nov;53(10):1233-8. Epub 2009 Aug 13. Grände PO Reinstrup P Romner B Department of Anaesthesia and Intensive Care, Lund University Hospital, Lund, Sweden.

- A review of our present knowledge of the use of active cooling in TBI patients, and some tentative explanations as to why active cooling has not been shown to be effective for outcome after TBI is discussed.
- A **Cochrane report** concluded that the majority of the trials published have been of low quality, with unclear allocation concealment.
- If only the high-quality trials are considered, TBI patients treated with active cooling were more likely to **die**, a conclusion supported by a recent high-quality Canadian Trial on children.

A review of Pharmacological Treatments used in experimental models of Traumatic Brain Injury

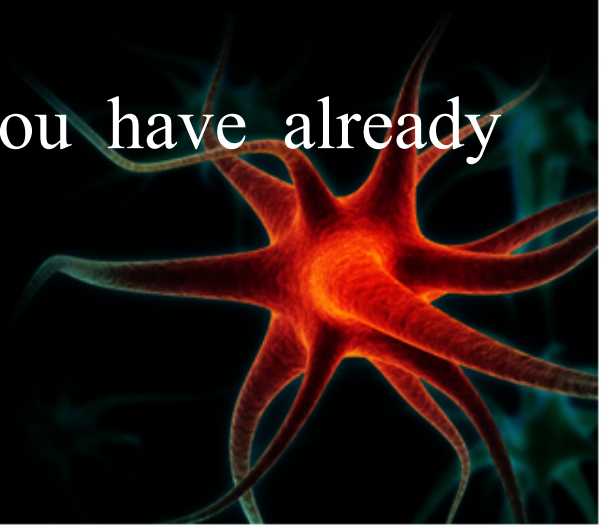
Brain Injury, March 2007; 21(3): 259–274 OLGA N. KOKIKO & ROBERT J. HAMM. Department of Psychology, Virginia Commonwealth University, Richmond, Virginia, USA.



ATX = the non-stimulant atomoxetine.
Nefiracetam is cytoprotective mediated by GABAergic, cholinergic, and monoaminergic neuronal systems.
CDP-Choline - increase dopamine receptor densities and memory. (PC)
DCS - partial **NMDA** agonist facilitate the extinction of fear and the treatment of anxiety disorders..

Causation and Failure

- Monotherapy just does not work!!
- The global impact of Traumatic Brain Injury affects a multitude of brain and bodily systems that need attention CONCURRENTLY.
- Adding one product does not make sense when we are looking for a safe system of treatment that relies upon synergism.
- Try putting your shoes on after you have already tied the laces. Ain't gona happen.

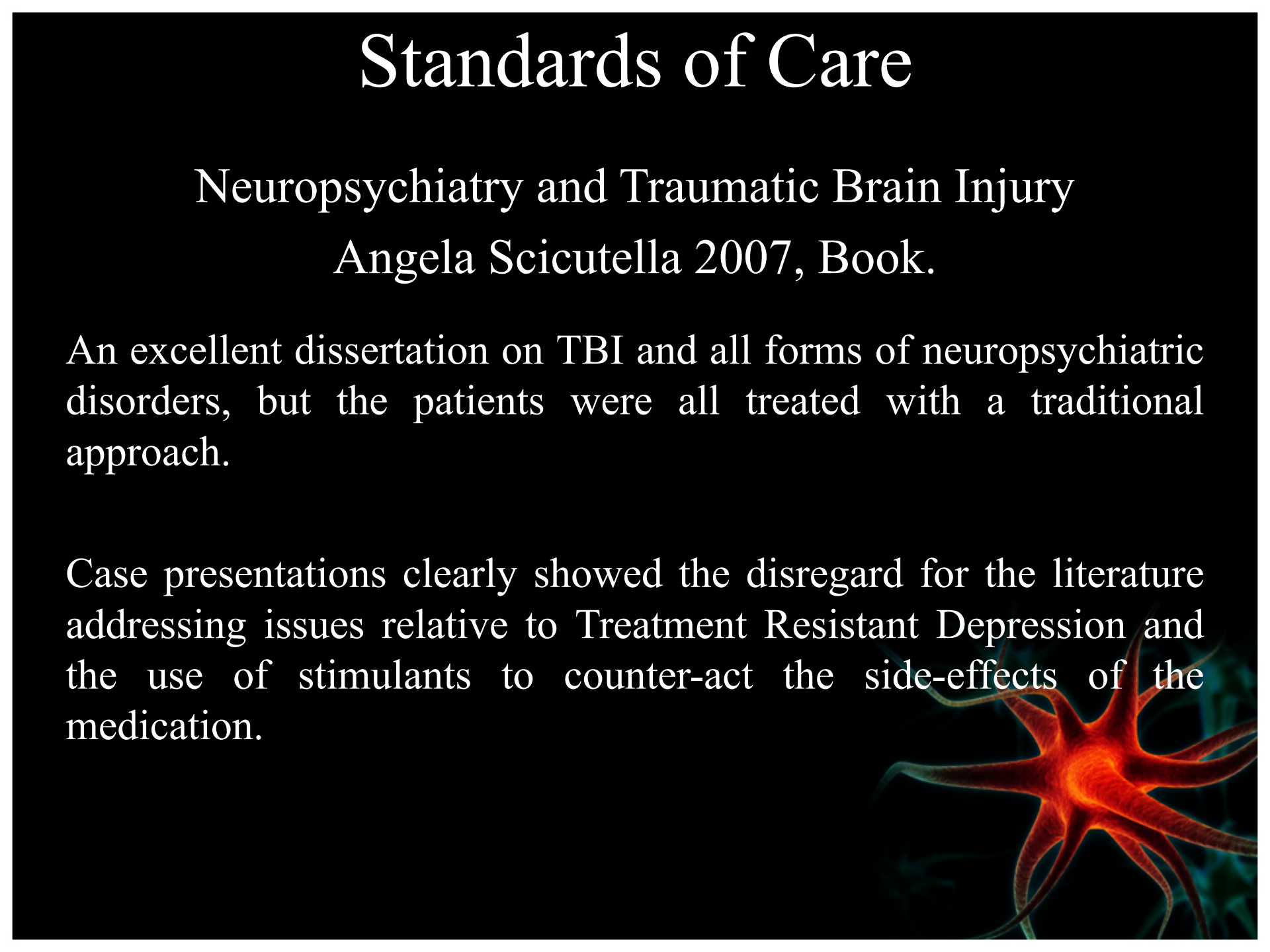


Standards of Care

Neuropsychiatry and Traumatic Brain Injury
Angela Scicutella 2007, Book.

An excellent dissertation on TBI and all forms of neuropsychiatric disorders, but the patients were all treated with a traditional approach.

Case presentations clearly showed the disregard for the literature addressing issues relative to Treatment Resistant Depression and the use of stimulants to counter-act the side-effects of the medication.



The words we use.

- **Replacement:** The act of restoring to a former place or position.
- **Restorative:** The act of bringing back to a state of health, soundness, or vigor
- **Supplementation:** The act of added something to make up for a deficiency, or extend or strengthen the whole.
- **Replenishment**: The act of filling or making complete again.



An alternative way of interpreting laboratory results for optimal response.

Basics:

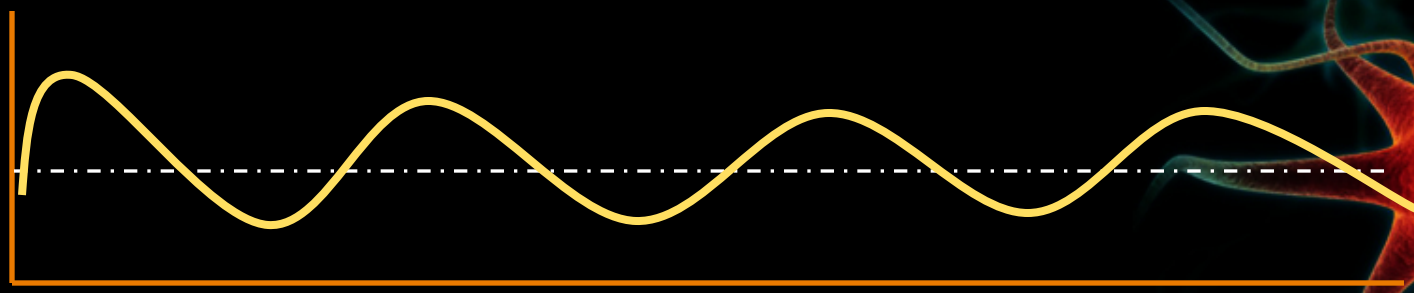
- Standard hormone ranges are based upon pooled data from a range of patients (males, females, age, and with limited health data).
- Usually, a one or two standard deviation from the means is obtained to give the range.
- Sometimes the ranges are narrow, like with Progesterone in a male or very broad like with Total Testosterone: 300 to 1080ng/ml.



An alternative way of interpreting laboratory results.

Advanced:

- Hormones are in constant flux being regulated by the homeostatic mechanism of the Hypothalamic-Pituitary – End-Target Gland - Axis.
- As an example: the HPA axis, cortisol regulates the hypothalamic production of CrH which regulates the anterior pituitary production of ACTH.



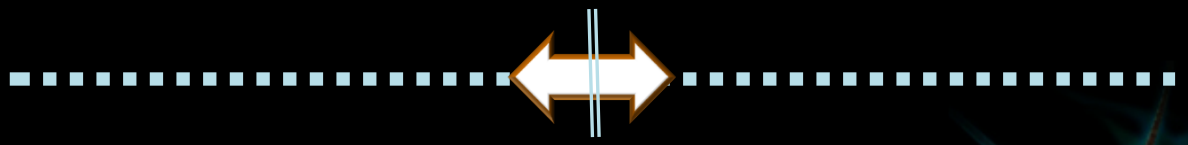


An alternative way of interpreting laboratory results.

Advanced:

- Therefore, in an ideal hormonal environment, the levels of any one hormone should be centered around the median level of its acceptable range.

" The Optimal Physiological Level"



The ideal net effect is that the levels are close to the median of the range.

An alternative way of interpreting laboratory results.

Advanced:

► **Total Testosterone** by Access:

Range is 300ng/ml – 1080ng/ml with a median of :

(300 + 1080)/ 2 = 69**0ng/ml**



Compensatory Responses

Compensatory Thyroid: Case 1 (58y/o):		
Marker	Result	Median
TSH	5.35 HN	<2.5 mcu/ml
Free T4	1.24 LN	>1.5 ng/ml
Free T3	2.92 N	>2.5 pg/dl
Reverse T3	210 HN	<165 ng/dl
T3/rT3 ratio	1.39 N	Above 1.06

TSH is above the median pushing the Thyroid gland to make more T4.

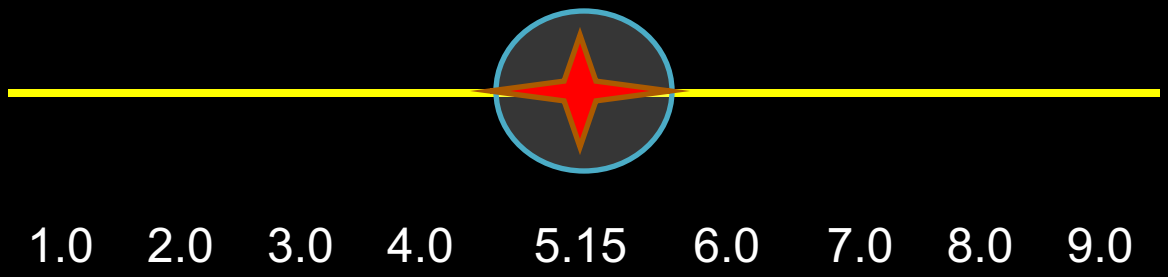
TSHi = 5.51 H

Compensatory Androgen: Case 2 (43y/o)		
Marker	Result	Median
DHEA-s	210 N	>200 ug/dL
Total Testosterone	319 LN	690 pg/ml
Free Testosterone	3.37 L	14 ng/ml
DHT	36 N	<52ng/dL
SHBG	41 N	<45 pg/ml
Estrone	7 N	<60 pg/ml
Estradiol	48 H	25 pg/ml
FSH	4.2 LN	7.0 mIU/ml
LH	8.9 HN	5.15 mIU/ml
Zinc	23 LN	95 mcg/dL

Free-T is Low with Total-T low-normal and a high-normal LH.

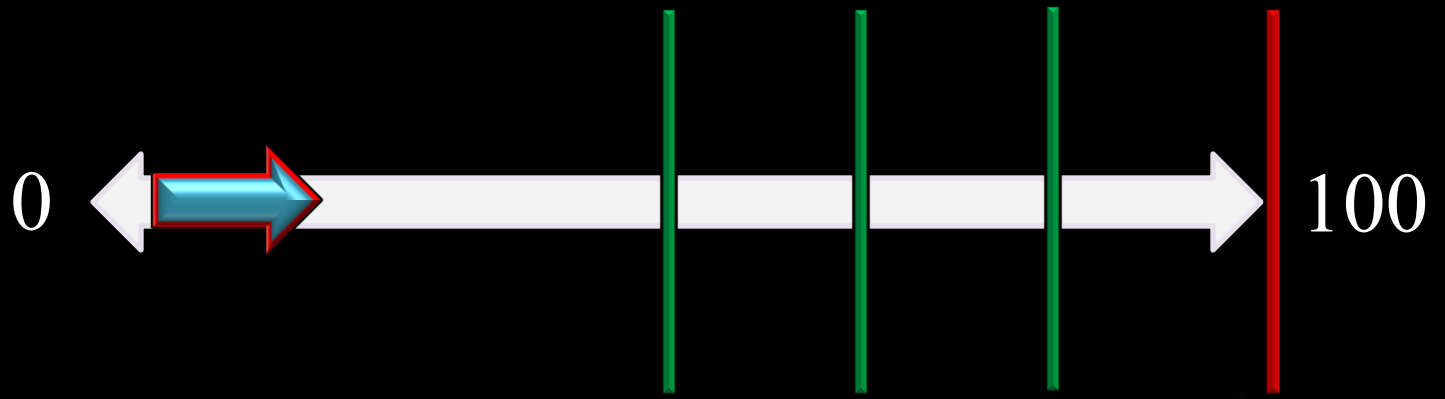
Testosterone Regulation:

Luteinizing Hormone	**1.7 – 8.6 mIU/ml**	**5.15 mIU/ml**



The Goal we seek.

50% and above

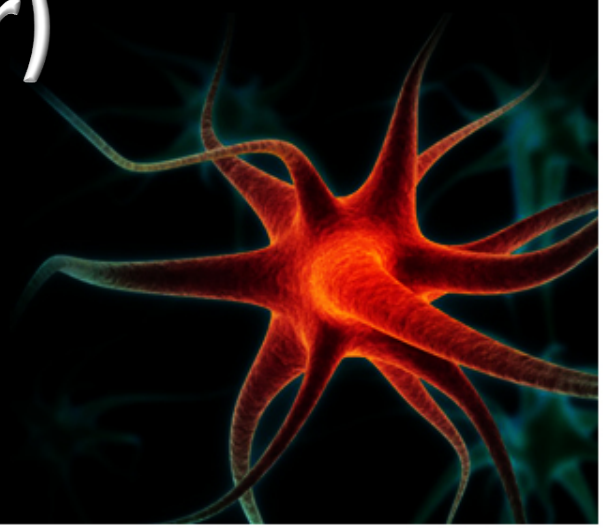


Optimal Physiological Levels

Treating Traumatic Brain Injury

Treatment will always be based upon your interpretation

(AI Interpreter)



Bullet Case 1

Male, 28 years old	**Investment Banking**
Motor Vehicle Accident (MVA) at age 25 years (**3 years ago**).	
He was the driver of the car, stopped, when T-Boned on driver's side. Patient was wearing seatbelt.	
At impact, head whipped into side window cracking the glass. Denies loss of consciousness (LOC). Was slightly disoriented, developed immediate headache without nausea or vomiting.	
Seen by ER doctor; Labs normal, CT-Scan normal. Released with follow-up with neurologist.	
Seen by Neurologist 7 days post, who examined and discharged the patient with instructions to call if any symptoms develop.	
Three years later presents with complaints of experiencing; subtle decrease in memory, cognitive performance, mood issues, anger, insomnia with daytime sleepiness, and drop in libido.	
Played football in high school and college.	
NSAID, Sleep Aide, multi-vitamin,	
Panel 1 labs were drawn.	Assume draws at 9-10am

1: Growth Hormone

- Central

2: Androgens

- Central

3: Pregnenolone Steal

4: Hypovitaminosis D

5: Low T3 Syndrome

- Stress Related?

6: Cortisol elevation.

- ▲ rT3

TSHi = 2.45

Bullet Case 1: Male (28) MVA		
Marker	Result	Median
Growth Hormone	0.39 LN	5.0 ng/ml
IGF-1*	137 LN	>200 ng/ml
IGFBP-3*	2135 LN	4000 ng/ml
DHEA-s	215 LN	245 ug/dL
Total Testosterone*	293 L	690 pg/ml
Free Testosterone*	3.97 L	14 ng/ml*
DHT	17 N	52ng/dL
SHBG	31 N	45 pg/ml
Estrone	5 N	60 pg/ml
Estradiol*	31 HN	25 pg/ml
Pregnenolone*	23 LN	110 ng/dl
Progesterone	1.03 HN	0.8 ng/ml
FSH	2.39 LN	7.0 mIU/ml
LH	1.27 LN	5.1 mIU/ml
Zinc*	74 LN	95 mcg/dL
Prolactin	7.5 N	11.25 ng/ml
Insulin	9.4 N	12.5 miu/L
Vitamin D3*	27 L	60 ng/dL
TSH	2.30 N	2.5 mcu/ml
Free T4	1.24 LN	1.5 ng/ml
Free T3	2.30 LN	2.5 pg/dl
Reverse T3	172 HN	165 ng/dl
T3/rT3 ratio	1.337 N	Above 1.06
ACTH	27.4 N	35 pg/ml
Cortisol	21.3 H	15ug/dl_a /7.3ug/dl_p



Treatment: Bullet 1 – Age 28 Male

Product	Dosing	Labs
Secretagogue (rhGH)	3 sprays a night	12 weeks.
Clomid (50mg)	1 tab: Mon-Fri	12 weeks on Monday before Clomid
DHEA (25mg)	1 cap hs	
Pregnenolone (30mg)	2 caps hs	
Vitamin D3 (10Kiu)	1 cap	3-6 months
Armour Thyroid (30mg)	1 tab	4-6 months
Triiodothyronine (+/-)	5mcg to 10mcg	12 weeks.
Adrenal Support	2 caps	3-6 months
B-complex w/ PQQ	2 caps BID	
Ultranutrient	2 caps BID	
Zinc Citrate	1 cap BID (15mg)	
N-Acetyl Cysteine	**2 caps BID (NA92)**	
Mixed Tocopherols	**2 caps BID (USE1)**	

This is just a starting point for about 3 months or less based upon response.

Bullet Case 2

Male, 37 years old	**Hospital IT/Corpsmen**
Deployed as corpsmen in Iraq. Blast trauma from Tanks, Artillery and, guns. Advanced behind Abramson tank – Body shuddered with each firing.	
Never had any physical contact trauma.	
Developed depression, fatigue, loss of libido and lack of concentration. Has had suicide ideation when he reflects on personal mental status.	
Seen at VA and placed on medication – Bupropion 150mg.	
Three years later presents with complaints of experiencing; subtle decreases in memory, cognitive performance, mood issues, anger, insomnia with daytime sleepiness, and drop in libido.	
Panel 1 labs were drawn.	Assume draws at 9-10am

1: Hypogonadism

- Central

3: Hypovitaminosis D

Anything Else?

If he is not using rhGH then why are the GH parameters elevated?

Hypothalamic Dysregulation

Bullet Case 2: Male (37) MVA		
Marker	Result	Median
Growth Hormone	5.19 HN	5.0 ng/ml
IGF-1	344 N	200 ng/ml
IGFBP-3	6735 N	4000 ng/ml
DHEA-s	247 HN	200 ug/dL
Total Testosterone	341 LN	690 pg/ml
Free Testosterone	5.67 LN	14 ng/ml
DHT	23 N	52ng/dL
SHBG	39 N	45 pg/ml
Estrone	14 N	60 pg/ml
Estradiol	17 N	25 pg/ml
Pregnenolone	47 LN	110 ng/dl
Progesterone	0.73 N	0.8 ng/ml
FSH	4.05 LN	7.0 mIU/ml
LH	3.86 LN	5.1 mIU/ml
Zinc	78 LN	95 mcg/dL
Prolactin	6.7 N	11.25 ng/ml
Insulin	10.4 N	12.5 miu/L
Vitamin D3	24 LN	60 ng/dL
TSH	1.94 N	2.5 mcu/ml
Free T4	1.41 LN	1.5 ng/ml
Free T3	3.1 N	2.5 pg/dl
Reverse T3	132 N	165 ng/dl
T3/rT3 ratio	2.34 N	Above 1.06
ACTH	17.4 N	35 pg/ml
Cortisol	11.6 LN	15ug/dl_a /7.3ug/dl_p



Treatment: Bullet 2: Male 37

Product	Dosing	Labs
Clomid	50mg Mon-Friday	12 weeks on Monday before Clomid
DHEA	25mg QHS	
Pregnenolone	60mg QHS	3-6 months
Vitamin D3	10,000iu	3-6 months
Adrenal Support	2 caps	3-6 months
B-complex w/ PQQ	2 caps BID	
Ultranutrient	2 caps BID	
N-Acetyl Cysteine	**2 caps BID**	
Mixed Tocopherols	2 caps BID	

MRI of the Pituitary did not disclose an adenoma. Survey of the Hypothalamus showed areas of punctate calcifications;

Bullet Case 3

Female, 47 years old	**Business Owner**
Slipped on liquid falling backwards striking the back of her head on cement ground at age 43. Canadian.	
Upon striking the ground she lost consciousness for about 30 minutes. Awoke in the hospital ER.	
Initial CT scan was negative for SDH but contusion of the occipital lobe right. Subsequent, MRI showed areas of micro-calcifications.	
Holds on to wall or chair-back when standing. Hold husbands arm while walking. Personality, a little giddy, cosmic, ethereal, abstract at times. Depression and anxiety. Visual fields fuzzy.	
Historically, multiple “minor” ice skating accident as child including fracture of wrist and head bumps.	
Presently on Bupropion 150mg BID for 18-24 months. She was initially on 75mg QD then BID which did not help her depression.	
Panel 1 labs were drawn.	Assume draws at 9-10am

1: Androgens

- Central?

2: Estrogen Dominance

3: Hyperinsulinemia

4: Hypovitaminosis D

5: Central Hypothyroid

- TSHi = 0.98

6: Cortisol

- Normal or ??

Bullet Case 3: Female (47) MVA		
Marker	Result	Median
Growth Hormone	0.12 LN	5.0 ng/ml
IGF-1	221 N	200 ng/ml
IGFBP-3	4350 N	4000 ng/ml
DHEA-s	123 LN	190 ug/dL
Total Testosterone	23 LN	44 pg/ml*
Free Testosterone	.43 LN	3-4 ng/ml
DHT	22 N	<30ng/dL
SHBG	119 N	75 pg/ml
Estrone	98 N	pg/ml
Estradiol	34 N	pg/ml
Pregnenolone	63 LN	110 ng/dl
Progesterone	.065 LN	5-7 ng/ml
FSH	1.10 LN	7.0 mIU/ml
LH	<0.10 LN	5.1 mIU/ml
Zinc	88 N	95 mcg/dL
Prolactin	5.9 N	11.25 ng/ml
Insulin	23.4 N*	12.5 miu/L
Vitamin D3	29 L	60 ng/dL
TSH	0.738 N	2.5 mcu/ml
Free T4	1.15 LN	1.5 ng/ml
Free T3	2.77 N	2.5 pg/dl
Reverse T3	92 N	165 ng/dl
T3/rT3 ratio	3.01 N	Above 1.06
ACTH	4.97 ?	35 pg/ml
Cortisol	6.30 ?	15ug/dl_a /7.3ug/dl_p

EP Ratio: 2030 H



Treatment: Bullet 3

Product	Dosing	Labs
EC w/ P100mg/T2mg	½ gram QHS	3 months
DHEA (25mg)	1 cap QHS	3 months
Pregnenolone (30mg)	2 caps QSH	
Vitamin D3 (10Kiu)	1 cap QDay	3-6 months
B-Complex w/ PQQ	2 caps BID	
Melatonin	1 mg QHS	
Ultranutrient	2 caps BID	
N-Acetyl Cysteine	2 caps BID	
Tocopherols (A,D,G)	2 caps BID	

Bio-Identical HRT Formulas

The MHC helped develop the combination creams below since 2005. The efficacy of vaginally applied creams is superior to the topical without the side-effects from testosterone.

Millennium-UCP					
TYPE	Estradiol	Estriol	Prog	Test	Apply
Standard	0.2mg	2.0mg	100mg	1-2mg	Vaginal†
Breast	0.1mg	2.0mg	100mg	1 mg	Vaginal
Fatigue	0.2mg	2.0mg	50mg	1 mg	Vaginal
Libido	0.2mg	2.0mg	100mg	2 mg	Vaginal
Standard	0.2mg	2.0mg	100mg	NO	Topical
Breast	0.1mg	2.0mg	100mg	NO	Topical

†Vaginal ¼ to ½ gram every night.

Bullet Case 4

Female, 33 years old	
Motor Vehicle Accident (MVA) at age 31 years.	
She was a passenger in an older model sedan that was rear ended at a stop by a drunk driver traveling (est.) 50 miles an hour. Upon impact, she was thrown forwards with her head hitting the dashboard. Loss of consciousness (LOC) was momentary. Disoriented and neck pain. Hematoma at point of impact on right forehead.	
Seen in ER; Labs normal, CT-Scan normal. Released home with recommendation to see neurologist who she saw 5 days after accident.	
18 months after accident she developed phobia of being in a car and enclosed spaces. Repeat MRI was only positive for small calcifications in the left frontal lobe.	
About the same time she developed irregular menses and Mood Disorder and was seen by Neuropsychiatrist and diagnosed with PTSD.	
Lamictal 10mg, Xanax 0.25mg bid-tid. (6 months on each)	
LNMP: 34 days after last menses blood was drawn.	
Panel 1 labs were drawn.	Assume draws at 9-10am

1: Hypogonadism

2: Hypovitaminosis D

3: Hypocortisolemia

Consider

Hypothalamic Amenorrhea

Bullet Case 4: Female (33) MVA		
Marker	Result	Median
Growth Hormone	**0.17 LN**	**5.0 ng/ml**
IGF-1	**242 N**	**200 ng/ml**
IGFBP-3	**4735 N**	**4000 ng/ml**
DHEA-s	**199 N**	**200 ug/dL**
Total Testosterone	**13 LN**	**44 pg/ml**
Free Testosterone	**.19 LN**	**3-4 ng/ml**
DHT	**11 N**	**<30ng/dL**
SHBG	**27 N**	**75 pg/ml**
Estrone	**5 N**	**<200 pg/ml**
Estradiol	**11 LN**	**pg/ml***
Pregnenolone	**23 LN**	**110 ng/dl**
Progesterone	**1.03 LN**	**5-7 ng/ml**
FSH	**1.99 LN**	**7.0 mIU/ml**
LH	**1.24 LN**	**5.1 mIU/ml**
Zinc	**74 LN**	**95 mcg/dL**
Prolactin	**7.5 N**	**11.25 ng/ml**
Insulin	**9.4 N**	**12.5 miu/L**
Vitamin D3	**27 L**	**60 ng/dL**
TSH	**2.2 N**	**2.5 mcu/ml**
Free T4	**1.47 N**	**1.5 ng/ml**
Free T3	**2.95 N**	**2.5 pg/dl**
Reverse T3	**144 N**	**165 ng/dl**
T3/rT3 ratio	**2.04 N**	**Above 1.06**
ACTH	**7.4 LN**	**35 pg/ml**
Cortisol	**4.1 LN**	**15ug/dl_a /7.3ug/dl_p**



Treatment: Bullet 4

Product	Dosing	Labs
Estradiol (0.2mg) Estriol (2.0-4.0mg)	Vag: Days 1-25(30)	12 weeks
Progesterone 200mg	1 cap HS	12 weeks
DHEA (25mg)`	1 cap QHS	12 weeks
Pregnenolone (30mg)	2 caps QHS	3-6 months
Vitamin D3 (10Kiu)	1 cap	3-6 months
Adrenal Support	1 cap BID	3-6 months
B-Complex w/ PQQ	2 caps BID	
N-Acetyl Cysteine	**2 caps BID**	
Tocopherols (A,D,G)	**2 caps BID**	

Bullet Case 5

Female, 55 years old	**Physician's Assistant**
Fell down the stairs (tripped over cat) 10 months prior to her office visit.	
Slid down the carpet covered wooden steps landing on left temple, marble tiled floor.	
Loss of consciousness (LOC) for indeterminate amount of time but less than 60 minutes (maybe). She was disoriented, headache with nausea. Bleeding from scalp.	
Went to her hospital's ER (KP) and had 6 stiches to her scalp after a negative CT Scan. Seen in ER by Neurologist, who examined and discharged her after 11 hours.	
Present complaints: Cognitive issues, insomnia, irritability and sluggish.	
LNMP at age 52 years.	
Tylenol. Omega's, Curcumin, and PS100.	
Panel 1 labs were drawn.	Assume draws at 9-10am

?-Partial GHD

Primary Ovarian Failure

HN-Prolactin

Hypocortisolemia

Bullet Case 5: Female (55): BHT		
Marker	Result	Median
Growth Hormone	0.39 LN	5.0 ng/ml
IGF-1	167 LN	200 ng/ml
IGFBP-3	4350 N	4000 ng/ml
DHEA-s	205 HN	200 ug/dL
Total Testosterone	32 N	44 pg/ml
Free Testosterone	.75 LN	2-4 ng/ml
DHT	11 N	0ng/dL
SHBG	44 N	g/ml
Estrone	15 N	<200 g/ml
Estradiol	31 N	g/ml
Pregnenolone	68 LN	ng/dl
Progesterone	.36 HN	ng/ml
FSH	15.90 LN	.0 mIU/ml
LH	43.38 LN	5.1 mIU/ml
Zinc	101 HN	95 mcg/dL
Prolactin	13.5 HN	11.25 ng/ml
Insulin	4.7 N	12.5 miu/L
Vitamin D3	42 LN	60 ng/dL
TSH	1.73 N	2.5 mcu/ml
Free T4	1.21 LN	1.5 ng/ml
Free T3	2.56 N	2.5 pg/dl
Reverse T3	97 N	165 ng/dl
T3/rT3 ratio	2.63 N	Above 1.06
ACTH	8.74 N	35 pg/ml
Cortisol	3.53 LN	15ug/dl_a /7.3ug/dl_p



Treatment: Bullet 5

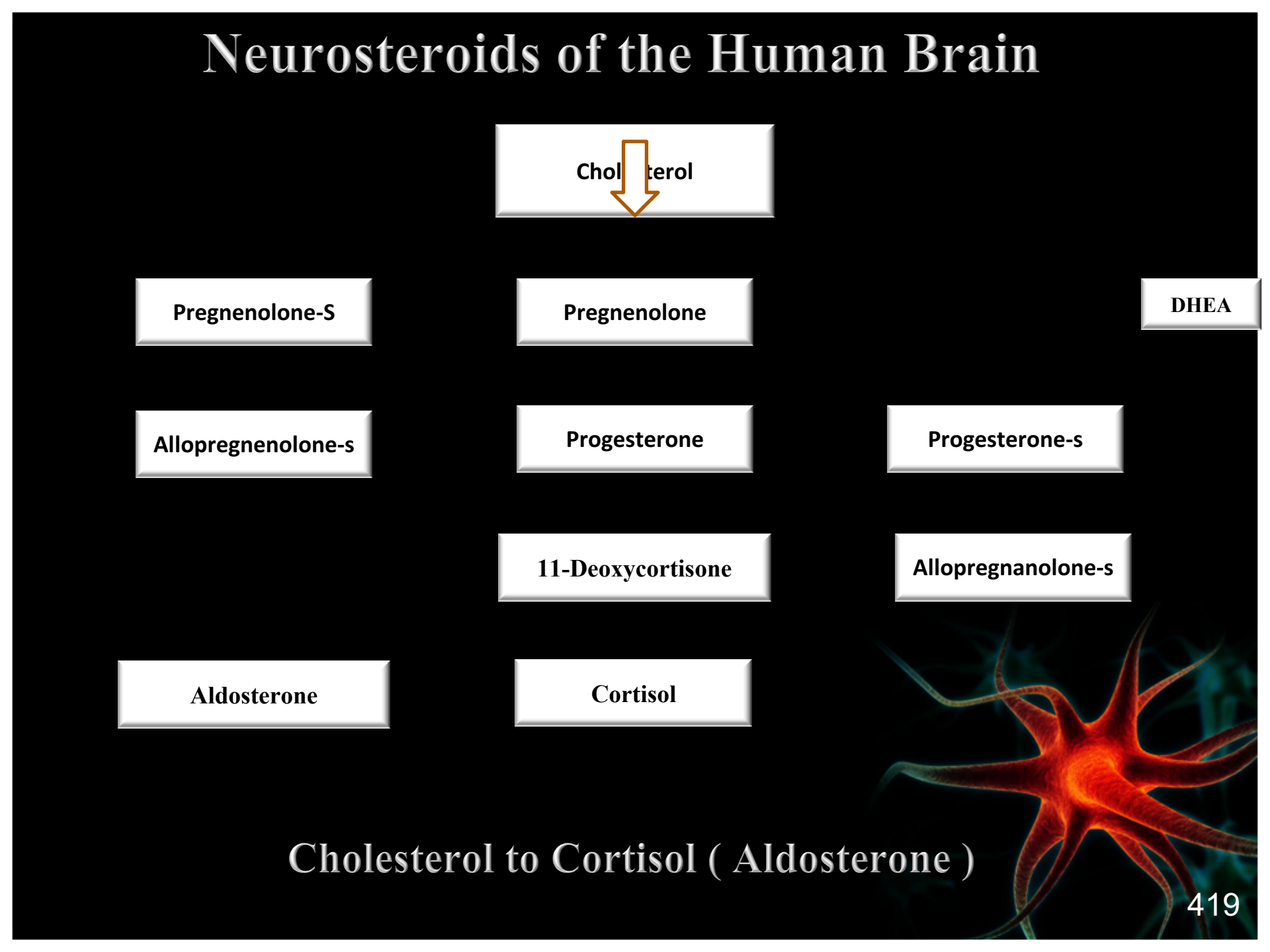
Product	Dosing	Labs
Secretagogue (rhGH)	3 sprays a night	8 -12 weeks.
ECP 2% Vaginal	½ Gram QHS	8 -12 weeks.
DHEA (25mg)	25mg hs	8 -12 weeks.
Pregnenolone (30mg)	2 caps.	
Vitamin D3 (5Kiu)	1 cap	4-6 months
Adrenal Support	2 caps	4-6 months
B-complex w/PQQ	2 caps BID	
Ultranutrient	2 caps BID	
N-Acetyl Cysteine	**2 caps BID**	
Tocopherols (A,D,G)	**2 caps BID**	

Simplified Treatment

Treatment is based upon Deficiencies as much as Insufficiencies!



Neurosteroids of the Human Brain



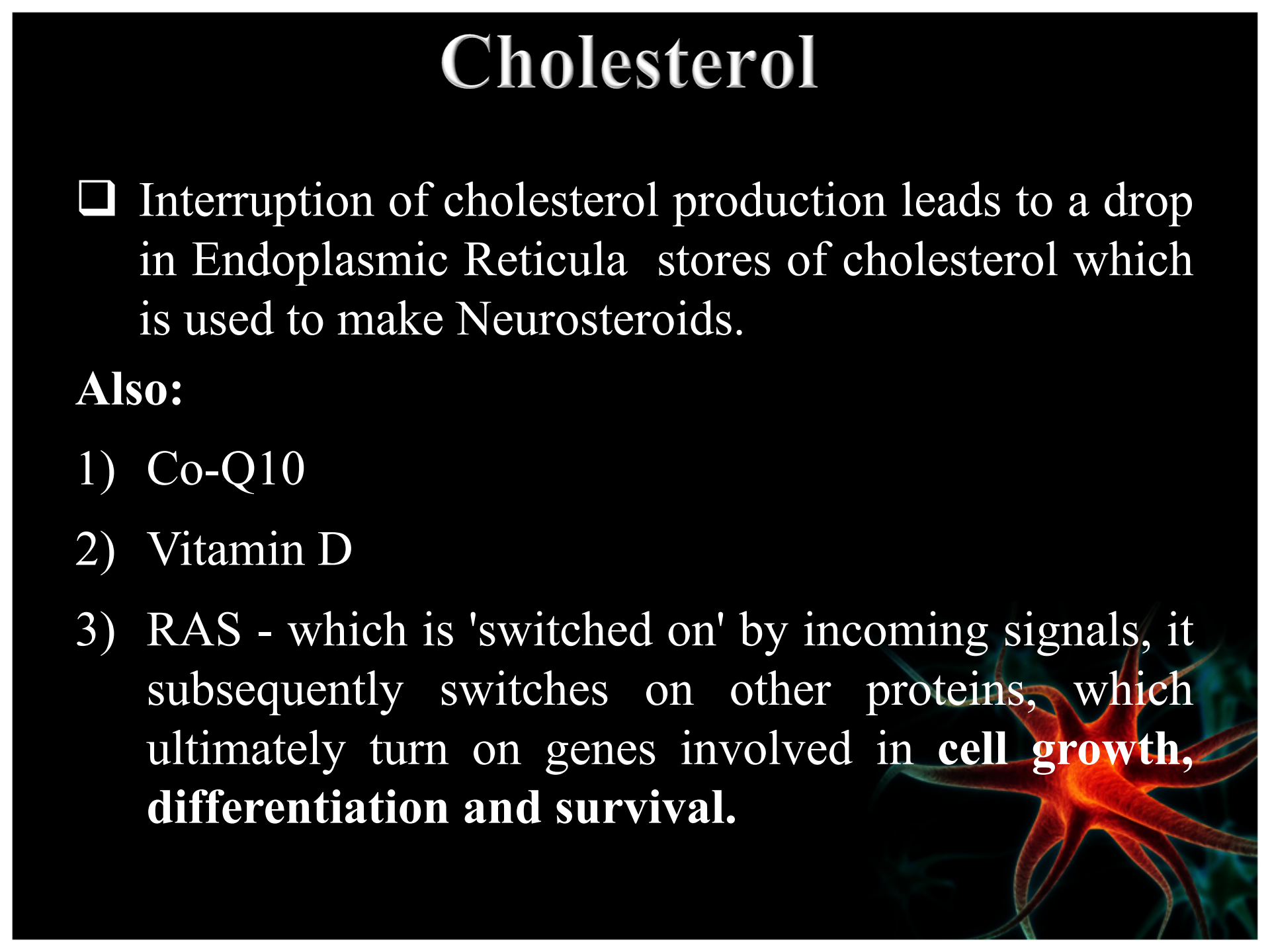
Cholesterol to Cortisol (Aldosterone)

Cholesterol

- Interruption of cholesterol production leads to a drop in Endoplasmic Reticula stores of cholesterol which is used to make Neurosteroids.

Also:

1) Co-Q10
2) Vitamin D
3) RAS - which is 'switched on' by incoming signals, it subsequently switches on other proteins, which ultimately turn on genes involved in **cell growth, differentiation and survival.**

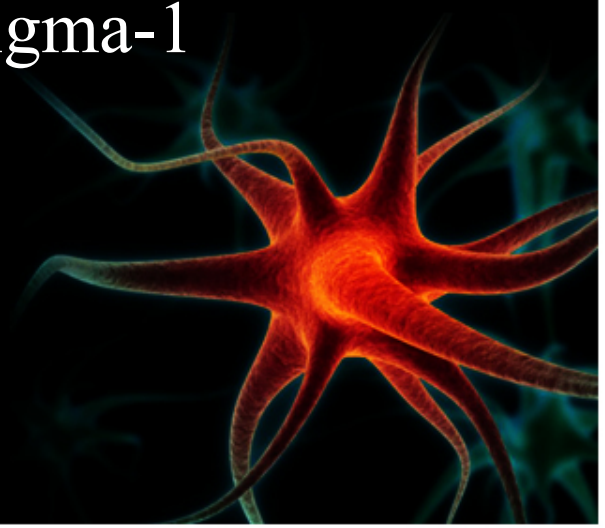


Pregnenolone

Pregnenolone levels can drop by:

1. Statins
2. Pregnenolone Steal Syndrome
3. Rapid conversion to Cortisol (under stressors)

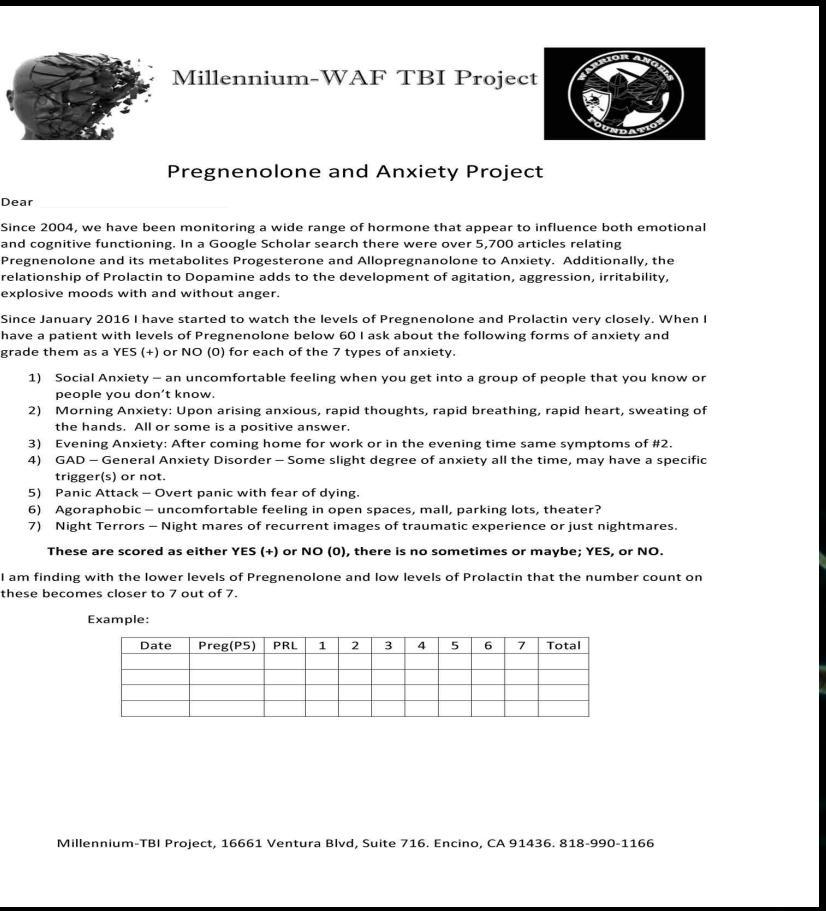
Benefits: Direct modulation of neurotransmission with stabilization of NMDA, $GABA_A$ and Sigma-1 Receptors.



Pregnenolone

Dosing:

1. Pregnenolone 30-60mg at bed time to start based upon lab results and symptomatology.



Millennium-WAF TBI Project

Pregnenolone and Anxiety Project

Dear

Since 2004, we have been monitoring a wide range of hormone that appear to influence both emotional and cognitive functioning. In a Google Scholar search there were over 5,700 articles relating Pregnenolone and its metabolites Progesterone and Allopregnanolone to Anxiety. Additionally, the relationship of Prolactin to Dopamine adds to the development of agitation, aggression, irritability, explosive moods with and without anger.

Since January 2016 I have started to watch the levels of Pregnenolone and Prolactin very closely. When I have a patient with levels of Pregnenolone below 60 I ask about the following forms of anxiety and grade them as a YES (+) or NO (0) for each of the 7 types of anxiety.

1) Social Anxiety – an uncomfortable feeling when you get into a group of people that you know or people you don't know.
2) Morning Anxiety: Upon arising anxious, rapid thoughts, rapid breathing, rapid heart, sweating of the hands. All or some is a positive answer.
3) Evening Anxiety: After coming home for work or in the evening time same symptoms of #2.
4) GAD – General Anxiety Disorder – Some slight degree of anxiety all the time, may have a specific trigger(s) or not.
5) Panic Attack – Overt panic with fear of dying.
6) Agoraphobic – uncomfortable feeling in open spaces, mall, parking lots, theater?
7) Night Terrors – Night mares of recurrent images of traumatic experience or just nightmares.

These are scored as either YES (+) or NO (0), there is no sometimes or maybe; YES, or NO.

I am finding with the lower levels of Pregnenolone and low levels of Prolactin that the number count on these becomes closer to 7 out of 7.

Example:

Date	Preg(P5)	PRL	1	2	3	4	5	6	7	Total

Millennium-TBI Project, 16661 Ventura Blvd, Suite 716. Encino, CA 91436. 818-990-1166

Progesterone

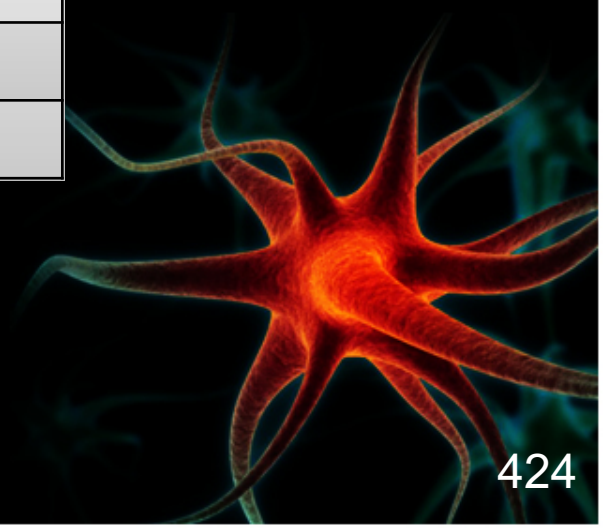
- Progesterone in a female patient, as well as in some males, can significantly influence sleep and clarity of mind.
- Additionally, its impressive benefits for promoting a Neuropermissive Environment (NPE); anti-oxidant, neuroprotective and neuroregenerative, mandates its use either as Progesterone and/or Pregnenolone.
- Female we give 100mg to 200mg a night to get serum levels up to the Median Level.
- Males we give 5mg at bedtime and monitor to achieve Median Levels or a response.



Cortisol

- DHEA and Pregnenolone are **substrates** for Progesterone, 11-deoxycortisol, Cortisol, Cortisone and Aldosterone.

DHEA-s	
Under 200	25mg BID
Over 250 < 350	25mg QHS
Pregnenolone	
Under 100	30mg QHS
Over 100	60mg QHS



❑ Adrenal Fatigue

Adrenal Support

1: DHEA 25mg

2: Pregnenolone 60mg

3: Desiccated Adrenals (AD1)

To date we have never used any of the traditional pharmaceuticals such as Medrol, Solu-medrol or Cortef.

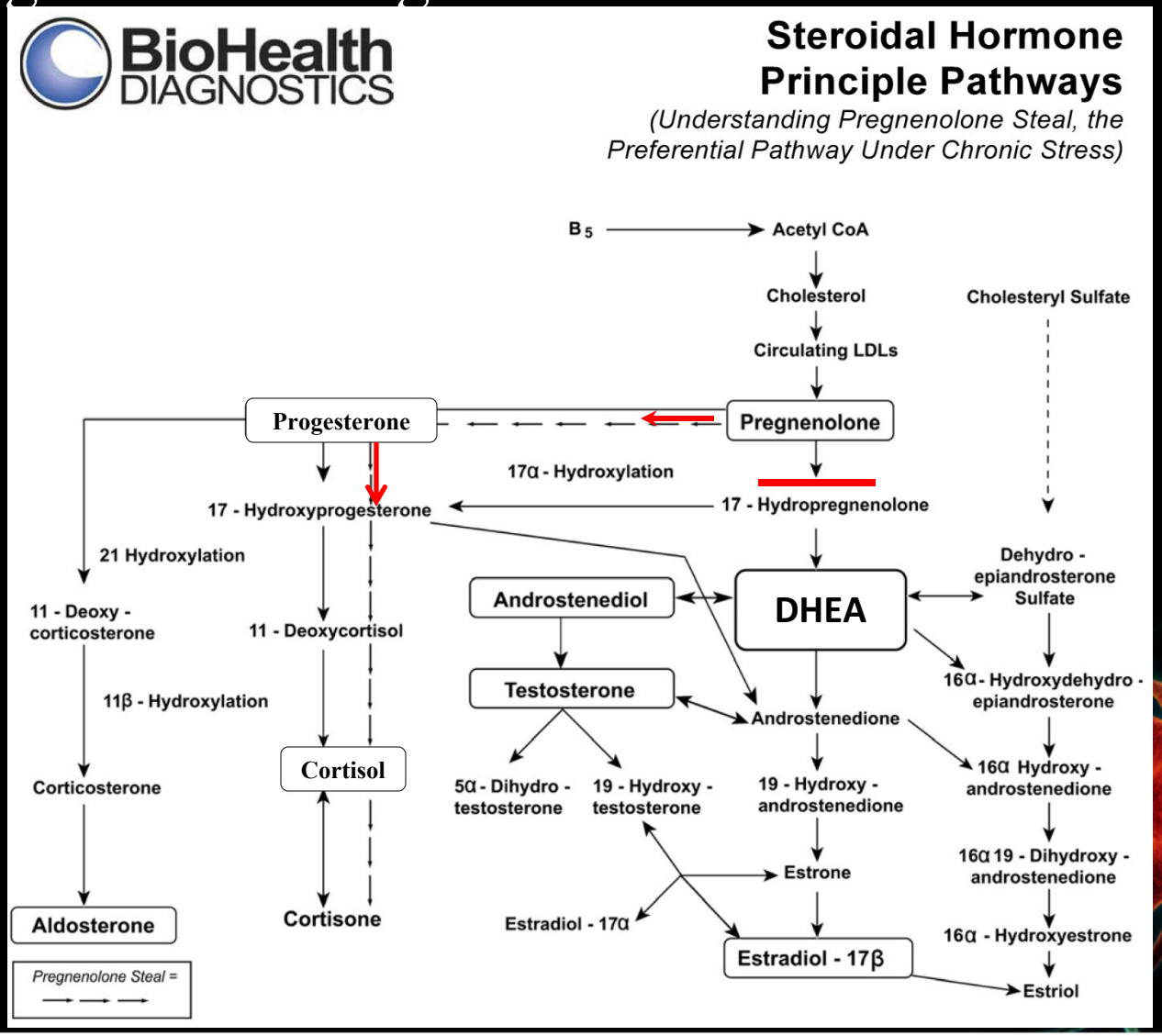
Adrenal Fatigue: Male (32) TBI		
Marker	Result	Median
Growth Hormone		**5.0 ng/ml**
IGF-1		**200 ng/ml**
IGFBP-3		**4000 ng/ml**
DHEA-s		**245 ug/dL**
Total Testosterone		**690 pg/ml**
Free Testosterone		**14 ng/ml**
DHT		**52ng/dL**
SHBG		**45 pg/ml**
Estrone		**60 pg/ml**
Estradiol		**25 pg/ml**
Pregnenolone		**210 ng/dl**
Progesterone		**0.8 ng/ml**
FSH		**7.0 mIU/ml**
LH		**5.1 mIU/ml**
Zinc		**95 mcg/dL**
Prolactin		**11.25 ng/ml**
Insulin		**12.5 miu/L**
Vitamin D3		**60 ng/dL**
TSH		**2.5 mcu/ml**
Free T4		**1.5 ng/ml**
Free T3		**2.5 pg/dl**
Reverse T3		**165 ng/dl**
T3/rT3 ratio		**Above 1.06**
ACTH	**43 HN**	**35 pg/ml**
Cortisol	**1.8 L**	**15ug/dl_a /7.3ug/dl_p**

What do you think is going on?

Pregnenolone Steal Syndrome

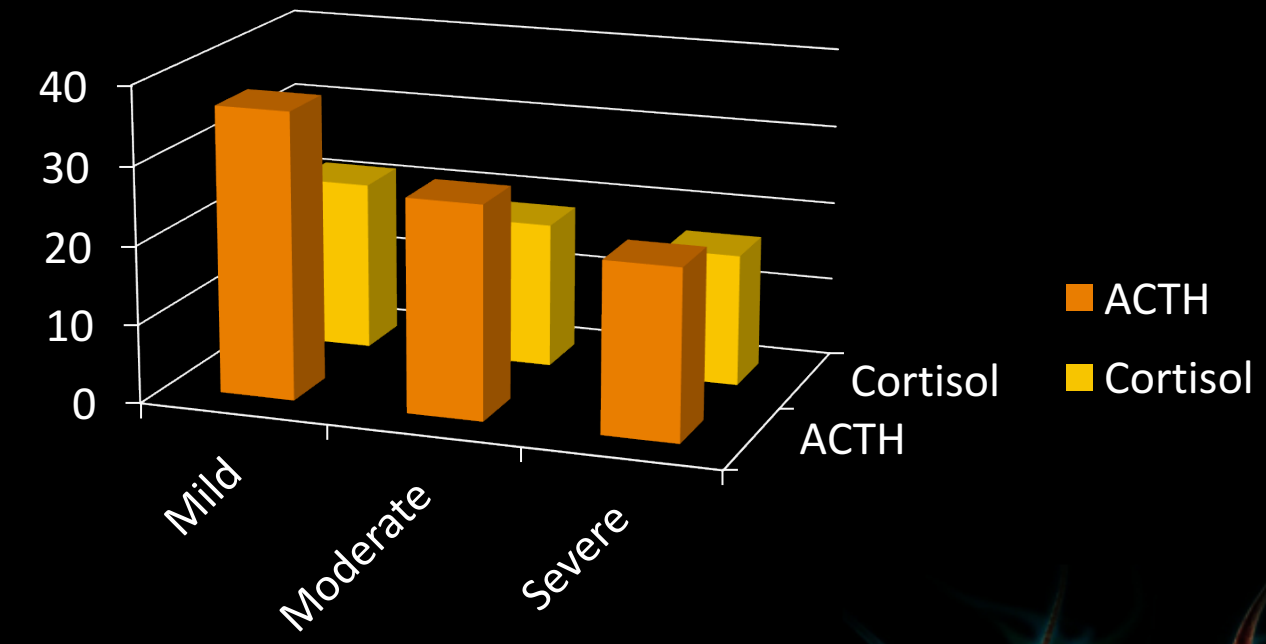
Pregnenolone Steal: Male (28) MVA		
Marker	Result	Median
Growth Hormone		5.0 ng/ml
IGF-1		200 ng/ml
IGFBP-3		4000 ng/ml
DHEA-s	89 LN	245 ug/dL
Total Testosterone	328 LN	690 pg/ml
Free Testosterone	5.23 LN	14 ng/ml
DHT		52ng/dL
SHBG		45 pg/ml
Estrone		60 pg/ml
Estradiol		25 pg/ml
Pregnenolone	63 LN	110 ng/dl
Progesterone	0.91 HN	0.8 ng/ml
FSH		7.0 mIU/ml
LH		5.1 mIU/ml
Zinc		95 mcg/dL
Prolactin		11.25 ng/ml
Insulin		12.5 miu/L
Vitamin D3		60 ng/dL
TSH		2.5 mcu/ml
Free T4		1.5 ng/ml
Free T3		2.5 pg/dl
Reverse T3		165 ng/dl
T3/rT3 ratio		Above 1.06
ACTH	18 N	35 pg/ml
Cortisol	17.3 HN	15ug/dl_a /7.3ug/dl_p

Under severe stress, Pregnenolone is shunted towards cortisol and away from DHEA/DHEA-s at the expense of all the androgens and estrogens:



Acute ACTH-Cortisol Levels

15% of moderate to severe TBI Patients develop Adrenal failure within 7-60 days.



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

DHEA – DHEA-s

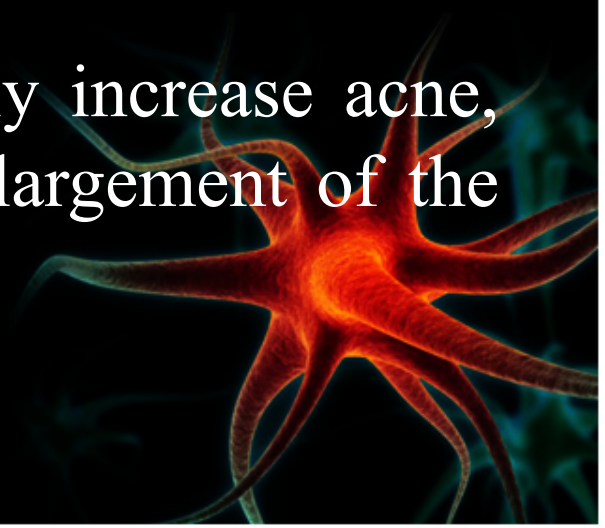
The multitude of benefits from DHEA-s makes is an important hormone to track.

- It stimulates oligodendrocytes to make myelin.
- It reduces Glia production of the inflammatory Cytokine IL-6.
- It protects the heart from Ischemic Heart Disease.
- It raises GH production during the night.
- Anti-depressant effects (1952).
- Improved wound healing.
- DHEA-s less than 250ug/dL need 25mg of DHEA either BID or QHS based upon side-effects.



Testosterone

- Free Testosterone is the most important form of testosterone since it gets past the BBB and into cells.
- Even though DHT is 4x more anabolic and 10x more effective in other effects, it is the intracellular concentration of these hormones that perform the function.
- Elevated levels of serum DHT only increase acne, oily skin, hair loss or thinning, enlargement of the prostate and testicular atrophy.

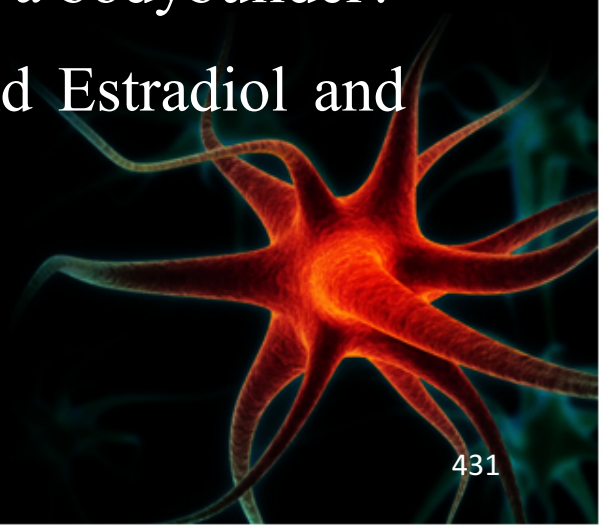


Testosterone Production Rates In Normal Adults.

Journal of Clinical Investigation Vol. 42, No. 11, ***1963***, Stanley G. Korenman, Hildegard Wilson, Mortimer Lippsett, Endocrinology Branch, National Cancer Institute, Bethesda, MD.

- Male daily Testosterone production rates ranged from *4 to 11.8 mg per day.* Ave = 28mg - 80mg/week.
- Female daily Testosterone production rates ranged from *.9mg to 2.8 mg per day*. Ave = 6.3mg to 20mg/week.

- **Questions**: So why do we give 100mg, 200mg, 300mg a week?? Why are we treating everyone like a bodybuilder?
- **Answer**: So that we can induce DHT and Estradiol and then use an aromatase inhibitor?



Female sexual dysfunction and use of hormone therapy in postmenopausal women Semin Reprod Med **2005** May;23(2):180-7. Kovalevsky G Department of Obstetrics and Gynecology, CONRAD, Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, 601 Colley Avenue, Norfolk, VA 23507, USA

- 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, while low testosterone does diminish libido.



Free Testosterone f(T)

- 2% of the bioavailable testosterone is unbound.
- This is the form that can passed the BBB.
- Once in the brain it is converted to DHT.
- If the patient is on any 5-Alpha reductase products it will inhibit the conversion of (T) to DHT and increase Depression.



Sex hormones and cognitive function in older men. Journal American Geriatric Society **2002** Apr;50(4):707-12. Yaffe K; Lui LY; Zmuda J; Cauley J Department of Psychiatry, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

- Higher levels of bioavailable testosterone are associated with better cognitive function in older men.
- Bioavailable measures of free testosterone f(T) may better reflect hormone levels available to the brain and thus be more closely associated with central nervous system benefits such as cognition.



Total Testosterone t(T)

- The non-specific measurement of all forms of testosterone in the serum.
- Like total cholesterol it does not give you any specificity of quality. This is predicated by the amount of Free Testosterone.
- Levels of t(T) are kept at the Normal to Low-Normal ranges.

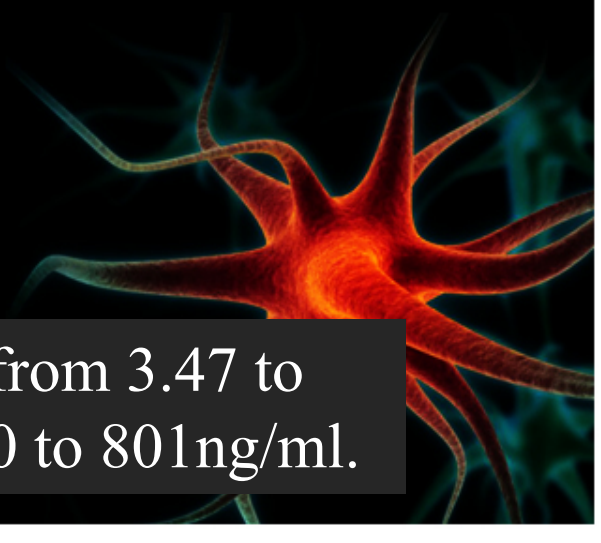


Testosterone Options

Product	Dose	Lab Level	Comments
Clomid**	50mg 3-5x a week	2-3 months	Less than 40 years of age and prophylaxis.
AndroGel 1%	1-4 pumps/day	T(T)>350-750ng/dL	Apply to shoulder and upper arms only.
AndroGel 1.62%	1 x day	T(T)>350-750ng/dL	High DHT levels and Estradiol.
Testim 1% Gel	5-10g/day	T(T) 300-1000ng/dL	High DHT levels and Estradiol.
TestoCream 10%	½ - 1 gram/day	F(T)> 10-14ng/dL	Apply to flank if not in contact with other people.
Testosterone Cypionate IM	40-100mg/week-Male 10-30mg/week - Female	F(T)> 10-14ng/dL T(T)>300-1000ng/dL	Once weekly subcutaneous or IM injection.
Testosterone Pellets	Based upon weight.	F(T)> 10-14ng/dL T(T)>300-1000ng/dL	Initially high levels dropping over 4-6 months. Once implanted cannot remove.
Testosterone Lozenge (Troche)	Males: 25-50mg BID3x/wk Female:12.5-25mg.BID3x/wk	F(T)> 10-14ng/dL T(T)>300-1000ng/dL	Short half-life needing frequent dosing.
Testosome®	Males: 1cc Oral AM, Daily Females: 1cc Oral, TIW	Male: F(T)> 10-14ng/dL Female: F(T)> 2-4ng/dL	Short half-life with excellent absorption. CNS benefits include improved focus, concentration, decrease anxiety, improved depression, rise in libido and mental energy.¥
	¥ - Based upon 3 months of testing with 10mg dose sampling.		

Clomiphene citrate 50mg:

- Three year study (2014-2016) on the use of Clomid in two groups: Less than 40 and greater than 40.
- 2016 study: Less than 40 with a Free T of 5-10 get one tablet every 3rd day. Blood work in 12 weeks.
- Older than 40 get UL-Testosterone protocol (20mg) every 3rd day with 25/50mg tablet of Clomid or no clomid. Blood work in 8-12 weeks.



JC on C5 protocol at 3 months: Free T from 3.47 to 13.99ng/ml and total testosterone from 270 to 801ng/ml.

Dihydrotestosterone (DHT)

- Dihydrotestosterone, touted to be the active form of Testosterone is best to be elevated within the cell and not in the serum.
- We aim to have the serum levels below the Median Level knowing that the availability of free testosterone will dictate the intracellular levels of DHT which is key to mental health.



Sex Hormone Binding Globulin

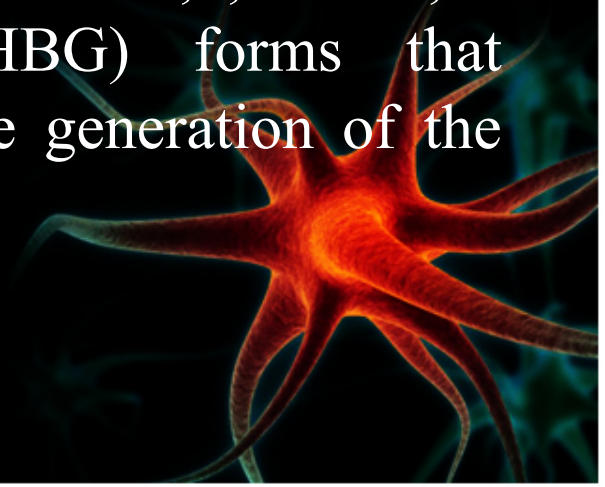
- Estradiol increase the production of SHBG while Androgens reduce it.
- Previously believed that SHBG would bind to free testosterone creating a non-physiological Ligand.
- Now, it appears that SHBG-T has its own unique cell wall receptor that still propagates the same intracellular, genomic affects as when (T) binds to the cell wall AR site.

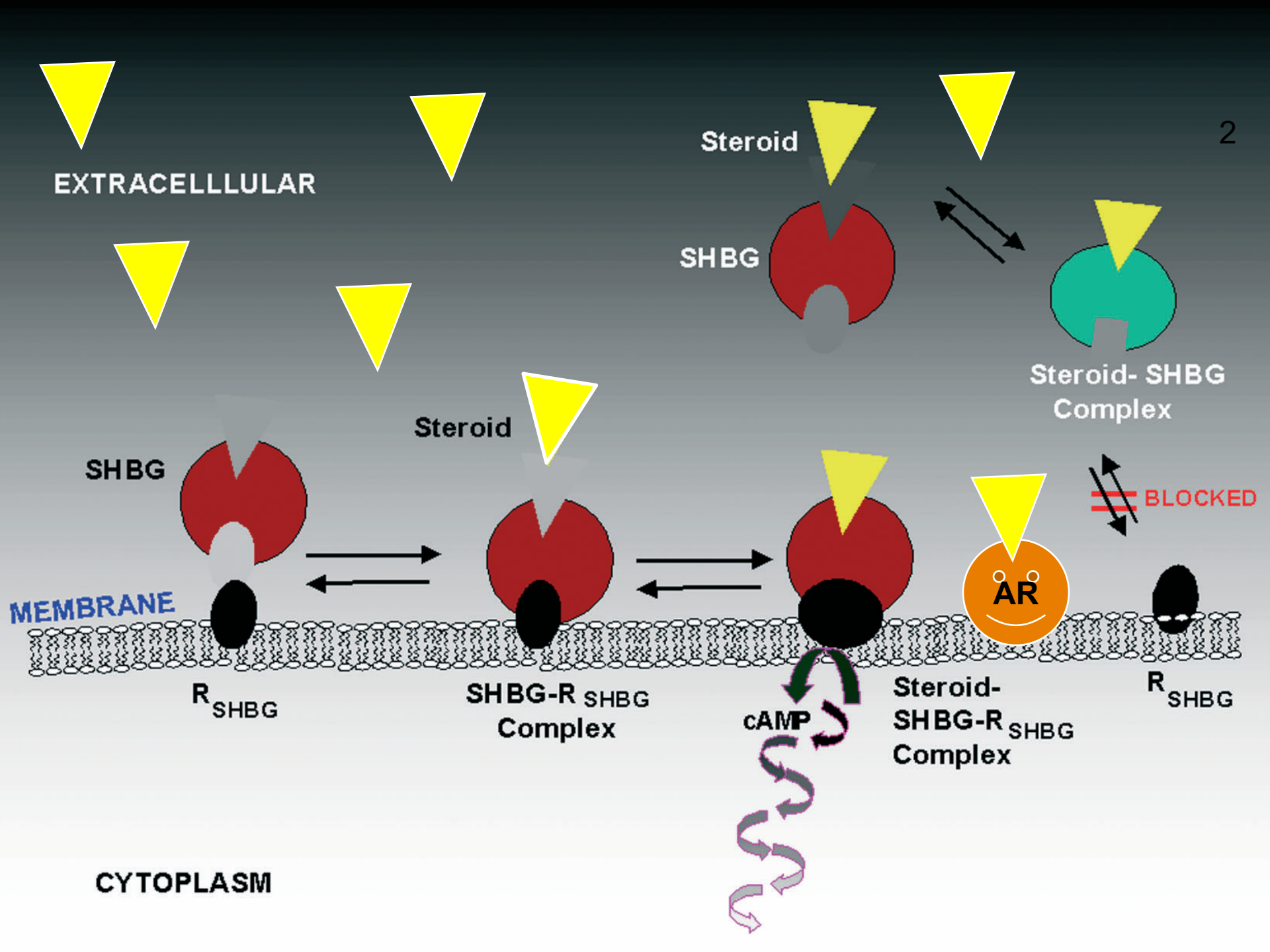
- MHC Note: Think of the SHBG as the net-effect of Estrogens causing to go up and Testosterones that cause it to go down.

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, NY 10019, USA. Dept of Urology, St Luke's/Roosevelt Hospital Center, and College of Physicians and Surgeons, Columbia University, NY, NY 10019, USA.

- In its steroid-free configuration, SHBG binds to RSHBG on cell membranes, forming a bipartite complex (SHBG–RSHBG).
- SHBG, already bound to a steroid, non-competitively inhibits the binding of SHBG to RSHBG.
- However, within minutes after exposure of SHBG–RSHBG to a steroid agonist, e.g. estradiol or 5-androstan,3,17-diol, a tripartite complex (steroid–SHBG–RSHBG) forms that activates **adenylyl cyclase**, leading to the generation of the second messenger, cAMP.




EXTRACELLLULAR
Steroid
SHBG
Steroid- SHBG Complex
Steroid
SHBG
BLOCKED
AR
MEMBRANE
R SHBG
SHBG-R SHBG Complex
cAMP
Steroid-SHBG-R SHBG Complex
R SHBG
CYTOPLASM

Testosterone Algorithm

Injection Protocol

Provocative Testing (60mg)

Start Tc/Tp Blend 60mg Q7days ⟷ **Repeat test**

1mo blood and Questionnaire

All Good Continue

Adjustment Needed

40mg every 3rd day

1mo blood and Questionnaire



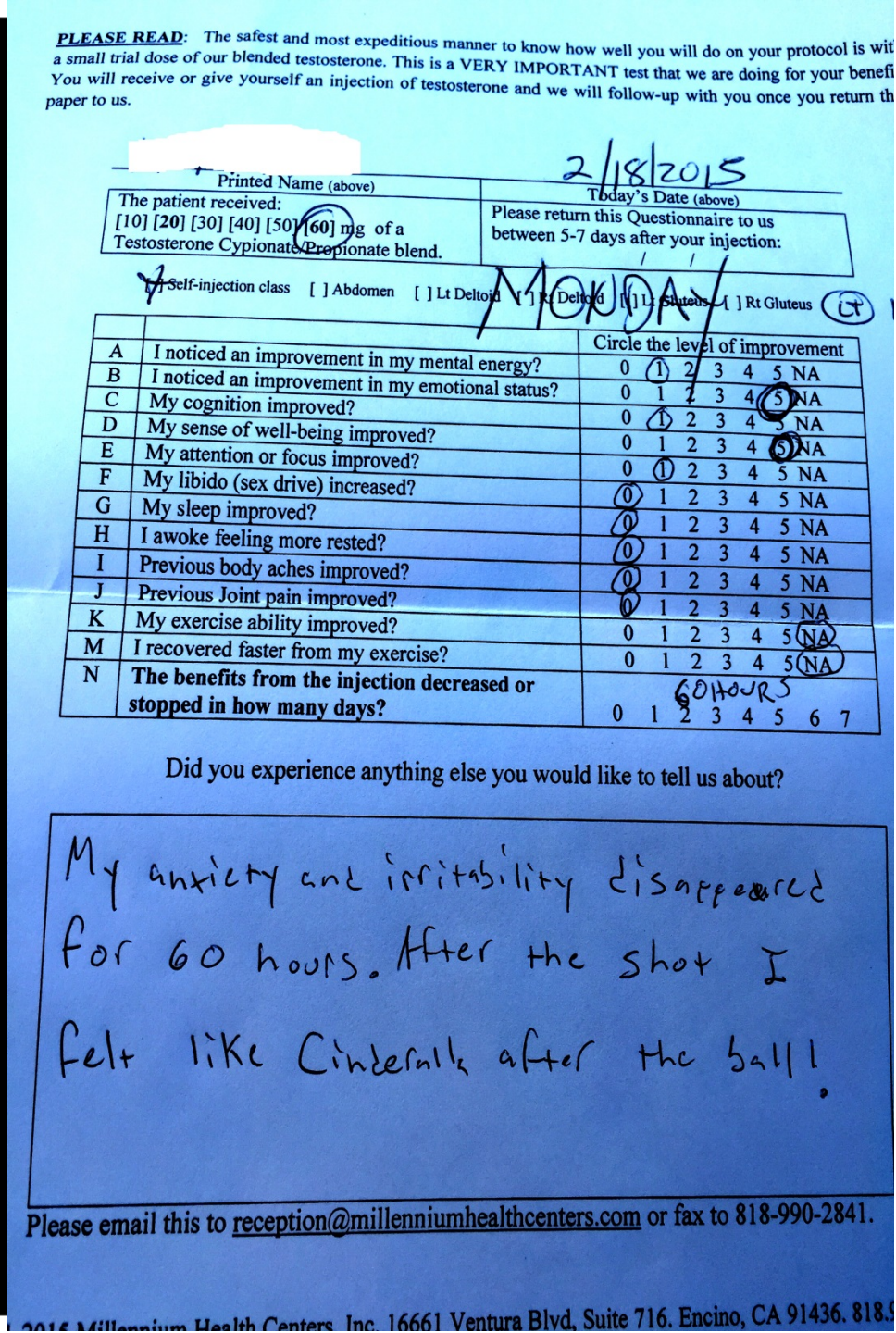
03-22-2015 (AM)

I am so blessed; all my headaches, vision, vestibular and most cognitive symptoms have been healed through Carrick Brain Center.

The things that continued were anxiety, irritability, isolation, anger and rage to name a few. 48 hours after receiving the neurosteroid treatment I notice a complete 180-degree turn around with all of those symptoms.

It has been that way since I started treatment 3 weeks ago. My wife and parents are the most outspoken on the noticeable changes.

My Mother said she feels as though she has her son back, and my wife said just this last Sunday that she never thought I would be able to act/live the way I am able to now.



PLEASE READ: The safest and most expeditious manner to know how well you will do on your protocol is wit
a small trial dose of our blended testosterone. This is a VERY IMPORTANT test that we are doing for your benefi
You will receive or give yourself an injection of testosterone and we will follow-up with you once you return th
paper to us.

[redacted] 2/18/2015

Printed Name (above)	Today's Date (above)
The patient received: [10] [20] [30] [40] [50] [60] mg of a Testosterone Cypionate/Propionate blend.	Please return this Questionnaire to us between 5-7 days after your injection: / /

[ ] Self-injection class [ ] Abdomen [ ] Lt Deltoid [ ] Rt Deltoid [ ] Lt Gluteus [ ] Rt Gluteus (LT)

MONDAY

		Circle the level of improvement
A	I noticed an improvement in my mental energy?	0 (1) 2 3 4 5 NA
B	I noticed an improvement in my emotional status?	0 1 2 3 4 (5) NA
C	My cognition improved?	0 (1) 2 3 4 5 NA
D	My sense of well-being improved?	0 1 2 3 4 (5) NA
E	My attention or focus improved?	0 (1) 2 3 4 5 NA
F	My libido (sex drive) increased?	(0) 1 2 3 4 5 NA
G	My sleep improved?	(0) 1 2 3 4 5 NA
H	I awoke feeling more rested?	(0) 1 2 3 4 5 NA
I	Previous body aches improved?	(0) 1 2 3 4 5 NA
J	Previous Joint pain improved?	(0) 1 2 3 4 5 NA
K	My exercise ability improved?	0 1 2 3 4 5 (NA)
M	I recovered faster from my exercise?	0 1 2 3 4 5 (NA)
N	**The benefits from the injection decreased or stopped in how many days?**	60 HOURS 0 1 2 3 4 5 6 7

Did you experience anything else you would like to tell us about?

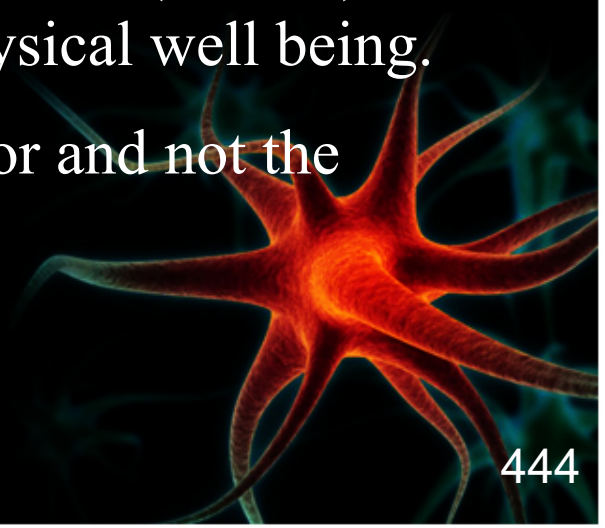
My anxiety and irritability disappeared for 60 hours. After the shot I felt like Cinderella after the ball!

Please email this to reception@millenniumhealthcenters.com or fax to 818-990-2841.

2016 Millennium Health Centers, Inc. 16661 Ventura Blvd, Suite 716. Encino, CA 91436. 818.9

Estrogens

- Estradiol(E2) and Estrone (E1) are interchangeable through a sulfated estrogen intermediary (Estrone sulfate) thereby, always trying to keep a balance.
- Estradiol is derived through Testosterone.
- Estrone is derived through Androstenedione in the ovaries and adipose tissue.
- The EP Ratio project by MHC has established a relationship, throughout all ages, where a balance between (E1+E2) and Progesterone can influence mental and physical well being.
- Therefore, this balance is what we strive for and not the actual level of the hormones.



EP Ratio examples

EP Ratio: Case 1 (38y/o): Average		
Marker	Result	Median
DHEA-s	**197**	**200 ug/dL**
Total Testosterone	**23**	**44 pg/ml**
Free Testosterone	**1.27**	**2-4 ng/ml**
DHT	**17**	**<30 ng/dL**
SHBG	**113**	**<75 pg/ml**
Estrone	**69**	**<200 pg/ml**
Estradiol	**110**	**90 pg/ml***
Pregnenolone	**54**	**110 ng/dl**
Progesterone	**0.30**	**5 ng/ml***
EP Ratio	**596**	**< 250 MHU**
FSH	**6.4**	**7.0 mIU/ml**
LH	**9.8**	**5.1 mIU/ml**
Zinc	**66**	**95 mcg/dL**
ACTH		**35 pg/ml**
Cortisol		**15ug/dl_a /7.3ug/dl_p**

EP Ratio: Case 2 (53y/o): Obese		
Marker	Result	Median
DHEA-s	163	**200 ug/dL**
Total Testosterone	19	**44 pg/ml**
Free Testosterone	**0.67**	**2-4 ng/ml**
DHT	**11**	**<30 ng/dL**
SHBG	**88**	**<75 pg/ml**
Estrone	**145**	**<200 pg/ml**
Estradiol	**68**	**90 pg/ml***
Pregnenolone	**37**	**110 ng/dl**
Progesterone	**0.05**	**5 ng/ml***
EP Ratio	**4260**	**< 250 MHU**
FSH	**9.1**	**7.0 mIU/ml**
LH	**22.7**	**5.1 mIU/ml**
Zinc	**51**	**95 mcg/dL**
ACTH		**35 pg/ml**
Cortisol		**15ug/dl_a /7.3ug/dl_p**

Growth Hormone Algorithm

- The most important hormone in the body.
- It regulates the functioning of all other hormones.
- Understanding the dynamic of GH, IGF-1 and IGFBP-3 will help to avoid mistreatment.



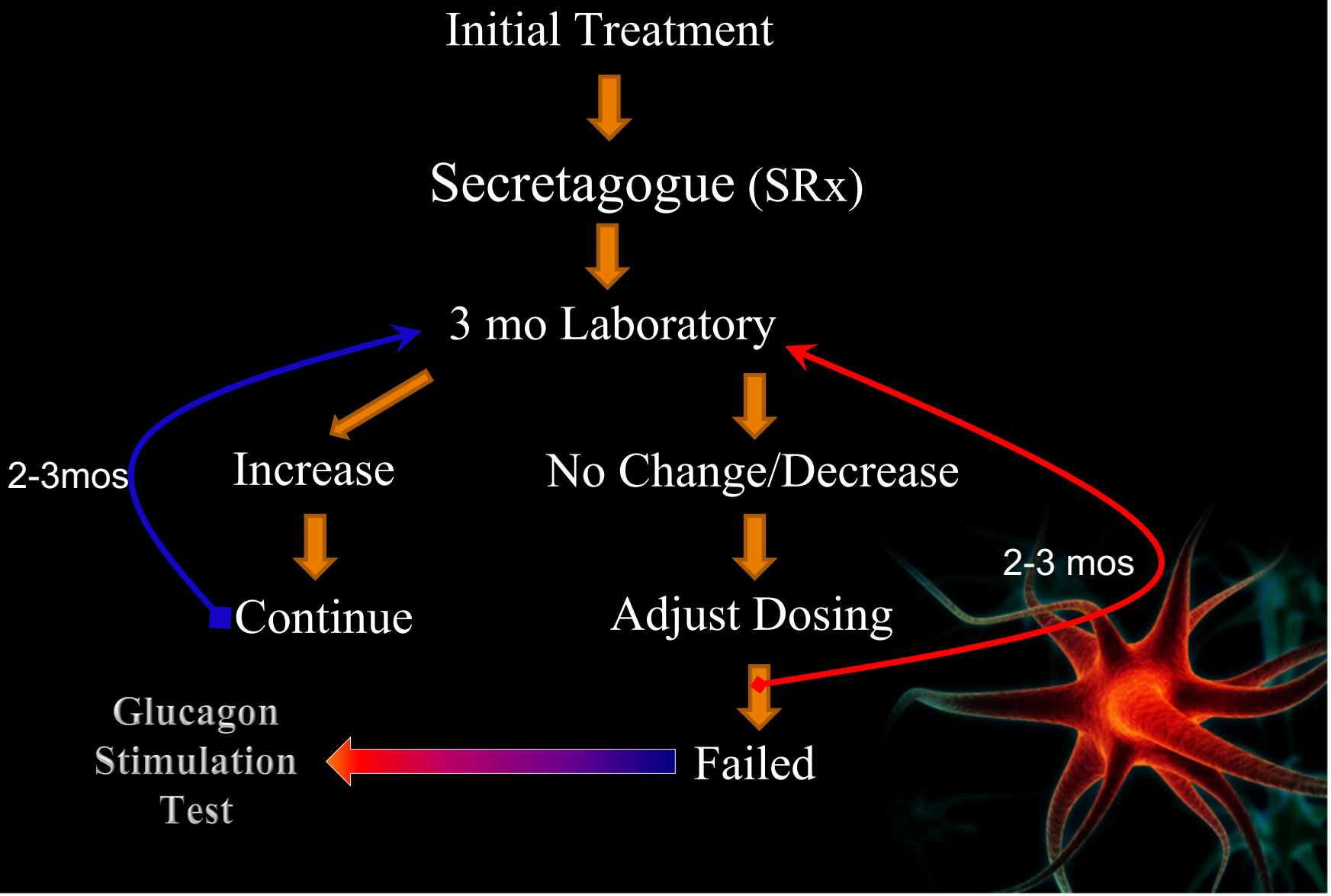
Growth Hormone Algorithm

Serum Testing	GH	IGF-1	IGFBP-3	Comments
Normal	N	N	N	No treatment
Questionable	N	N	▼	No treatment/ Liver
Laron's	N	▼	▼	Give L-IGF-1.
Questionable	N	▼	N	Rapid clearance/check for IGF-Ab.
Positive	▼	▼	▼	Challenge Testing/ Central
Positive	▼	▼	N	Challenge Testing/ Liver/Meds
Positive	▼	N	▼	Challenge Testing/ Liver/Meds
Normal	▼	N	N	GH in the morning is low short t1/2

Growth Factor	Half-life
Growth Hormone	20min
GH-Binding Protein	36min
IGF-1	8-10min
IGFBP-3	20-24 hrs



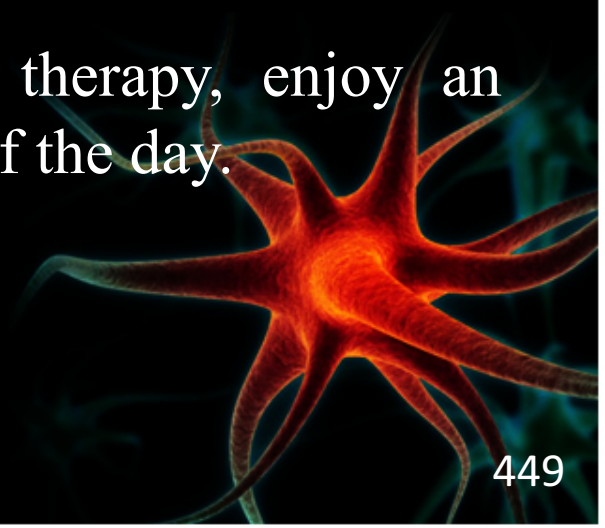
Growth Hormone Tx Algorithm



Stimulation of Human-Growth-Hormone Secretion by L-Dopa.

N Engl J Med 1970; 283:1425-1429 Dec. 24, **1970**. A. E. Boyd, III, M.D., Harold E. Lebovitz, M.D., and John B. Pfeiffer, M.D.
From the divisions of Endocrinology and Neurology, Department of Medicine, Duke University Medical Center

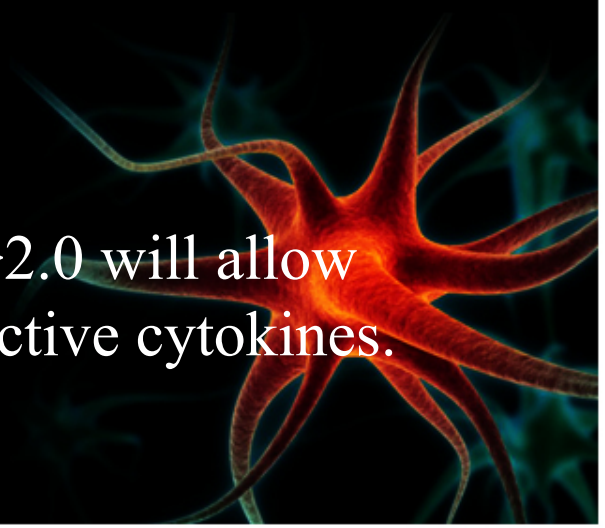
- Oral doses (0.5 g) caused a significant rise in plasma GH.
- The rise in plasma GH persisted for 120 minutes after the administration of the drug.
- The data suggest that a dopaminergic mechanism in the median eminence or a norepinephrine-sensitive site in the hypothalamus or limbic system may be involved in the regulation of growth-hormone secretion.
- Parkinson's disease patients, on L-dopa therapy, enjoy an elevated plasma GH for a substantial part of the day.



Thyroid

- The notable benefits of T3 and T4 on brain recovery and neurobehavior are clear.
- Controversy still exists between monotherapy with T4 and combination therapy with T3.
- If adequate levels of fT3 are obtained without the surreptitious presence of rT3, then neuroregeneration is possible.

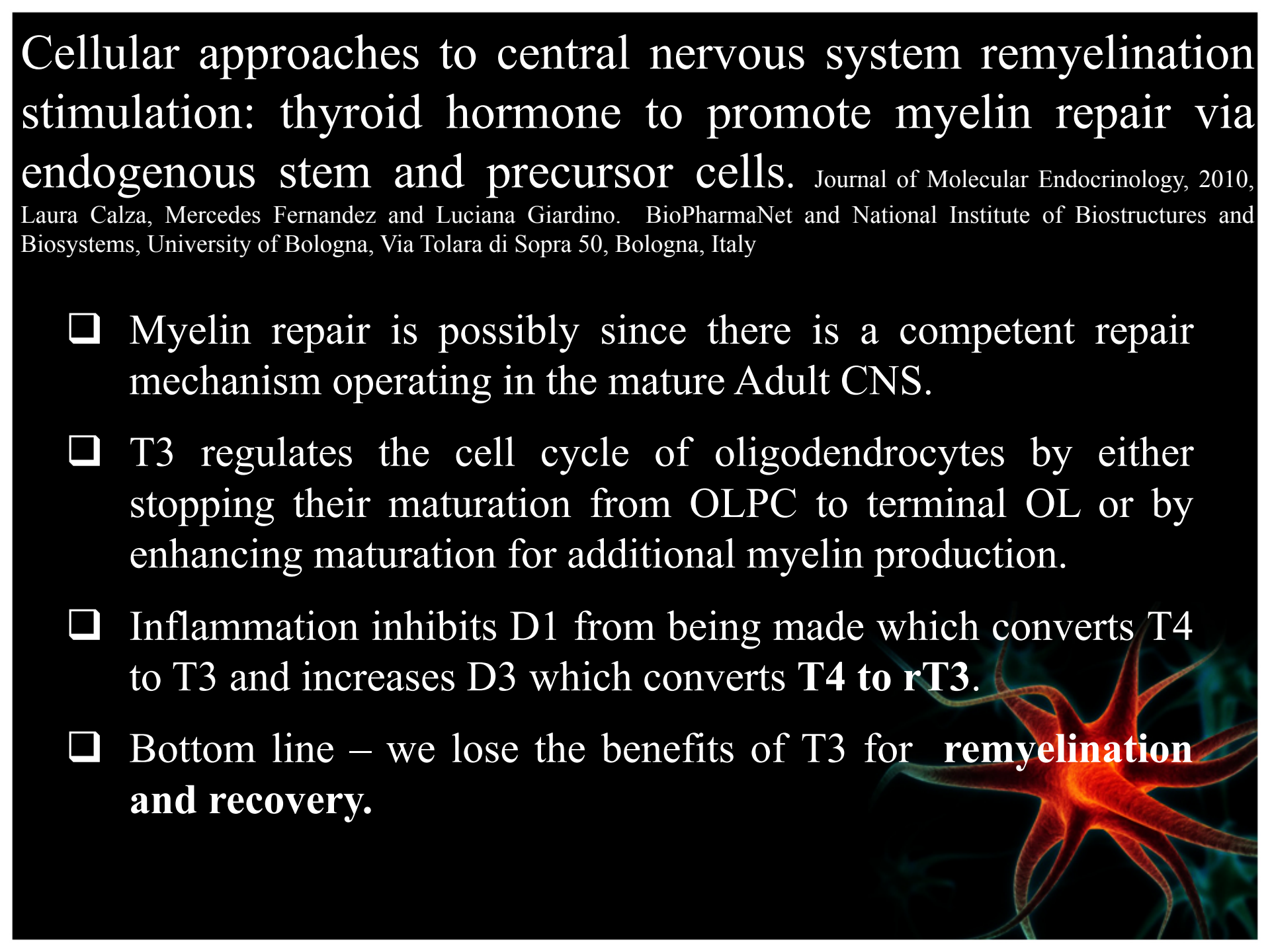
A fT3 of ≥3.0pg/dL and a fT3/rT3 ratio >2.0 will allow OLPC to produce growth factors and protective cytokines.



Cellular approaches to central nervous system remyelination stimulation: thyroid hormone to promote myelin repair via endogenous stem and precursor cells.

Journal of Molecular Endocrinology, 2010,
Laura Calza, Mercedes Fernandez and Luciana Giardino. BioPharmaNet and National Institute of Biostructures and Biosystems, University of Bologna, Via Tolara di Sopra 50, Bologna, Italy

- Myelin repair is possibly since there is a competent repair mechanism operating in the mature Adult CNS.
- T3 regulates the cell cycle of oligodendrocytes by either stopping their maturation from OLPC to terminal OL or by enhancing maturation for additional myelin production.
- Inflammation inhibits D1 from being made which converts T4 to T3 and increases D3 which converts **T4 to rT3**.
- Bottom line – we lose the benefits of T3 for **remyelination and recovery.**



Prolactin

- Prolactin less than 25%; (Low-Normal) consider elevation in Dopamine (medication?) or GABA. Can be associated with anxiety, panic attacks, restlessness, and fidgetiness.
- Prolactin above the 75th% must consider HP axis damage with loss of Dopamine or GABA and Pituitary Adenoma or Prolactinoma.
- Rarely does a microprolactinoma become a macroprolactinoma.
- Early intervention is recommended.



Why we do Prolactin levels

(JF) 27 year old male with history of MCA and assault to right temporal area.
Post Concussion Syndrome and his:
Prolactin was 22.7 (Normal to 18.4 ng/dL)

Brain: Normal diffusion. There is an area of encephalomalacia in the inferior right temporal lobe. There are a few scattered subcortical and periventricular white matter FLAIR hyperintensities. No evidence of intracranial mass lesion.. The right mastoid and middle ear cavity appear opacified. There may be erosive changes involving the right sigmoid plate and internal auditory canal. There is scattered mucosal thickening in the paranasal sinuses.

Sella: There is a small potential focus of hypoenhancement in the right portion of the pituitary that measures approximately 3 mm. There is uncertain if this may be a real finding or artifactual.

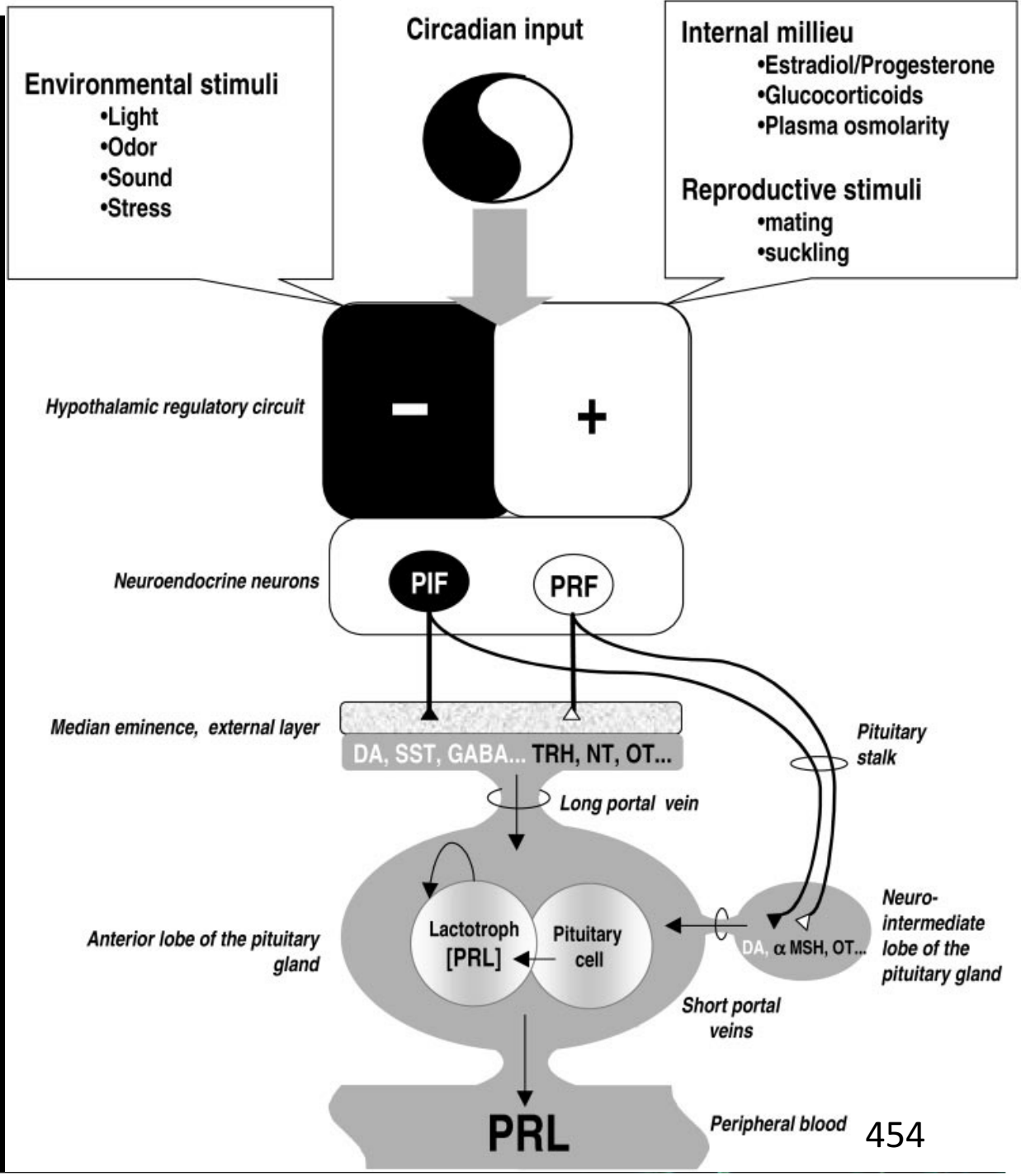
IMPRESSION

PIF = Dopamine

▲Dopamine ▼Prolactin

▼ Dopamine ▲ Prolactin

To ▼ Dopamine
1) No Caffeine.
2) Increase 5 HTP.
3) Decrease Cortisol.
4) No Nicotine.



Why we include Prolactin

1. Elevation in Prolactin diminishes LH production and release

a) Lowers testosterone

2. Causes of elevation:

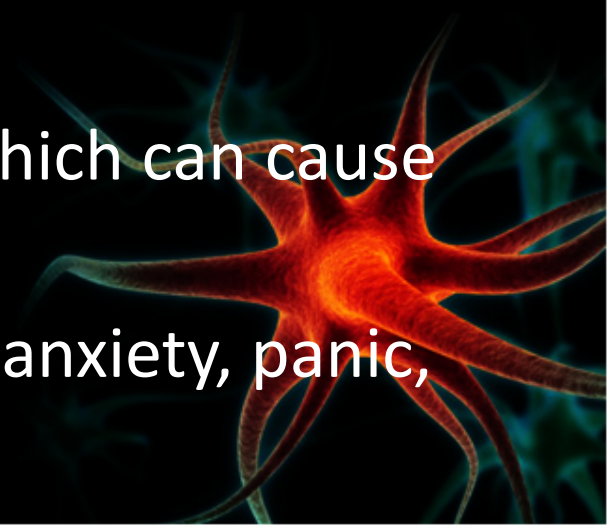
a) Hypothalamic dysregulation of pituitary

b) Adenoma

3. Decreases of Prolactin:

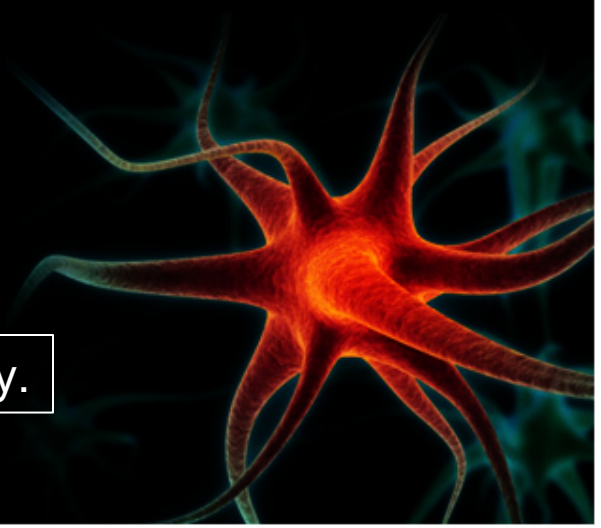
a) Caused by elevation in Dopamine which can cause symptoms of:

b) Edginess, agitation, aggressiveness, anxiety, panic,



Vitamin D

- The new miracle HORMONE is important for a multitude of processes especially for control of inflammation, production of testosterone, anti-depression, anti-dementia, better pain tolerance.
- Use 5000IU a day if total 25(OH) Vitamin D3 is above 60ng/dL
- Use 10,000IU a day if total 25(OH) Vitamin D3 is below 60ng/dL and Calcium levels are below 10mg.



Vitamin D3 5,000 – 10,000 iu a day.

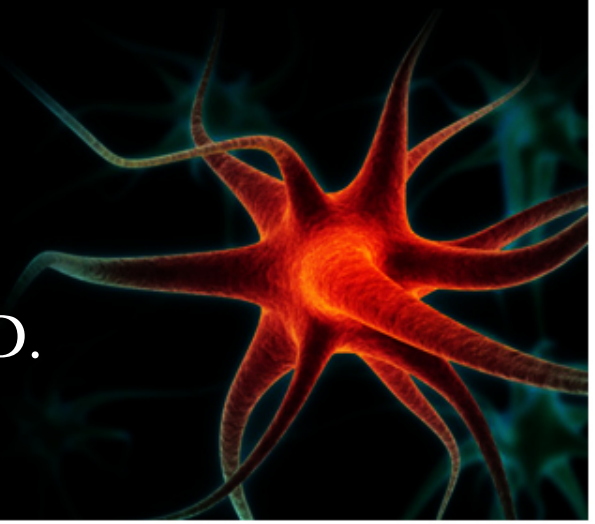
Combination Treatment with Progesterone and Vitamin D Hormone May Be More Effective than Monotherapy for Nervous System Injury and Disease. Front Neuroendocrinolgy. 2009 July ; 30(2): 158–172 System Injury and Disease Milos Cekic, M.A., Iqbal Sayeed, Ph.D., and Donald G. Stein, Ph.D. Department of Emergency Medicine, Emory University School of Medicine, Atlanta, Georgia, USA

- Emerging data on 1,25-dihydroxyvitamin D3, itself a steroid hormone, have begun to provide evidence that, like Preg/Prog, it too is **neuroprotective**.
- Vitamin D deficiency is prevalent in a large segment of the population, especially the elderly and institutionalized, and can significantly affect recovery after CNS injury.



Insulin and the Metabolic Syndrome

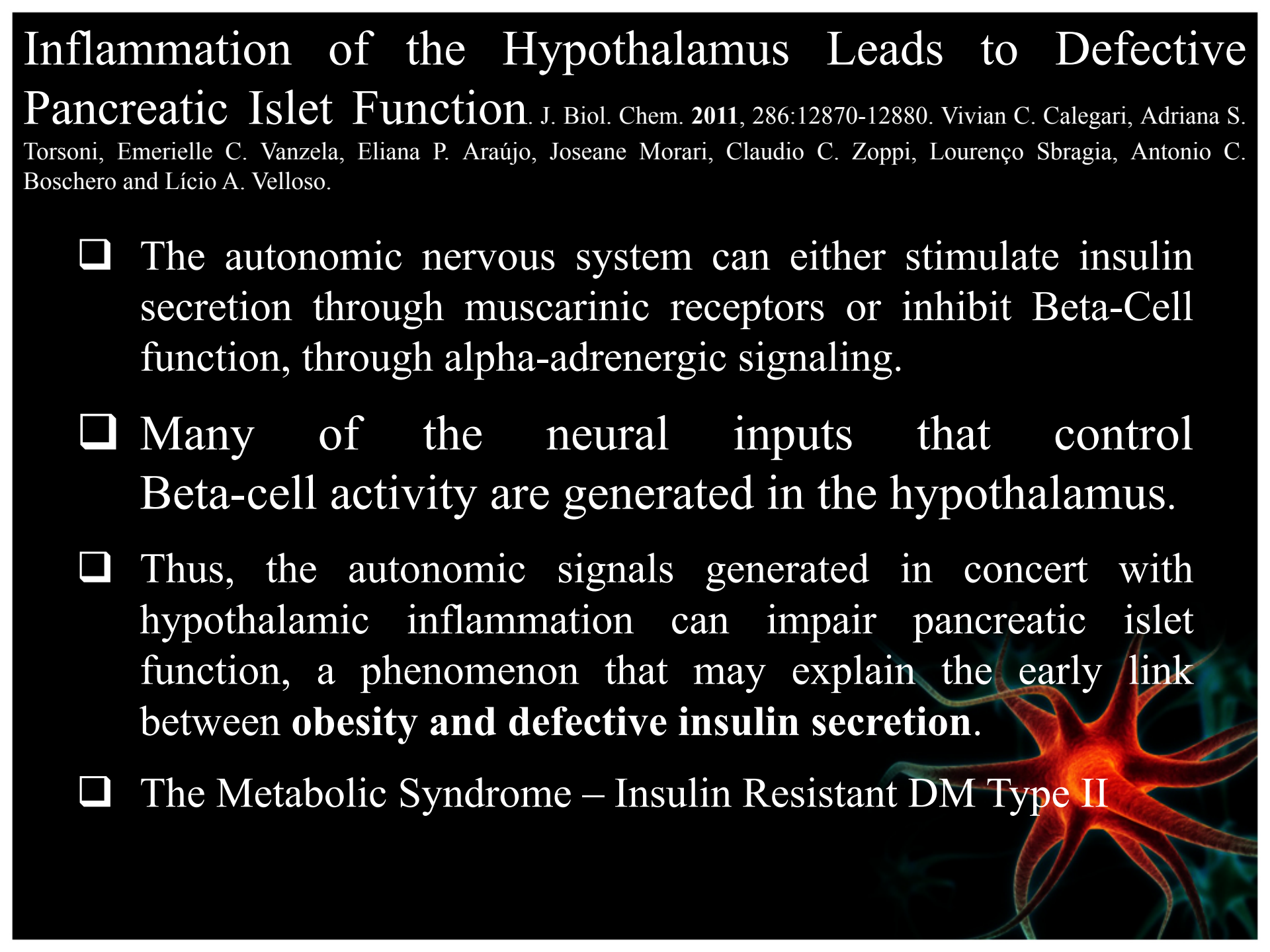
- The relationship of Hyperinsulinemia - Insulin Resistance(IR) or the Metabolic Syndrome to hypogonadism was established over 15 years ago.
- A level over 25xx is suggestive of IR, but one in the 50 and above is indicative. This associated with elevation in Lips and serum glucose are confirmatory. A distended beer belly is almost always present too.
- Correct testosterone deficiency.
- Low glycemic Diet and Exercise adding.
- Chromate (chromium polynicotinate) 1 BID.



Inflammation of the Hypothalamus Leads to Defective Pancreatic Islet Function

J. Biol. Chem. **2011**, 286:12870-12880. Vivian C. Calegari, Adriana S. Torsoni, Emerielle C. Vanzela, Eliana P. Araújo, Joseane Morari, Claudio C. Zoppi, Lourenço Sbragia, Antonio C. Boschero and Lício A. Velloso.

- The autonomic nervous system can either stimulate insulin secretion through muscarinic receptors or inhibit Beta-Cell function, through alpha-adrenergic signaling.
- Many of the neural inputs that control Beta-cell activity are generated in the hypothalamus.
- Thus, the autonomic signals generated in concert with hypothalamic inflammation can impair pancreatic islet function, a phenomenon that may explain the early link between **obesity and defective insulin secretion**.
- The Metabolic Syndrome – Insulin Resistant DM Type II



Sex hormone and neuroendocrine aspects of the metabolic syndrome.

Hajime Nawata et al. Dept of Medical Biochemistry, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan. Division of Endocrinology and Metabolism, School of Medicine, UCSD, La, Jolla, CA,

- Recent advances in the knowledge that the steroids testosterone (T), estradiol and DHEA-s are involved in the development of visceral obesity and of the metabolic syndrome.
- Cross talk between leptin and the androgen receptor (AR) in the hypothalamus as well as the peripheral conversion of DHEA and T to Estrone, Estradiol and DHT in adipocytes and hepatocytes play important roles in development of the metabolic syndrome in men.

Molecular Mechanisms of Chromium in Alleviating Insulin Resistance.

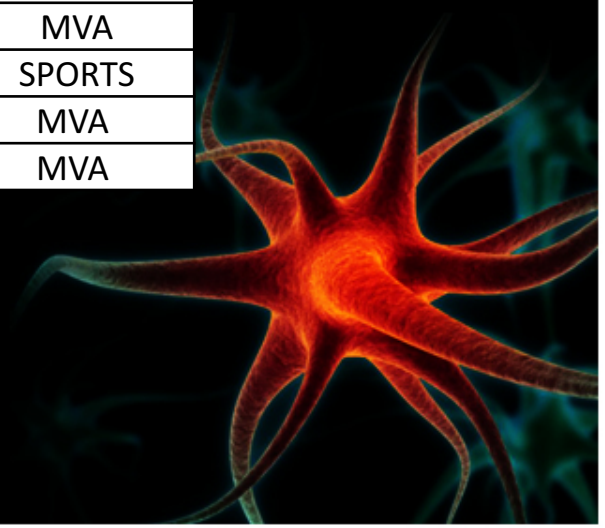
Yinan Hua, Suzanne Clark, Jun Ren, and Nair Sreejayan* University of Wyoming, College of Health Sciences, School of Pharmacy, Center for Cardiovascular Research and Alternative Medicine, Laramie, WY 82071, USA

- Chromium both in-vivo and in-vitro augments insulin-dependent Glut4 membrane translocation under insulin resistant conditions
- that may partly explain the beneficial effects attributed to chromium.



Study of Blast trauma and Elevated Insulin.

1	57.2	6.2	Co	Ch	23-Mar-92	24	MCA/SAH
2	86.4	5.9	Zw	Ch	8-Oct-78	37	MMA
3	43.3		Bo	An	20-Feb-78	38	Assault
4	48.7	10.3	Ev	Ch	12-Mar-75	41	MVA
5	94.8	16.2	Bu	Mi	11-Nov-69	46	BLAST
6	44.6		Jo	El	30-Mar-87	29	BLAST
7	34.5		Co	Sp	13-Aug-94	22	ANOXIA
8	27.8		Br	WI	21-Mar-90	26	SPORTS
9	34.5		Ke	An	12-Apr-90	26	PTSD
10	36.2		Su	Ch	4-Aug-89	27	COMA
11	26.3		An	Fr	28-Apr-87	29	MVA
12	40.5		Ma	Or	17-May-74	42	MVA
13	25.4		Br	Ke	8-Oct-72	43	SPORTS
14	61.5		Go	Al	9-Dec-68	47	MVA
15	54.5		At	Li		116	MVA



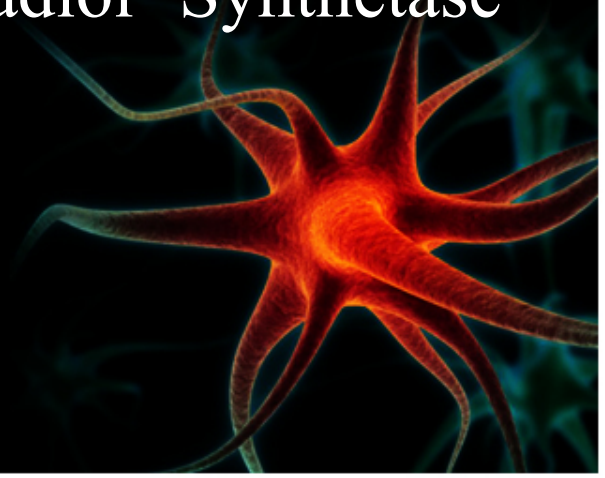
Dietary Zinc Deficiency Alters 5α-Reduction and Aromatization of Testosterone, Androgen, and Estrogen Receptors. The Journal of Nutrition 126: 842-848, **1996**. Ae-Son Om and Kyang-Woh Chung. Department of Food and Nutrition,, Hanyang University, Seoul, Korea and *Department of Anatomical Sciences, University of Oklahoma College of Medicine, Oklahoma City, OK04

- Zinc deficiency is associated with decreased Testosterone, increased Estradiol.
- Has an essential role in the synthesis and secretion of luteinizing hormone and follicle-stimulating hormone, gonadal differentiation, testicular growth and development of seminiferous tubules, spermatogenesis, testicular steroidogenesis, androgen metabolism and interaction with steroid receptors.

Zinc status and serum testosterone levels of healthy adults.

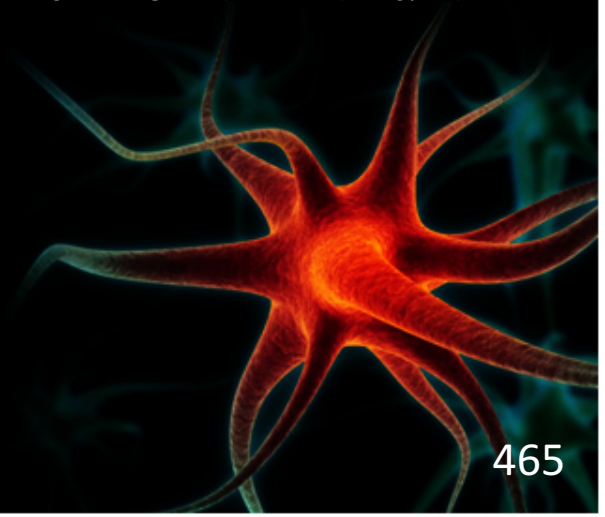
Prasad AS, Mantzoros CS, Beck FW, Hess JW, Brewer GJ. Department of Internal Medicine, Wayne State University School of Medicine, Detroit, Michigan, USA

- Zinc deficiency is prevalent throughout the world. Severe and moderate deficiency of zinc is associated with hypogonadism in men.
- Zinc supplementation of zinc-deficient elderly men for six months resulted in an increase in serum testosterone.
- Zinc acts as an Aromatase (Estradiol Synthetase Enzyme).



Zinc

- After measuring Zinc levels with the Royal Blue tube for intracellular metals:
- Zinc less than 50mcg/dL we give 30mg Zinc Citrate BID to TID
- Zinc greater than 50mcg/dL we give 30mg/Day.
- This is especially important if you are using Testosterone in a male since Zinc is a natural aromatase inhibitor.



30mg Zinc Citrate BID to TID

Dehydroepiandrosterone and allopregnanolone protect sympathoadrenal medulla cells against apoptosis via antiapoptotic Bcl-2 proteins. Proc Natl Acad Sci U S A 2004;101:8209–14. Charalampopoulos I, Tsatsanis C, Dermitzaki E, Alexaki VI, Castanas E, Margioris AN, Gravanis A.

- Finasteride lowers the concentration of 3α5α tetrahydroprogesterone, otherwise known as **allopregnanolone** (ALLO), a downstream metabolite of dihydroprogesterone that protects neurons from apoptosis via the Bcl-2 and Bcl-xL genes.
- Bcl-xL = B-cell lymphoma-extra-large is a transmembrane molecule in the mitochondria and acts as a pro-survival protein by preventing the release of mitochondrial contents such as cytochrome c, which would lead to caspase activation and cell death.

Regulation of axonal regeneration following the central nervous system injury in adult mammalian. Neuroscience bulletin, **2008** 24(6) 395-400. Ran Liu et al.

- Evidence supports the hypothesis that the failure of the CNS neurons to regenerate is not due to their intrinsic inability to grow new axons, but due to their growth state and due to lack of a Permissive Growth Environment.
- **Comment:** Oxidative stress and the diminished levels of growth encouraging hormones (IGF-I & II, DHEA-s, T3, THPreg, and THProg) are the factors involved in the lack of providing a;

Neuro-permissive environment.

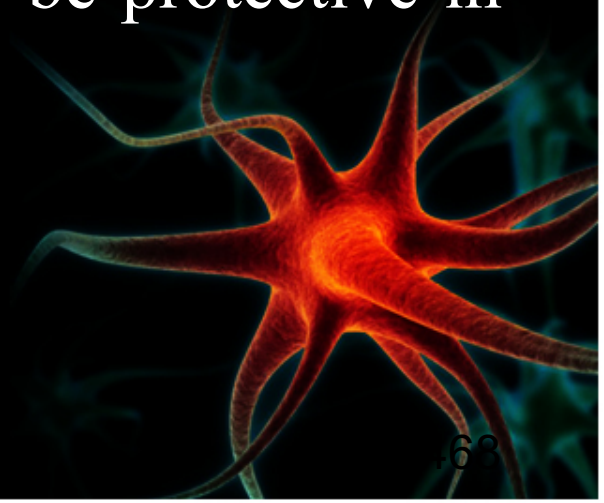


Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides

. Proc Natl Acad Sci U S A. **2000**; 97(3):1202-5. Gouras GK; Xu H; Gross RS; Greenfield JP; Hai B; Wang R; Greengard P. Laboratory of Molecular and Cellular Neuroscience and Fisher Center for Research on Alzheimer's Disease, The Rockefeller University, 1230 York Avenue, **New York**, NY 10021, USA.

- Treatment with Testosterone increases the secretion of the **non-amyloidogenic APP fragment**, A-alpha, and decreases the secretion of A-beta peptides from N2a cells and primary cerebrocortical neurons.

- These results raise the possibility that testosterone supplementation in elderly men may be protective in the treatment of AD.

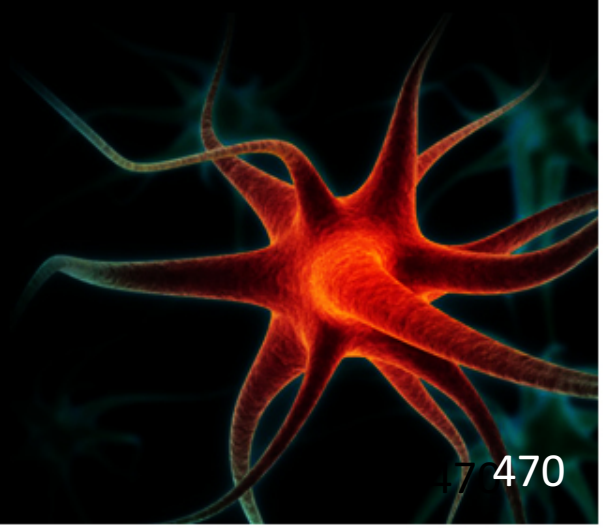


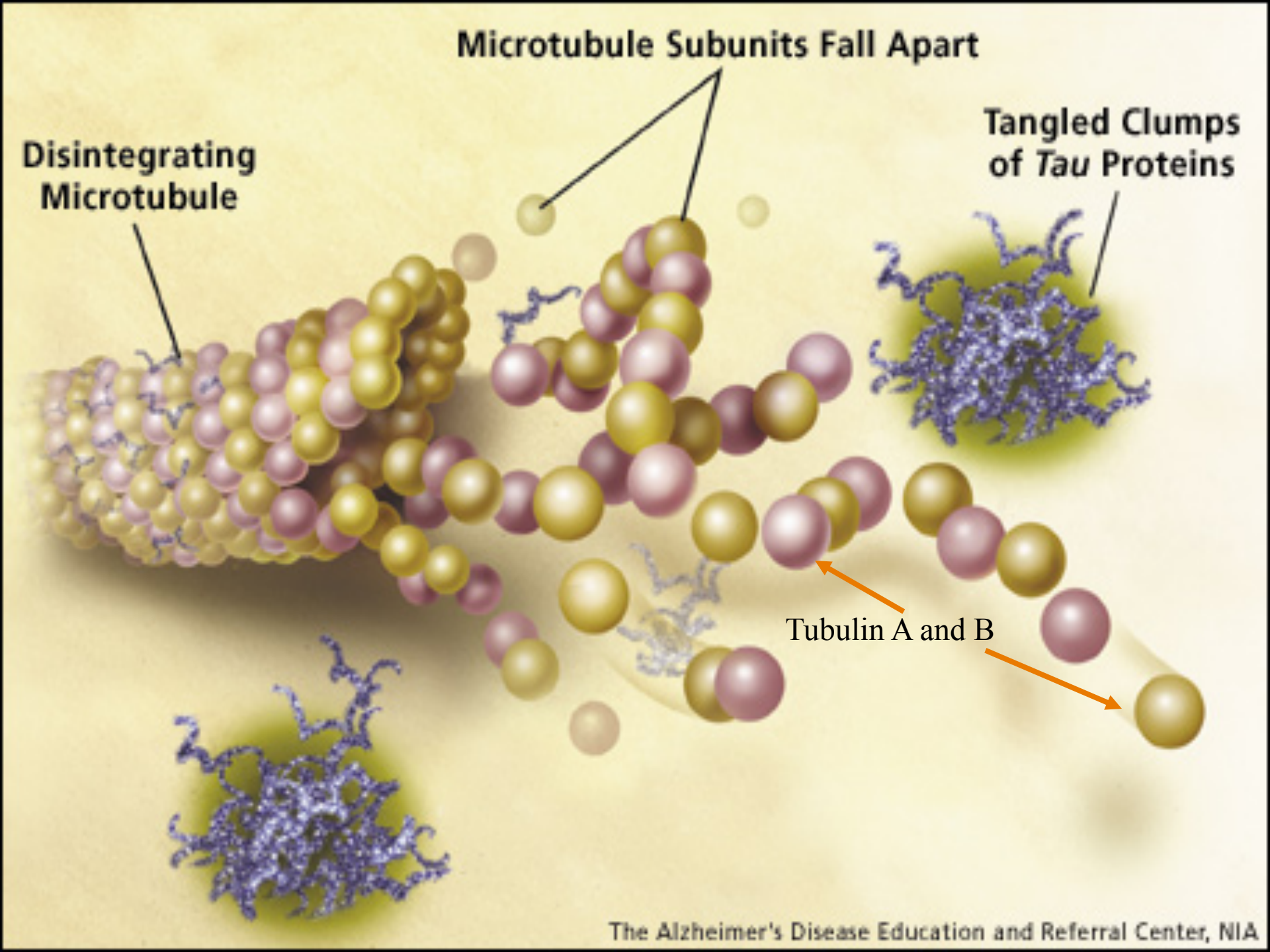
Anti-pituitary antibodies after traumatic brain injury: is head trauma-induced pituitary dysfunction associated with autoimmunity? European Journal of Endocrinology (2008) 159 7–13. Fatih Tanriverdi, Annamaria De Bellis1, et al. Dept of Endocrinology, Erciyes University Medical School, Kayseri, Turkey, Chair of Endocrinology and Chair of Immunology, 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.

- In TBI patients assessed three years after their injuries, Anti-pituitary antibodies (APA) were detected in 44.8% of TBI patients but, in none of the controls (non-TBI).
- Pituitary dysfunction was found in 46.2% of the patients.
- Those patients with APA and Pituitary Dysfunction had a positive correlation with failed challenge testing.

Cleaved Tau Proteins Quantification of axonal damage in traumatic brain injury: affinity purification and characterization of cerebrospinal fluid tau proteins. J Neurochem. 1999 Feb;72(2):741-50. Zemlan FP, Rosenberg WS, Luebbe PA, Campbell TA, Dean GE, Weiner NE, Cohen JA, Rudick RA, Woo D. Department of Psychiatry, University of Cincinnati College of Medicine, Ohio 45267-0559, USA

- Tau proteins are structural microtubule binding proteins primarily localized in the axonal compartment of neurons.
- CSF Tau levels were elevated >1,000-fold in Traumatic Brain Injury patients.




Microtubule Subunits Fall Apart
Disintegrating Microtubule
Tangled Clumps of *Tau* Proteins
Tubulin A and B
The Alzheimer's Disease Education and Referral Center, NIA

Predicting Alzheimer's disease in the Baltimore longitudinal study of aging. J Geriatr Psychiatry Neurol. 2005; 18(4):192-5. Zonderman AB. National Institute on Aging, Laboratory of Personality & Cognition, Cognition Section, Baltimore, Maryland 21224, USA.

- The premorbid levels of Free Testosterone were lower in men who developed Alzheimer's disease and premorbid depressive symptomatology was a risk for Alzheimer's disease as many as **6 years before the onset of dementia**.



Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 2002 Nov;87(11):5001-7 Moffat SD; Zonderman AB; Metter EJ; Blackman MR; Harman SM; Resnick SM Laboratory of Personality and Cognition, Gerontology Research Center, National Institute on Aging/National Institutes of Health, 5600 Nathan Shock Drive, Baltimore, MD 21224, USA.

- Of 477 men, 50-91yo, followed for 10 yr, with assessments of multiple cognitive functions and contemporaneous determination of serum total T, SHBG, and a free T index (FTI).
- Higher FTI was associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning and a reduced rate of longitudinal decline in visual memory.
- Men classified as hypogonadal had significantly lower scores across all tests.



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 common.
- Symptoms include dysphoria, fatigue, and low libido.
- **Median Total Testosterone levels** varied for those with:
  - Dysthymic disorder (295 ng/dl),
  - Major depressive disorder (425 ng/dl), and
  - No depression (423 ng/dl).

(What about the relationship with Free Testosterone).



Pituitary changes in head trauma. Alaskan Journal of Medical Science 1966 Apr;3(2):185-98. Ceballos R.

- Based upon autopsy results in 102 consecutive cases of head injury, patients who died from TBI, there was evidence of injury to the hypothalamus, the pituitary gland or the pituitary stalk in **26-86% of the patients**.



The interaction between growth hormone and the thyroid axis in hypopituitary patients.

Clinical Endocrinology (2011) 74, 281–288Lucy Ann Behan*, John P. Monson† and Amar Agha* *Academic Departments of Endocrinology, Beaumont Hospital, Dublin, Ireland and †St Bartholomew's Hospital, London, England.

- In adult hypopituitary patients, GH replacement has been reported to unmask central hypothyroidism in 36–47% of apparently Euthyroidism patients.
- Alterations in the hypothalamo-pituitary-thyroid axis have been reported following GH administration in both adults and children with and without growth hormone deficiency.
- Reductions in serum (fT4), increased (T3) with or without a reduction in serum TSH secretion have been reported following GH replacement.



Pregnenolone sulfate and aging of cognitive functions: behavioral, neurochemical, and morphological investigations. Hormones 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.



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.



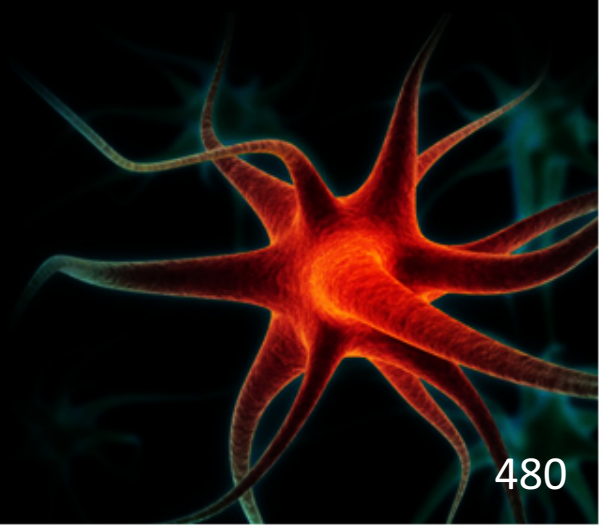
ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury. Annals of Emergency Medicine, **2006.**07.932.Wright DW et al.

- 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.



Mechanisms of progesterone-induced neuroprotection. Ann N Y Acad Sci **2005** Jun;1052:145-51. Singh M. Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, 3500 Camp Bowie Blvd., Fort Worth, TX 76107.

- Estrogen and Progesterone can no longer be considered strictly as reproductive hormoes having been found to exert effects on extra-hypothalamic structures within the brain such as the cerebral cortex. Functions of:
- Anti-Oxidant.
- Neuroprotective
- Neuro-regenerative



Sex hormones and brain aging. Exp Gerontology **2004** Nov-Dec;39(11-12):1623-31. Veiga S;et al. Instituto Cajal, CSIC, Avenida Doctor Arce 37, 28002 Madrid, Spain.

- **Progesterone**, **testosterone** and **estradiol** prevent neuronal loss in the central nervous system**.**
- As a neurosteroid, **Estradiol** in the brain is neuroprotective.
- **Progesterone** and its reduced derivatives DHPprogesterone and tetrahydroprogesterone diminish age-associated morphological abnormalities of myelin and aging-associated myelin fiber loss in peripheral nerves.



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



Replacement of DHEA in aging men and women. Potential remedial effects.

Ann NY Academy of Science 1995;774:128-142. Yen SS, Morales AJ, Khorrram O.

- A double-blind, cross-over study of 30 subjects, age 40 to 70 years, supplementing 50 mg/day DHEA or placebo for three months, 67% of men and 84% of women in the DHEA group reported a remarkable increase in physical and psychological well-being.



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 T levels and cognition are consistent with an effect of androgen treatment.



Androgen Effects on Cognitive Function.

Suzanne Craft, Monique Cherrier, Stephen Plymate, Sanjay Asthana, 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. (NAS and NS)



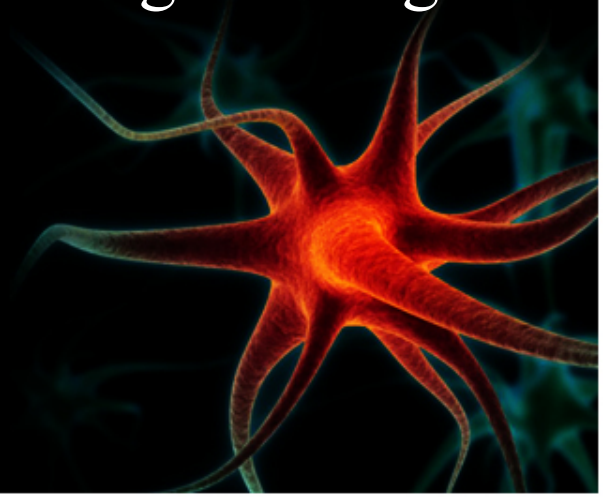
Sex hormones modulate brain damage in Multiple Sclerosis: MRI evidence. J Neurol Neurosurg Psychiatry 2005 Feb;76(2):272-5 Tomassini V; et al. Department of Neurological Sciences, University La Sapienza, viale dell'Universita 30, 00185 Rome,

- The hormone related modulation of pathological changes supports the hypothesis that sex hormones play a role in the inflammation, damage, and repair mechanisms typical of **Multiple Sclerosis**.



Concluding Statement

- Treatment is like art, some of the stuff works for you, but not necessary everyone else.
- Understand that the greatest impediment to successful treatment is not trying.
- Establish a comprehensive understanding of the NS and NAS environment and then replenish towards the optimal always maintaining physiological ranges with physiological doses.



Case Reviews in Traumatic Brain Injury

Q

Putting it together





List of Cases

Case	Slides	Name	Gender	Age	Condition
NA	5:8	None	Male Rpt	NA	Example of Male report format
NA	9:12	None	Female Rpt	NA	Example of female report format
1	13:17	WN	Male	32	Hockey w/o LOC, Assault w/LOC.
2	18:22	GI	Male	37	No memory of any injury.
3	23:27	CT	**Female**	68	MVA with Concussion.
4	28:32	BM	Male	45	Blast Trauma w/LOC
5	33:37	SS	Male	42	BHT w// Coma x 8wks.
6	38:42	VS	**Female**	48	MVA – flipped and rolled
7	43:47	FJ	Male	27	MCA in COMA 3wks.
8	50:54	JD	Male	43	Combat Trauma Syndrome (CTS)
9	58:62	HD	Male	48	Blast Trauma w/LOC
10	63:67	BC	male	57	Denies TBI history
TX1	68:72	HB	Male	48	NFL – 3 seasons
TX2	73:77	RJ	Male	38	Concussion w/ LOC
TX3	78:82	MK	**Female**	54	BHT, MVA..
TX4	83:87	PM	Male	32	Age 6, Fall from Balcony w/LOC
TX5	88:92	WA	**Female**	57	Surgical Menopause



2016 Patient's Report Template - Male

Millennium Health Group
Medicine for the 21st Century

ALLERGIES:

TBI

MALE (Age)
Lab Date: MM/DD/2015

Testosterone:

Hormone Testing	Results	Range				
Growth Hormone		5ng/ml*				
Somatomedin C (IGF-1)		> 200 ng/ml*				
IGF BP-3		4000 ng/ml*				
DHEA-S		245 ug/dl*				
Testosterone Free		12-14 pg/ml*				
Testosterone Total		690 ng/ml*				
Dihydrotestosterone (DHT)		< 30 ng/Dl*				
Sex Hormone Binding Gb		< 45 pg/ml*				
Estrone (E1)		< 60 pg/ml*				
Estradiol (E2)		<25 pg/ml*				
Progesterone		0.8ng/ml*				
Pregnenolone		110 ng/dl*				
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		<2.5 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				

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Status	Doctor	Phone	ICD-10
1967	Fall – Fx Skull ?/LOC				
1988	MVA w/ LOC < 30min				
2001	Rt Arm Fx with plate				
2015	Adult GH Deficiency	1°/3°			
2015	Central Hypogonadism	3°	Mark L. Gordon, M.D.	818.990.1166	
2015	Hypovitaminosis D	NA	Mark L. Gordon, M.D.	818.990.1166	
2015	Subclinical Hypothyroidism	1°	Mark L. Gordon, M.D.	818.990.1166	
2015	Hyperurecemia (gout)	NA	Mark L. Gordon, M.D.	818.990.1166	
2015	Hypercholesterolemia	NA	Mark L. Gordon, M.D.	818.990.1166	

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ALLERGIES:

TBI

MALE (Age)
Lab Date: MM/DD/2015

Chemistry Profile	Result	Range				
Glucose		< 100mg/dl				
Sodium (NA)		133-149 meq/L				
Potassium(K)		3.5 – 5.5 meq/L				
Chloride (Cl)		96-108 meq/L				
Iron (Fe)		35-200 mcg/L				
LIVER TESTING						
SGOT		<34 U/L				
SGPT		< 33 U/L				
Total Protein		6 – 8.4 gm/dl				
Albumin		3.2 – 4.8 gm/dl				
Globulin		2.0 – 3.7 gm/dl				
Alkaline Phosphatase		30-125 U/L				
Lactose Dehydrogen		80 – 225 U/L				
GGTP		2 – 60 mg/dl				
Total Bilirubin		0.1 – 1.2 mg/dl				
BONE, JOINTS						
Calcium (Ca)		8.4 – 10.8 mg/dl				
Phosphorus		2.3- 5 mg/dl				
Uric Acid		2.5 – 6.8 mg/dl				
Magnesium (Mg)		1.5 – 3.0 mg/dl				
LIPIDS						
Triglycerides (FAT)		<162 mg/dl				
Cholesterol		< 200 mg/dl				
HDL (Good)		>45 mg/dl				
LDL (Bad)		<100 mg/dl				
Cardiovascular Risk		2x risk				
RENAL FUNCTION						
Blood Urea Nitrogen		6 – 25 mg/dl				
Creatinine		< 1.0 mg/dl				
GFR						
BLOOD COUNT						
ESR		0 – 20 mm/hr				
WBC		4.0 – 10.8 $x10^3$				
RBC		4.0 – 5.4 $x 10^6$				
Hemoglobin		13 – 17 gm/dl				
Hematocrit		39 – 52%				
MCV		80 – 99 fL				
Granulocytes		45 – 75%				
Lymphocytes		20 – 50%				
Eosinophils		0-8%				
Urine Analysis		Normal				

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Millennium Health Group
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ALLERGIES:

TBI

MALE (Age)
Lab Date: MM/DD/2015

Welcome to the practice. This is the preliminary part of our process, the report. It is followed by a handbook that will be sent to you by Federal express. In the meantime, we can arrange for a Skype call to review your lab results and what they mean in terms of treatment. Then we will truly begin the process.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; Low-normal pattern. Need a Glucagon test to determine origin of this deficiency. DHEA-s is the precursor to Testosterone and Estrogens and is High-Normal. This is not an issue as long as there is no acne or oily skin. The important Free testosterones is low with a low Total Testosterone. DHT is high-nromal. Sex Hormone Binding is normal. Estrogens are normal with a high-normal progesterone. The neuroprotective Pregnenolone is low-normal. FSH and LH reflect either the body's ability to make hormones from the testes/ovaries when elevated, or low when supplementing or TBI. Both FSH and LH are low-normal with low testosterones identifying this as a Brain related deficiency. Prolactin is a marker for hypothalamic-pituitary functioning; normal. Insulin is normal. Vitamin D is low-normal. Your brain-thyroid system is normal, but your thyroid is not producing sufficient amount of thyroid hormone – T3. ACTH is produced by the pituitary to produce Cortisol from the adrenal glands; both normal.

Chemistry Profile: Blood sugar is normal . Liver functions and markers, bone metabolism, fats , and kidney functions. Cholesterol is elevated which can be due to the low thyroid and testosterone.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
		Secretropin	4 pumps at bed time as directed.		
		Testosterone C/P 80/20.	0.20cc every 3rd day.		
		Armour Thyroid 30mg	1 tablet		
		Ultranutrient	2 caps		2 caps
		Pregnenolone 30mg			2 caps
		Cognitive Aminos	2 caps	2 caps	
		Ultra B-Complex w/ PQQ	1 cap		1 cap
		Vitamin D3 5000IU	1 cap		

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
	ON	Crestor	20mg	QD	
	ON	Lamictal	20mg	BID	
	ON	Ativan	0.5mg	BID-QID	

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing
	ON	Omega	2K				Vit D3	2K	

Anticipated Scheduled Visits

Next Visit	Review of lab results, Physical exam, products dispensed

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ALLERGIES:
TBI

MALE (Age)
Lab Date: MM/DD/2015

Additional Notes:

02/20/2015	Remote Blood Draw
03/09/2015	Final Report sent and Fed X TBI Handbook
03/20/2015	SKYPE CALL: Reviewed History, Lab results, and treatment protocol. Arrange for shipment of program to patient. Follow-up in 2 weeks with 15' Skype.

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI

Additional Files to Handbook or email to patient if a follow-up office visit.

	Gout		PLAC Test		Estrogen Dominance
	Polycythemia	XX	Vitamin D Deficiency	XX	Metabolic Syndrome.
XX	Traumatic Brain Injury		TPO - Thyroiditis		PSA-Low Testosterone

Bio-available Testosterone Calculator
http://www.issam.ch/freetesto.htm



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ALLERGIES:

TBI

Name (age)
Lab Date: 01/20/2015

Chemistry Profile	Result	Range				Date
Glucose		65-100mg/dl				
Sodium (NA)		133-149 meq/L				
Potassium(K)		3.5 – 5.5 meq/L				
Chloride (Cl)		96-108 meq/L				
Iron (Fe)		35-200 mcg/L				
LIVER TESTING						Normal
SGOT		0- 34 U/L				
SGPT		< 33 U/L				
Total Protein		6 – 8.4 gm/dl				
Albumin		3.2 – 4.8 gm/dl				
Globulin		2.0 – 3.7 gm/dl				
Alkaline Phosphatase		30-125 U/L				
Lactose Dehydrogen		80 – 225 U/L				
GGTP		2 – 60 mg/dl				
Total Bilirubin		0.1 – 1.2 mg/dl				
BONE, JOINTS						*Normal*
Calcium (Ca)		8.4 – 10.8 mg/dl				
Phosphorus		2.3- 5 mg/dl				
Uric Acid		2.5 – 6.8 mg/dl				
Magnesium (Mg)		1.5 – 3.0 mg/dl				
LIPIDS						*Normal*
Triglycerides (FAT)		<162 mg/dl				
Cholesterol		< 200 mg/dl				
HDL (Good)		>45 mg/dl				
LDL (Bad)		<100 mg/dl				
Cardiovascular Risk		¼ - 1/2 risk				
RENAL FUNCTION						*Normal*
Blood Urea Nitrogen		6 – 25 mg/dl				
Creatinine		< 1.0 mg/dl				
BLOOD COUNT						*Normal*
ESR		0 – 20 mm/hr				
WBC		4.0 – 10.8 $x10^3$				
RBC		4.0 – 5.4 $x\ 10^6$				
Hemoglobin		12 – 16 gm/dl				
Hematocrit		36 – 48%				
MCV		80 – 99 fL				
Granulocytes		45 – 75%				
Lymphocytes		20 – 50%				
Eosinophils		<5%				
Urine Analysis		Normal				Normal

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Millennium Health Group
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ALLERGIES:

TBI

Name (age)
Lab Date: 01/20/2015

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; normal pattern. DHEA-s is the precursor to Testosterone and Estrogens and is normal. Estrogens and progesterone are normal with a normal Estrogen Progesterone Ratio (EP Ratio). The neuroprotective Pregnenolone is normal. The important free testosterone is normal as is the Total Testosterone. DHT and Sex Hormone Binding protein are normal. FSH and LH reflect the brains regulation of the ovarian/testicular hormones. When above the median the body is trying to produce more DHEA, Estrogens, Testosterone and Progesterone and when below the median the body perceives there is an adequate amount of hormones in the blood. In TBI or damage to the HP axis, these will be low-normal to low with low-normal to low circulating hormones. Prolactin is used as a marker of hypothalamic – pituitary functioning; normal. Zinc is normal. Insulin is normal. Vitamin D is normal. Overall, your Thyroid hormone panel suggests that you are producing a normal amount of thyroid hormones to run your body. ACTH is the hormone from the brain that stimulates your adrenal glands (above the kidneys) to make Cortisol, the hormone associated with our adaptation to stress. These are normal.

Chemistry Profile: Blood sugar is normal. Liver enzymes and markers, bone metabolism, fats and cholesterol, kidney functions, and cell counts and indices are all normal.

Urine Analysis: Normal

Lipid Profile 6: See separate report.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
		Secretropin	3 pumps at bed time as directed.		
		EC-PRO w/___mg Testosterone	½ gram vaginally each night.		
		Progesterone 100mg			1 cap
		Armour Thyroid ___mg	1 tablet		
		Ultranutrient	2 caps		2 caps
		DHEA 25mg			1 cap
		Pregnenolone 30mg/cap			2 caps
		Cognitive Aminos	2 caps	2 caps	
		AD1 – Adrenal Support	1 cap		1 cap
		Ultra B w/ PQQ	1 cap		1 cap

Present Medication

Status	Medication	Dosage	Timing	Comments
OFF	Paxil	20	BID	
OFF	Premarin	0.625	QD	

Present Supplements

Status	Supplement	Dosage	Timing	Status	Supplement	Dosage	Timing

Anticipated Scheduled Visits

September 2015	P1521, CBC. Add Thyroid and Adrenal.

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MPQ

Every 30 days the patient returns this fillable form to us and we respond.

An efficient means of following the patient every month.

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Monthly
Program
Questions

Name: Date:

Please rate your relative improvement from the beginning of your treatment protocol to this date.

A	**Mental/psychological/emotional status.**	**Rate**	
1	I have noticed an increase in Mental Energy.	0 <	> 10 NA
2	My sleep has improved in ___quantity, ___quality,___ less interruption. .	0 <	> 10 NA
3	I am sleeping less and wake up feeling more refreshed.	0 <	> 10 NA
4	My over-all emotional status has improved.	0 <	> 10 NA
5	My memory has improved.	0 <	> 10 NA
6	My libido (sex drive) has increased.	0 <	> 10 NA
7	My erections have improved. (male)	0 <	> 10 NA
8	My orgasms have improved	0 <	> 10 NA
9	I have an increased sense of well-being.	0 <	> 10 NA
10	I feel calmer under stress.	0 <	> 10 NA
B	**Physical Status**		
1	I have generally more physical energy.	0 <	> 10 NA
2	When I exercise I have more energy and feel stronger.	0 <	> 10 NA
3	I can perform physically longer without the expected fatigue.	0 <	> 10 NA
4	My athletic performance has improved over-all.	0 <	> 10 NA
5	I recover faster after exercise.	0 <	> 10 NA
6	Joint aches and pains are less.	0 <	> 10 NA
7	My hair is growing faster.	0 <	> 10 NA
8	The color of my hair is darker.	0 <	> 10 NA
9	My nails are harder.	0 <	> 10 NA
10	Facial texture has improved.	0 <	> 10 NA
11	Wrinkles have decreased.	0 <	> 10 NA
12	Skin thickness has increased.	0 <	> 10 NA
13	The numbers of cold or illnesses I experience a year have decreased.	0 <	> 10 NA
14	Colds, flu-symptoms are less intense and last less time.	0 <	> 10 NA
F	**FEMALE**: First day of Last Menses: ____ - ____ - 201_	0 <	> 10 NA
Ω	**If you have had any injuries or are Post Surgical**		
	I have noticed that my injury/surgery is improving faster than expected.	0 <	> 10 NA
	Scars are lightening or reducing much faster now than in the past.	0 <	> 10 NA
	My surgeon has stated that I am healing faster than usual.	0 <	> 10 NA
	Joint or muscle pains from past injuries have improved.	0 <	> 10 NA
	My over-all improvement from the start of treatment to now is = ►	0 <	> 10
MD	**Psychological**		
MD	**Physiological**		
MD	**Physical**		

Please make your comments here about anything else we should know about your treatment experience:

The scoring is from base-line to the present.



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Name: Date: 4/30/16

Please rate your relative improvement from the beginning of your treatment protocol to this date.

		Rate			
A	**Mental/psychological/emotional status.**				
1	I have noticed an increase in Mental Energy.	0 <	8	> 10	NA
2	My sleep has improved in ___quantity, ___quality, ___ less interruption. .	0 <	8	> 10	NA
3	I am sleeping less and wake up feeling more refreshed.	0 <	8	> 10	NA
4	My over-all emotional status has improved.	0 <	8	> 10	NA
5	My memory has improved.	0 <	8	> 10	NA
6	My libido (sex drive) has increased.	0 <	8	> 10	NA
7	My erections have improved. (male)	0 <	8	> 10	NA
8	My orgasms have improved	0 <	8	> 10	NA
9	I have an increased sense of well-being.	0 <	8	> 10	NA
10	I feel calmer under stress.	0 <	8	> 10	NA
B	**Physical Status**				
1	I have generally more physical energy.	0 <	7	> 10	NA
2	When I exercise I have more energy and feel stronger.	0 <	7	> 10	NA
3	I can perform physically longer without the expected fatigue.	0 <	8	> 10	NA
4	My athletic performance has improved over-all.	0 <	8	> 10	NA
5	I recover faster after exercise.	0 <	8	> 10	NA
6	Joint aches and pains are less.	0 <	8	> 10	NA
7	My hair is growing faster.	0 <	NA	> 10	NA
8	The color of my hair is darker.	0 <	7	> 10	NA
9	My nails are harder.	0 <	NA	> 10	NA
10	Facial texture has improved.	0 <	7	> 10	NA
11	Wrinkles have decreased.	0 <	8	> 10	NA
12	Skin thickness has increased.	0 <	NA	> 10	NA
13	The numbers of cold or illnesses I experience a year have decreased.	0 <	8	> 10	NA
14	Colds, flu-symptoms are less intense and last less time.	0 <	8	> 10	NA
F	**FEMALE**: First day of Last Menses: ____ - ____ - 201_	0 <		> 10	NA
Ω	**If you have had any injuries or are Post Surgical**				
	I have noticed that my injury/surgery is improving faster than expected.	0 <	8	> 10	NA
	Scars are lightening or reducing much faster now than in the past.	0 <	8	> 10	NA
	My surgeon has stated that I am healing faster than usual.	0 <	NA	> 10	NA
	Joint or muscle pains from past injuries have improved.	0 <	NA	> 10	NA
	My over-all improvement from the start of treatment to now is = ▶	0 <	8	> 10	
MD	**Psychological**				
MD	**Physiological**				
MD	**Physical**				

Please make your comments here about anything else we should know about your treatment experience:

Continued decrease in frequency of anxiety. Continued improvement in quality and duration of sleep. Reduction in cronic joint pain.

*Please refer to email sent to gordon md@mill... on 4/8/16 subject: Clomid adjustment

SCANNED

Labs: March 2016 / Emailed ✓

RECEIVED MAY 12 2016 BB



Case History: 1*

32 y/o male (WN): Years of football followed by an intense assault in a bar.				
History	Sports Concussions	Assault w/o LOC	MVA w/o LOC	Slip and Fall w/o LOC
Symptoms	Depression	Fatigue	Mood Swings	Anxiety
Medication	~~Norco~~	~~Naprosyn~~		
Diagnoses	Hypogonadism 1°	Hypo-Vitaminosis D	Hyper-Cortisolemia	
Treatment				

Bozy.. I'll take the Bald Guy.. Now!





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ALLERGIES:

TBI

WN (33)
Lab Date: 08/06/2015

Clomid 50mg New: Q3D

Hormone Testing	Results	Range				2/23/2015
Growth Hormone		5ng/ml*				0.07 LN
Somatomedin C (IGF-1)	182.0 LN	> 200 ng/ml*				242 N
IGF BP-3	5300 N	4000 ng/ml*				5700 N
DHEA-S	699.6 H	~255 ug/dl*				322.9 HN
Testosterone Free*	13.28 N	~14 pg/ml*				10.8 LN
Testosterone Total*	580 LN	690 ng/ml*				517 LN
Dihydrotestosterone (DHT)	15.5 N	< 55 ng/Dl*				36.5 HN
Sex Hormone Binding Gb	28 N	< 45 pg/ml*				30 N
Estrone (E1)	<1 N	< 60 pg/ml*				21 N
Estradiol (E2)	51.5 HN	<25 pg/ml*				22.8 N
Progesterone		0.8ng/ml*				0.96 N
Pregnenolone*		110ng/dl*				56 LN
FSH		7 mIU/ml*				6.1 LN
LH*	18.1 H	5.1 mIU/ml				8.9 HN
Prolactin* (narcotics)		14 ng/ml*				18.2 H
Zinc*		95 mcg/dL*				73 LN
Insulin		< 25mIU/L				10.7 N
Vitamin D3		>60 ng/dl*				28 L
TSH		<2.5 mcu/ml*				2.26 N
T3, Free		> 2.5 pg/ml				3.0 N
T4, Free		> 1.5 ng/ml				1.5 N
rT3		80-250 pg/ml				105 N
T3/rT3 Ratio		>1.06				2.85 N
TPO		<35				NT
ACTH*		< 35pg/ml *				42.91 H
Cortisol*		< 15 ug/dl				22.1 H

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Dissection of results:

Warning: Patient Benefits are achieved only upon use of new knowledge on laboratory interpretations.

Normal is the Median.
Low Normal is below the median.
High Normal is above the median.
LOW is below the range.
HIGH is above the range.

Active	Diagnosis	Status	Doctor	Phone	ICD-10
2004	Contact Sports w/ Concussions				
2004	Assault w/o LOC				
2004	Hydrocephalia 2nd assault				
	MVA w/o LOC				
2014	Left Hip surgery.				
2014	Slip and fall w/o LOC				
2014	Blunt Head Trauma w/o LOC				
2014	Post-Concussion Syndrome				
2015	Low Free Testosterone		Mark L. Gordon, MD	818.990.1166	
2015	ELEVATED Prolactin		Mark L. Gordon, MD	818.990.1166	
2015	Hypovitaminosis D		Mark L. Gordon, MD	818.990.1166	
2015	Hypercortisolemia		Mark L. Gordon, MD	818.990.1166	

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Normal

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ALLERGIES:

TBI

WN (33)
Lab Date: 08/06/2015

Chemistry Profile	Result	Range				2/23/2015
Glucose		< 100mg/dl				89
Sodium (NA)		133-149 meq/L				145
Potassium(K)		3.5 – 5.5 meq/L				4.8
Chloride (Cl)		96-108 meq/L				104
Iron (Fe)		35-200 mcg/L				NT
LIVER TESTING						Normal
SGOT		< 35 U/L				24
SGPT		< 38 U/L				33
Total Protein		6 – 8.4 gm/dl				7.0
Albumin		3.2 – 4.8 gm/dl				4.8
Globulin		2.0 – 3.7 gm/dl				2.2
Alkaline Phosphatase		30-125 U/L				63
Lactose Dehydrogen		80 – 225 U/L				178
GGTP		2 – 60 mg/dl				53
Total Bilirubin		0.1 – 1.2 mg/dl				0.4
BONE, JOINTS						*Normal*
Calcium (Ca)		8.4 – 10.8 mg/dl				9.7
Phosphorus		2.3- 5 mg/dl				
Uric Acid		2.5 – 6.8 mg/dl				5.2
Magnesium (Mg)		1.5 – 3.0 mg/dl				2.0
LIPIDS						*Normal*
Triglycerides (FAT)		<162 mg/dl				97
Cholesterol		< 200 mg/dl				213 H
HDL (Good)		>45 mg/dl				60
LDL (Bad)		<100 mg/dl				134
Cardiovascular Risk		¼ risk				3.55 ☺
RENAL FUNCTION						*Normal*
Blood Urea Nitrogen		6 – 25 mg/dl				15
Creatinine		< 1.0 mg/dl				0.8
GFR						119
BLOOD COUNT		0 – 20 mm/hr				*Normal*
ESR		4.0 – 10.8 x10^3				1
WBC		4.0 – 5.4 x 10^6				5.5
RBC		13 – 17 gm/dl				5.17
Hemoglobin		39 – 52%				16.1
Hematocrit		80 – 99 fL				47.8
MCV		45 – 75%				92
Granulocytes		20 – 50%				51.3
Lymphocytes		0-8%				40.3
Eosinophils		Normal				1.7
Urine Analysis		< 100mg/dl				NT

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Provocative Testing

Within 24 to 48hrs the patient's response to the injection can predict the anticipated benefits from increased levels of testosterone.

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Provocative Testosterone Testing Questionnaire

PLEASE READ: The safest and most expeditious manner to know how well you will do on your protocol is with a small trial dose of our blended testosterone. This is a VERY IMPORTANT test that we are doing for your benefit. You will receive or give yourself an injection of testosterone and we will follow-up with you once you return this paper to us.

Printed Name (above)	Today's Date (above)
The patient received: [10] **[20]** [30] [40] [50] **[60]** mg of a Testosterone Cypionate/Propionate blend.	Please return this Questionnaire to us between 5-7 days after your injection: / /

[___] Self-injection class [___] Abdomen [___] Lt Deltoid [___] Rt Deltoid [___] Lt Gluteus [___] Rt Gluteus

		Enter a number from 1 to 10
A	I noticed an improvement in my mental energy?	
B	I noticed an improvement in my emotional status?	
C	My cognition improved?	
D	My sense of well-being improved?	
E	My attention or focus improved?	
F	My libido (sex drive) increased?	
G	My sleep improved?	
H	I awoke feeling more rested?	
I	Previous body aches improved?	
J	Previous Joint pain improved?	
K	My exercise ability improved?	
M	I recovered faster from my exercise?	
N	**The benefits from the injection stopped in how many days?**	

Did you experience anything else you would like to tell us about?

Males 60mg blended Testosterone

Please email this to reception@millenniumhealthcenters.com or fax to 818-990-2841.

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ALLERGIES:

TBI

WN (33)
Lab Date: 08/06/2015

Dear Nathan,

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; Low-normal pattern. We are seeing this occur with the increase in testosterone levels. It tends to level off in time. If there is a need we will use Secretropin. DHEA-s is the precursor to Testosterone and Estrogens and is High. This is not an issue unless there is acne or oily skin. DHEA-s is protective to the heart and brain and improves mood (depression). The important Free testosterones is normal with a low-normal Total Testosterone. DHT is normal. Sex Hormone Binding is normal. This pattern is good. Estrone is normal with a high-normal Estradiol LH has increased as the cuase for your improved Testosterone production.

Chemistry Profile:

We will review your protocol when we have your labs in.

Verify	Status	Product	Morning	Afternoon	Evening
Discuss	**Start**	Secretropin	2 sprays a night.		
Change	**ON**	Clomid 50mg	Every 3rd Day = C xx C xx C xx C xx C		
√	**ON**	Ultranutrient	2 caps		2 caps
√	**ON**	DHEA 25mg			1 cap
√	**ON**	Pregnenolone 30mg			2 caps
√	**ON**	Cognitive Aminos	2 caps	2 caps	
√	**ON**	AD1 – Adrenal support (1 bottle)	1 cap		1 cap
√	**ON**	Ultra B-complex w/ PQQ	1 cap		1 cap
√	**ON**	Vitamin D3 10,000	1 cap		
√	**ON**	Mineral 650	1 cap		1 cap
Increase	**ON**	Zinc Citrate	2 cap		2 cap
Discussed	**NC**	DL-Phenyalanine	2 caps	2 caps	2 caps.

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
	ON	Medical Marijuana	10mg	QD	
	OFF	Norco	10mg	3QD	Stopped Jan 10th.
	OFF	Naproxen	500mg	2QD	

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing
	ON	Fish Oil	600mg	QD		ON	Cod Liver Oil	300mg	QD
	ON	Vitmain D	6000iu	QD		ON	Brazil Nuts		5QD

Follow-up and Lab Services

Jan 2016	P1520, Prolactin, Vitamin D, and Cortisol.

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Clomiphene increases free testosterone levels in men with both secondary hypogonadism and erectile dysfunction: who does and does not benefit? International Journal of Impotence Research (2003) 15, 156–165. AT Guay1*, J Jacobson, JB Perez, MB Hodge and E Velasquez, Center for Sexual Function, Peabody, Massachusetts, USA

- Hypogonadism produced by functional suppression of pituitary gonadotropins has been shown to correct with clomiphene citrate, with a modest effect on sexual function.
- Men with anxiety-related disorders responded best with normalization of testosterone.



Case History:2

37 y/o Male (GI): **Denies history of any head or body trauma.**				
History	NONE	? Amnesia ?		
Symptoms	Depression	Poor Libido	Seasonal Allergies	Anxiety
Medication	Flonase			
Diagnoses	Central Hypogonadism	Hyper-prolactinemia	Hypo-Vitaminosis D	Hyper-cortisolemia
Treatment				





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ALLERGIES:

TBI

G I l (37)
Lab Date: 02/13/2015

Testosterone:

Hormone Testing	Results	Range				
Growth Hormone	4.59 N	5ng/ml*				
Somatomedin C (IGF-1)	466 N	> 200 ng/ml*				
IGF BP-3	4800 N	4000 ng/ml*				
DHEA-S*	204.5 LN	245 ug/dl*				
Testosterone Free*	8.12 LN	14 pg/ml*				
Testosterone Total*	274.5 L	690 ng/ml*				
Dihydrotestosterone (DHT)	62.9 H	< 30 ng/Dl*				
Sex Hormone Binding Gb	11.25 N	< 45 pg/ml*				
Estrone (E1)	11 N	< 60 pg/ml*				
Estradiol (E2)	23.83 N	25 pg/ml*				
Progesterone	0.673 N	0.8ng/ml*				
Pregnenolone*	9 LN	110 ng/dl*				
FSH	4.18 LN	7 mIU/ml*				
LH*	3.26 LN	5.1 mIU/ml				
Prolactin*	16.8 HN	14 ng/ml*				
Zinc	78 LN	95 mcg/dL*				
Insulin	2.8 N	< 30mIU/L				
Vitamin D3	26 L	60 ng/dl*				
TSH	2.25 N	<2.5 mcu/ml*				
T3, Free	3.5 N	> 2.5 pg/ml				
T4, Free	1.31 LN	> 1.5 ng/ml				
rT3	123 N	0-350 pg/ml				
T3/rT3 Ratio	2.8 N	>1.06				
TPO	NT	<35				
ACTH	22.79	< 35pg/ml *				
Cortisol	14.8 HN	< 15 ug/dl				

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Status	Doctor	Phone	ICD-10
Hx	Depression (on-set?)				
Hx	Libido				
Hx	Seasonal Allergies				
2015	Central Hypogonadism	3°	Mark L. Gordon, M.D.	818.990.1166	
2015	Hypovitaminosis D		Mark L. Gordon, M.D.	818.990.1166	
2015	Hypercortisolemia		Mark L. Gordon, M.D.	818.990.1166	
R/O	Prolactinoma need MRI		Mark L. Gordon, M.D.	818.990.1166	

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Effect of Prolactin on the Expression of Luteinizing Hormone Receptors during Cell Differentiation in Cultured Rat Granulosa Cells

Takashi Hirakawa, Takashi Minegishi, Mari Tano, Takashi Kameda, Hiroshi Kishi, Yoshito Ibuki, Tetsuya Mizutani, and Kaoru Miyamoto 1998/2013

- Chronic and transient hyperprolactinemia has been associated with luteal phase dysfunction.
- Recently, evidence has emerged to suggest that elevated PRL may exert its anti-gonadal effects through reducing available ovarian LH receptors.



Normal

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G: ı, I
Lab Date: 02/13/2015

Chemistry Profile	Result	Range				
Glucose	81	< 100mg/dl				
Sodium (NA)	142	133-149 meq/L				
Potassium(K)	4.2	3.5 – 5.5 meq/L				
Chloride (Cl)	105	96-108 meq/L				
Iron (Fe)	NT	35-200 mcg/L				
LIVER TESTING	Normal					
SGOT	22	<34 U/L				
SGPT	36	< 33 U/L				
Total Protein	6.9	6 – 8.4 gm/dl				
Albumin	4.6	3.2 – 4.8 gm/dl				
Globulin	2.3	2.0 – 3.7 gm/dl				
Alkaline Phosphatase	55	30-125 U/L				
Lactose Dehydrogen	146	80 – 225 U/L				
GGTP	16	2 – 60 mg/dl				
Total Bilirubin	0.4	0.1 – 1.2 mg/dl				
BONE, JOINTS	*Normal*					
Calcium (Ca)	9.5	8.4 – 10.8 mg/dl				
Phosphorus		2.3- 5 mg/dl				
Uric Acid	4.8	2.5 – 6.8 mg/dl				
Magnesium (Mg)	2.1	1.5 – 3.0 mg/dl				
LIPIDS	*Normal*					
Triglycerides (FAT)	77	<162 mg/dl				
Cholesterol	172	< 200 mg/dl				
HDL (Good)	77	>45 mg/dl				
LDL (Bad)	80	<100 mg/dl				
Cardiovascular Risk	2.23	¼ risk				
RENAL FUNCTION	*Normal*					
Blood Urea Nitrogen	22	6 – 25 mg/dl				
Creatinine	1.1	< 1.0 mg/dl				
GFR	80					
BLOOD COUNT	*TE*					
ESR		0 – 20 mm/hr				
WBC		4.0 – 10.8 $x10^3$				
RBC		4.0 – 5.4 $x\ 10^6$				
Hemoglobin		13 – 17 gm/dl				
Hematocrit		39 – 52%				
MCV		80 – 99 fL				
Granulocytes		45 – 75%				
Lymphocytes		20 – 50%				
Eosinophils		0-8%				
Urine Analysis	NT	Normal				

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ALLERGIES:

TBI

G: I:

Lab Date: 02/13/2015

Dear |,

Welcome to the practice. This is the preliminary part of our process, the report. It is followed by a handbook that will be sent to you by Federal express. In the meantime, we can arrange for a Skype call to review your lab results and what they mean in terms of treatment. Then we will truly begin the process.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; normal pattern. DHEA-s is the precursor to Testosterone and Estrogens and is low-Normal. The important Free testosterones is low-normal with a low Total Testosterone. DHT is high-normal (5-AR). Sex Hormone Binding is normal. Estrogens are normal with a normal progesterone. The neuroprotective Pregnenolone is low-normal. FSH and LH reflect either the body's ability to make hormones from the testes/ovaries when elevated, or low when on supplementation or after TBI. Both FSH and LH are low-normal in light of a low Testosterone. Prolactin is a marker for hypothalamic-pituitary functioning; is High-normal suggesting investigation for a pituitary adenoma (prolactinoma). Zinc is low-normal. Insulin is normal for a fast level. Vitamin D is low. At this point the brain-thyroid system is normal. ACTH is produced by the pituitary to produce Cortisol from the adrenal glands; Cortisol is high-normal.

Chemistry Profile: Blood sugar is Normal. Liver functions and markers, bone metabolism, fats and cholesterol, and kidney functions.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	Discuss	Testosterone	Provocative testing 60mg then 0.2cc(40mg) every 3rd day.		
	Discuss	Clomid 50mg	Discuss:		
	Start	Ultranutrient	2 caps		2 caps
	Start	DHEA 25mg			1 cap
	Start	Pregnenolone 30mg			2 caps
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	B complex w/ PQQ	1 cap		1 cap
	Start	AD1 Adrenal Support (1 bottle)	1 cap		1 cap

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
		Flonase		2QD	

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing
		Fish Oil							

Anticipated Scheduled Visits

Needs MRI of Pituitary	R/o Prolactinoma.

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TBI

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Lab Date: 02/13/2015

Additional Notes:

02/13/2015	Remote Blood Draw. California
02/26/2015	Emailed patient about TBI history and supplementatl use of any form of hormones. Will discuss MRI and Prolactinoma. Final Report sent and Fed X TBI Handbook. Office or skype call.
	SKYPE CALL:

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI

Additional Files to Handbook or email to patient if a follow-up office visit.

	Gout		PLAC Test		Estrogen Dominance
	Polycythemia		Vitamin D Deficiency		Metabolic Syndrome.
XX	Traumatic Brain Injury		TPO - Thyroiditis		PSA-Low Testosterone

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Case History:3

68 y/o Female (CT): Motor vehicle accident and then PTSD from Home Invasion.

History	MVA w/o LOC	Home Invasion	PTSD 2nd to TBI	
Symptoms	Anxiety	Depression	Panic/Phobia	
Medication	Vicodin			
Diagnoses	1° Ovarian Failure	Adult Growth Hormone Dif.	Hypo-Vitaminosis D	Hyper-Cortisolemia
Treatment				





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ALLERGIES:

TBI

C T (68)

Lab Date: 2/17/2015

LNMP: ??

Hormone Testing	Results	Range
Growth Hormone*	0.76 LN	5ng/ml*
Somatomedin C (IGF-1)*	115 LN	> 200 ng/ml*
IGF BP-3*	4000 N	>4000 ng/ml*
DHEA-S *	41.7 L	115 ug/dl*
Estrone (E1)	6.0 N	< 200 pg/ml*
Estradiol (E2) *	<5.0 L	90 pg/ml*
Progesterone	0.25 L	14ng/ml*
Pregnenolone	7.0 LN	110ng/dl*
EP Ratio	21 N	< 250
Testosterone Free*	0.09 L	2-4 pg/ml*
Testosterone Total*	6 LN	44 ng/ml*
Dihydrotestosterone (DHT)	6.5 N	< 30 ng/Dl*
Sex Hormone Binding Gb	40 N	< 75 pg/ml*
FSH*	38.3 H	7 mIU/ml*
LH*	15.3 H	5.1 mIU/ml
Prolactin	4.3 N	14 ng/ml*
Zinc*	68 LN	95 mcg/dL*
Insulin	8.3 N	< 30mIU/L
Vitamin D3*	30 L	60 ng/dl*
TSH	1.13 N	<2.5 mcu/ml*
T3, Free	3.0 N	> 2.5 pg/ml
T4, Free	1.24 LN	> 1.5 ng/ml
rT3	198 HN	80-250 pg/ml
T3/rT3 Ratio	1.51 N	>1.06
TPO	NT	<35xx
ACTH	6.2 N	35pg/ml *
Cortisol*	15.9 HN	< 15 ug/dl

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Status	Doctor	Phone	ICD-10
1993	MVA TBI?				
2014	PTSD Home invasion				
2015	Adult GH Deficiency	??			
2015	Primary Ovarian Failure	1°			
2015	Low Estrogens		Mark L. Gordon, M.D.	818.990.1166	
2015	Low Testosterone/DHEA				
2015	Hypovitaminosis D				
2015	Hypercortisolemia	1°			

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Elevated Luteinizing Hormone Expression Colocalizes With Neurons Vulnerable to Alzheimer's Disease Pathology. Journal of Neuroscience Research 70:514–518 (2002) Richard L. Bowen, et al. Voyager Pharmaceutical Corporation, Raleigh, North Carolina Institute of Pathology, Case Western Reserve University, Cleveland, Ohio Dept of Psychiatry and Neurogenetics, University of Western Australia, Perth, Australia.

- In individuals with Alzheimer's disease (AD), there is a two-fold elevation in the serum concentrations of the gonadotropins, luteinizing hormone (LH), and follicle stimulating hormone compared to age-matched controls.
- Whether this plays a role in disease pathogenesis is unclear. Nonetheless, gonadotropins are known to cross the blood brain barrier and the highest density of gonadotropin
- receptors in the brain are found within the hippocampus.
- We report for the first time the localization of LH in the cytoplasm of pyramidal neurons. In addition, we find a significant increase in LH in the cytoplasm of pyramidal neurons and neurofibrillary tangles of AD brain compared to age-matched control brain. Whereas the functional consequences of increased neuronal LH are unknown, it is notable that LH is primarily localized to those neurons that are known to be vulnerable to Alzheimer's disease-related neurodegeneration. Elevated serum and cortical neuron levels of LH, coupled with the decline in sex steroid production, could play important roles in the pathogenesis of AD.



Normal

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ALLERGIES:

TBI

C Γ
Lab Date: 2/17/2015

Chemistry Profile	Result	Range				
Glucose	110 H	65-100mg/dl				
Sodium (NA)	142	133-149 meq/L				
Potassium(K)	4.0	3.5 – 5.5 meq/L				
Chloride (Cl)	97	96-108 meq/L				
Iron (Fe)		35-200 mcg/L				
LIVER TESTING	Normal					
SGOT	18	0- 34 U/L				
SGPT	16	< 33 U/L				
Total Protein	6.9	6 – 8.4 gm/dl				
Albumin	4.5	3.2 – 4.8 gm/dl				
Globulin	2.4	2.0 – 3.7 gm/dl				
Alkaline Phosphatase	73	30-125 U/L				
Lactose Dehydrogen	143	80 – 225 U/L				
GGTP	10	2 – 60 mg/dl				
Total Bilirubin	0.7	0.1 – 1.2 mg/dl				
BONE, JOINTS	*Normal*					
Calcium (Ca)	9.9	8.4 – 10.8 mg/dl				
Phosphorus		2.3- 5 mg/dl				
Uric Acid	3.8	2.5 – 6.8 mg/dl				
Magnesium (Mg)	2.0	1.5 – 3.0 mg/dl				
LIPIDS	*Normal*					
Triglycerides (FAT)	95	<162 mg/dl				
Cholesterol	206	< 200 mg/dl				
HDL (Good)	83	>45 mg/dl				
LDL (Bad)	104	<100 mg/dl				
Cardiovascular Risk	2.48 ☺	¼ risk☺☺☺☺				
RENAL FUNCTION	*Normal*					
Blood Urea Nitrogen	20	6 – 25 mg/dl				
Creatinine	0.5	< 1.0 mg/dl				
GFR	176					
BLOOD COUNT	*Normal*					
ESR	3.0	0 – 20 mm/hr				
WBC	7.6	4.0 – 10.8 $x10^3$				
RBC	4.48	4.0 – 5.4 $x\ 10^6$				
Hemoglobin	13.4	12 – 16 gm/dl				
Hematocrit	41.1	36 – 48%				
MCV	92	80 – 99 fL				
Granulocytes	56.5	45 – 75%				
Lymphocytes	32.2	20 – 50%				
Eosinophils	1.5	0-8%				
Urine Analysis		Normal				

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ALLERGIES:

TBI

C T
Lab Date: 2/17/2015

Dear Terresa,

Welcome to the practice. This is the preliminary part of our process, the report. It is followed by a handbook that will be sent to you by Federal express. In the meantime, we can arrange for a Skype call to review your lab results and what they mean in terms of treatment. Then we will truly begin the process.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; LOW-Normal. DHEA-s is the precursor to Testosterone and Estrogens and is low. Estrogens and progesterone are both low to low-normal with a normal Estrogen Progesterone Ratio (EP Ratio). The neuroprotective Pregnenolone is Low-normal. The important free testosterone is low with a low-normal Total Testosterone. DHT and Sex Hormone Binding protein are normal. FSH and LH reflect the brains regulation of the sex hormones and they are elevated meaning that the body is trying to get your body to produce more DHEA, Estrogens, Testosterone and Progesterone. This pattern is seen in Primary Ovarian Failure when the ovaries stop making hormones or if surgical menopause was induced. Prolactin is normal. Zinc is low-normal. Vitamin D is Low. Overall, your Thyroid hormone panel suggests that you are producing a normal amount of hormone to run your body. ACTH is the hormone from the brain that stimulates your adrenal glands (above the kidneys) to make Cortisol, the hormone associated with our adaptation to stress which is high-normal.

Chemistry Profile: Blood sugar is elevated if it was a fasting blood sample otherwise it is acceptable as after eating? Liver functions and markers, bone metabolism, fats and cholesterol, kidney functions, and cell counts are all within acceptable normal ranges.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	Start	Secretropin	3 pumps at bed time as directed.		
	Start	ECP with Testosterone	(0.2mg-E2/2.0mg-E3/100mg-Prog/2mg-T) ½ gram a night. (Last PAP)		
	Start	Ultranutrient	2 caps		2 caps
	Start	DHEA 25mg			1 cap
	Start	Pregnenolone			1 cap
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	Ultra B Complex with PQQ	1 cap		1 cap
	Start	Vitamin D 5,000IU	1 cap		
	Start	Adrenal Support (1 bottle only)	1 cap		1 cap

Present Medication

Medication	Dosage	Timing	Comments
Vicodin		QD	

Present Supplements

Status	Supplement	Dosage	Timing	Status	Supplement	Dosage	Timing
ON	MSM	2000mg	QD	ON	Probiotics	50mg	QD
ON	Omega 3 Oil		QD	ON	Vitamin C & D	3000mg	QD

Anticipated Scheduled Visits

Initial dispensing visit	Review of lab results, Physical exam, products dispensed

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ALLERGIES:

TBI

C| T
Lab Date: 2/1 7/2015

Additional Notes:

02/17/2015	Remote Blood Draw
02/26/2015	Email report. Prepare Handbook.
	Skype Call:

X	**Mark L. Gordon, M.D., AAFP,ABAAM**		
	Medical Director,		
	Millennium Health Group		
	gordonmd@millenniumhealthcenters.com		

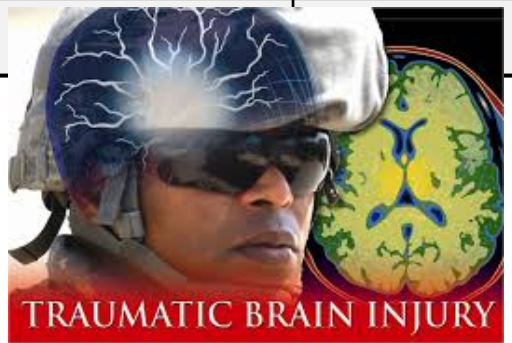
You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
Skype: **MLGordonTBI**

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Case History:4*

45 y/o Male (BM): Blast trauma in Gulf War, developed CFS and FM.				
History	Concussion w/o LOC	Blast Trauma w/ LOC	Chronic Fatigue Synd	Fibromyalgia
Symptoms	Fatigue	Arthralgia	Anxiety	Depression
Medication	Alprazolam	Fluoxetine	Oxycodone	GABApentin
	Tramadol	Meclizine	Loratadine	Simvastatin 40mg QAM
Diagnoses	Hypogonadism			
Treatment				





Statins

- Can interrupt the entire Cholesterol Cascade and lead to decreased production of Pregnenolone, Progesterone and Cortisol on one limb.
- DHEA, Testosterone, Estradiol and Estrone on the other.
- Vitamin D and CO-Q10 are affected too.

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BM (46)
Lab Date: 12/28/2015

Testosterone: 12/25/2015 0.2cc (40mg) Q3D

Hormone Testing	Results	Range			5/13/15	2/24/15
Growth Hormone		5ng/ml*				<0.03 LN
Somatomedin C (IGF-1)*	294 N	> 200 ng/ml*			288 N	155 LN
IGF BP-3	5700 N	4000 ng/ml*			5600 N	5700 N
DHEA-s	480 H	245 ug/dl*			410.7H	181.8 LN
Testosterone Free**	19.66 HN	14 pg/ml*			10.18 LN	2.75 L
Testosterone Total**	667 N	690 ng/ml*			375 LN	117 L
Dihydrotestosterone (DHT)	27.4 N	< 55 ng/Dl*			54.6 N	36.4 N
Sex Hormone Binding Gb	15 N	< 45 pg/ml*			16 N	18 N
Estrone (E1)	37.0 N	< 60 pg/ml*			30 N	20 N
Estradiol (E2)	77.7 H	25 pg/ml*			51 H	17.2 N
Progesterone		0.8ng/ml*				0.41 LN
Pregnenolone**		110 ng/dl*				11 L
FSH*		7 mIU/ml*				2.9 LN
LH*		5.1 mIU/ml				3.6 LN
Prolactin		14 ng/ml*				13.7 N
Zinc		95 mcg/dL*				65 LN
Insulin* **	16.2 N	< 25mIU/L				94.8 H
Vitamin D3**		60 ng/dl*				37 LN
TSH		<2.5 mcu/ml*				2.34 N
T3, Free		> 2.5 pg/ml				3.4 N
T4, Free**		> 1.5 ng/ml				0.95 LN
rT3		90-350 pg/ml				156 N
T3/rT3 Ratio		>1.06				2.17 N
TPO		<35				NT
ACTH		< 35pg/ml *				12.6 N
Cortisol		< 15 ug/dl				6.7 N

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Status	Doctor	Phone	ICD-10
1985	Fell from 25feet onto gym floor, occiput, age 16.				
1987	Concussion w/o LOC - Sports				
1991	Blast Trauma w/ LOC <1 min.				
1991	Gas Attack – LOC for 45min				
?1990's	CFS-FM maybe for 20+ years (mom+++)				
2015	Low IGF-1 (Insulin?)		Mark L. Gordon, M.D.	818.990.1166	
2015	Central Hypogonadism	3°	Mark L. Gordon, M.D.	818.990.1166	
Resolved	Hyperinsulinemia (Insulin Resistance)		Mark L. Gordon, M.D.	818.990.1166	
2015	Hypovitaminosis D3		Mark L. Gordon, M.D.	818.990.1166	

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166

Inflammation of the Hypothalamus Leads to Defective Pancreatic Islet Function

. J. Biol. Chem. 2011, 286:12870-12880. Vivian C. Calegari et al, Laboratory of Cell Signaling and the Departments of Physiology and Biophysics and Nursing, University of Campinas, Sao Paulo, Brazil, and the Department of Surgery, University of Sao Paulo-Ribeirao Preto, Sao Paulo, Brazil



- The autonomic nervous system can either stimulate insulin secretion through muscarinic receptors or inhibit Beta-cell function, through alpha-adrenergic signaling.
- Many of the neural inputs that control Beta-cell activity are generated in the hypothalamus.
- Thus, the autonomic signals generated in concert with hypothalamic inflammation can impair pancreatic islet function, a phenomenon that may explain the early link between obesity and defective insulin secretion.
- Metabolic Syndrome = Insulin Resistance, Type II DM



Abnormal

Pattern recognition

1) Blast Trauma
2) Hypogonadism
3) Elevated Insulin
4) Elevated Fats
5) +/- Hyperglycemia
6) Insulin Resistance

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ALLERGIES:

TBI

Bı , M
Lab Date: 2/24/2015

Chemistry Profile	Result	Range				
Glucose	108 H	< 100mg/dl				
Sodium (NA)	142	133-149 meq/L				
Potassium(K)	3.8	3.5 – 5.5 meq/L				
Chloride (Cl)	102	96-108 meq/L				
Iron (Fe)		35-200 mcg/L				
LIVER TESTING	Normal					
SGOT	25	<34 U/L				
SGPT	30	< 33 U/L				
Total Protein	7.5	6 – 8.4 gm/dl				
Albumin	4.8	3.2 – 4.8 gm/dl				
Globulin	2.7	2.0 – 3.7 gm/dl				
Alkaline Phosphatase	62	30-125 U/L				
Lactose Dehydrogen	201	80 – 225 U/L				
GGTP	23	2 – 60 mg/dl				
Total Bilirubin	0.6	0.1 – 1.2 mg/dl				
BONE, JOINTS	*Normal*					
Calcium (Ca)	9.9	8.4 – 10.8 mg/dl				
Phosphorus		2.3- 5 mg/dl				
Uric Acid	5.8	2.5 – 6.8 mg/dl				
Magnesium (Mg)	2.1	1.5 – 3.0 mg/dl				
LIPIDS	*Abnormal*					
Triglycerides (FAT)	202 H	<162 mg/dl				
Cholesterol	235	< 200 mg/dl				
HDL (Good)	49	>45 mg/dl				
LDL (Bad)	146	<100 mg/dl				
Cardiovascular Risk	4.7 H	1+ risk ☹				
RENAL FUNCTION	*Abnormal*					
Blood Urea Nitrogen	28	6 – 25 mg/dl				
Creatinine	1.1	< 1.0 mg/dl				
GFR	77					
BLOOD COUNT						
ESR	3	0 – 20 mm/hr				
WBC	7.7	4.0 – 10.8 $x10^3$				
RBC	5.01	4.0 – 5.4 $x 10^6$				
Hemoglobin	13.7 LN	13 – 17 gm/dl				
Hematocrit	42.3	39 – 52%				
MCV	84 LN	80 – 99 fL				
Granulocytes	57	45 – 75%				
Lymphocytes	34.7	20 – 50%				
Eosinophils	2.4	0-8%				
Urine Analysis		Normal				

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ALLERGIES:

TBI

B M

Lab Date: 2/24/2015

Dear M

Welcome to the practice. This is the preliminary part of our process, the report. It is followed by a handbook that will be sent to you by Federal express. In the meantime, we can arrange for a Skype call to review your lab results and what they mean in terms of treatment. Then we will truly begin the process.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; low-normal pattern. DHEA-s is the precursor to Testosterone and Estrogens and is low-normal. The important Free testosterones is low as is the Total Testosterone. DHT is high-normal. Sex Hormone Binding is normal. Estrogens are normal with low-normal progesterone. The neuroprotective Pregnenolone is low. FSH and LH reflect either the body's ability to make hormones from the testes/ovaries when elevated, or low with supplementation or TBI. FSH and LH are low when they should be elevated to make testosterone. This is a clear issue of interruption of production by brain trauma/Statin. Prolactin is a marker for hypothalamic-pituitary functioning; normal. Zinc is low normal. Insulin is HIGH (Insulin Resistant diabetes). Vitamin D is low-normal. At this point the brain-thyroid system is normal. ACTH is produced by the pituitary to produce Cortisol from the adrenal glands; both normal.

Chemistry Profile: Blood sugar is elevated. Liver functions and markers, bone metabolism, and cell counts are all within acceptable normal ranges. Triglycerides and cholesterol are elevated which can be due to the very high insulin levels. Kidney functions are good but possible low fluid intake – Dehydration. Changes in red cells might be a heralding iron deficiency anemia.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	Start	Secretropin	3 pumps at bed time as directed.		
	Start	Testosterone	0.2cc(40mg) every 3rd day,.		
	Start	Ultranutrient	2 caps		2 caps
	Start	DHEA 25mg			1 cap
	Start	Pregnenolone 30mg			1 caps
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	Vitamin D3 10,000 IU	1 cap		
	Start	Ultra B-Complex w/ PQQ	1 cap		1 cap
	Start	Chromate	1 cap		1 cap

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
	ON	Oxycodone	10 mg	PRN	
	ON	Naproxen	550 mg	3QD	
	ON	Alprazolam	0.5 mg	PRN	
	ON	Fluoxetine	80 mg	QD	
	STOPPED	Simvastatin	40 mg	QD	
	ON	Loratadine	10 mg	QD	
	ON	Medizine	25 mg	PRN	
	ON	Gabapentine	300 mg	2QD	
	ON	Tramadol	50 mg	3QD	

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing
	ON	Glucosamine	1500 mg	2QD		ON	MegaMen		
	ON	Potassium + Calcium							

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ALLERGIES:

TBI

B M

Lab Date: 2/24/2015

Anticipated Scheduled Visits

Initial dispensing visit	Review of lab results, Physical exam, products dispensed

Additional Notes:

02/24/2015	Remote Blood Draw
03/05/2015	Final Report sent and Fed X TBI Handbook
	SKYPE CALL: Review history, laboratory results and treatment protocol.

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Case History:5

42 y/o Male (SS)*: Severe Blast Trauma 20+ years earlier.

History	TBI w/LOC in Coma 8 wks.	Seizure Disorder	Migraines	Neurogenic Bladder
Symptoms	Depression	Speech impediment	Wheel-chair Dependent	Cognitive Deficit
Medication	Valproic Acid			
Diagnoses	Hypogonadism Central	Hypo-Vitaminosis D	Subclinical Hypothyroid	Hyperuricemia
Treatment				



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ALLERGIES:

TBI

St , S
Lab Date: 11/18/2014 (43)

Hi Mark, We are the parents of SS! He seems to be taking all his supplements correctly! Thank you! We see good changes, like he works 3 days a week from one at the VA. He takes long walks that he couldn't make before.

He even makes deeper cognitive insightful statements then before. From our standpoint we wanted you to know he is doing better. Sincerely, The Parents.
3 weeks after starting protocol.

Testosterone:

Hormone Testing	Results	Range				
Growth Hormone	<0.03 L	5*ng/ml				
Somatomedin C (IGF-1)	138 LN	> 200 ng/ml*				
IGF BP-3	4300 N	4000 ng/ml*				
DHEA-S	229.5 HN	145 ug/dl*				
Testosterone Free	7.96 LN	14 pg/ml*				
Testosterone Total	405 LN	690 ng/ml*				
Dihydrotestosterone (DHT)	40.7 N	< 44 ng/Dl*				
Sex Hormone Binding Gb	35 N	< 45 pg/ml*				
Estrone (E1)	16 N	< 60 pg/ml*				
Estradiol (E2)	21.1 N	25 pg/ml*				
Progesterone	0.53 LN	0.8ng/ml*				
Pregnenolone	22 LN	110ng/dl*				
FSH	1.4 LN	7 mIU/ml*				
LH	2.8 LN	5.1 mIU/ml				
Prolactin	7.7 N	14 ng/ml*				
Zinc	81 N	95 mcg/dL*				
Insulin	10.2 N	< 30mIU/L				
Vitamin D3	30 L	>60 ng/dl*				
TSH	3.09 HN	<2.5 mcu/ml*				
T3, Free	3.0 N	> 2.5 pg/ml				
T4, Free	1.09 LN	> 1.5 ng/ml				
rT3	160 N	80-250 pg/ml				
T3/rT3 Ratio	1.875 N	>1.06				
TPO	NA	<35				
ACTH	33.06 N	< 35pg/ml *				
Cortisol	15.7 HN	< 15 ug/dl				

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Doctor	Phone	ICD-10
1992	TBI w/ LOC w/Coma 8wks			R40.2114
1992	Seizure disorder (1992)			
1992	Migraines			
1992	Neurogenic Bladder?			
2014	Hypogonadism - Central	Mark L. Gordon, M.D.	818.990.1166	E29.1
2014	Hypovitaminosis D	Mark L. Gordon, M.D.	818.990.1166	E55.9
2014	Subclinical Hypothyroidism	Mark L. Gordon, M.D.	818.990.1166	E03.9
2014	Hyperurecemia	Mark L. Gordon, M.D.	818.990.1166	

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Normal

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ALLERGIES:

TBI

S S

Lab Date: 11/18/2014

Chemistry Profile	Result	Range				
Glucose	88	< 100mg/dl				
Sodium (NA)	141	133-149 meq/L				
Potassium(K)	5.0	3.5 – 5.5 meq/L				
Chloride (Cl)	105	96-108 meq/L				
Iron (Fe)		35-200 mcg/L				
LIVER TESTING	Normal					
SGOT	22	<34 U/L				
SGPT	22	< 33 U/L				
Total Protein	7.5	6 – 8.4 gm/dl				
Albumin	4.3	3.2 – 4.8 gm/dl				
Globulin	3.2	2.0 – 3.7 gm/dl				
Alkaline Phosphatase	51	30-125 U/L				
Lactose Dehydrogen	159	80 – 225 U/L				
GGTP	7.0	2 – 60 mg/dl				
Total Bilirubin	0.4	0.1 – 1.2 mg/dl				
BONE, JOINTS	*Normal*					
Calcium (Ca)	9.3	8.4 – 10.8 mg/dl				
Phosphorus		2.3- 5 mg/dl				
Uric Acid	6.4 HN	2.5 – 6.8 mg/dl				
Magnesium (Mg)	2.1	1.5 – 3.0 mg/dl				
LIPIDS						
Triglycerides (FAT)	235 H	<162 mg/dl				
Cholesterol	217 H	< 200 mg/dl				
HDL (Good)	30 L	>45 mg/dl				
LDL (Bad)	140 H	<100 mg/dl				
Cardiovascular Risk	7.2	>1 risk				
RENAL FUNCTION	*Normal*					
Blood Urea Nitrogen	17	6 – 25 mg/dl				
Creatinine	1	< 1.0 mg/dl				
GFR	87	>60				
BLOOD COUNT	*Normal*					
ESR	1.0	0 – 20 mm/hr				
WBC	7.3	4.0 – 10.8 $x10^3$				
RBC	5.08	4.0 – 5.4 $x 10^6$				
Hemoglobin	15.2	13 – 17 gm/dl				
Hematocrit	45.2	39 – 52%				
MCV	89.0	80 – 99 fL				
Granulocytes	53.3	45 – 75%				
Lymphocytes	35.9	20 – 50%				
Eosinophils	1.5	0-8%				
Urine Analysis	NA	Normal				

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ALLERGIES:

TBI

S , S

Lab Date: 11/18/2014

Dear Scott,

Welcome to the practice. It is our goal to provide the highest in personalized interaction with each one of our patients'. This begins with the following report of your recent laboratory testing which looks for hormonal patterns that can identify Traumatic Brain Injury associated hormonal dysfunction. This is a screening process and more advanced laboratory testing might be required. In the future you will receive a comprehensive TBI Handbook that will explain in detail your labs and offer a treatment protocol. As of June 1, 2014, we no longer require an office visit to start treatment as per California AB 415.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; Low to Low-normal patterns. DHEA-s is the precursor to Testosterone and Estrogens and is High-Normal. This is not an issue as long as there is no acne or oily skin. The important Free testosterones is low-normal as is the Total Testosterone. DHT is high-normal. Sex Hormone Binding is normal. Estrogens are normal with low-normal progesterone. The neuroprotective Pregnenolone is low-normal. FSH and LH reflect the body's response to low testosterone when they are elevated. When they are low with a low testosterone level it suggests a dysregulation problem in the brain. Prolactin is a marker for hypothalamic-pituitary functioning; normal. Zinc is important in 300 processes in the body and is accepted as normal. Insulin is normal. Vitamin D is low and helps with inflammation and brain functions. As TSH elevates is stimulated the body to produce more T4. The elwevation in TSH with a low level of T4 suggests a dysregulation problem in the brain. ACTH is produced by the pituitary to produce Cortisol from the adrenal glands; both at margin of normal suggesting stress.

Chemistry Profile: Blood sugar is normal. Liver functions and markers, bone metabolism, kidney functions, and cell counts are all within acceptable normal ranges. Uric acid (Gout), Fats and cholesterol are elevated and we will discuss when we Skype

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	Start	Secretropin	4 pumps at bed time as directed.		
	Send	Testosterone	Send - Provocative testing 60mg		
	Start	Testosterone IM: 80TC/20TP	Inject 0.2cc(mg) every 3rd day.		
	Hold	Armour Thyroid 30mg	1 tablet		
	Start	Ultranutrient	2 caps		2 Caps
	Start	DHEA 25mg			1 cap
	Start	Pregnenolone 30mg			1 caps
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	B-Complex PQQ	1 cap		1 cap
	Start	Quercetine	2 caps		2 caps.
	Start	Vitamin D 10,000	1 cap		
	Start	B-12 Hydroxycobolamin	½ cc		½ cc
	Hold	Amantadine	100mg		
	Start	Sublingual Progesterone 5mg			5 drops.

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
9/29/2014	ON	Divalproex	500mg	2QD	Valproic acid/Depokote

Present Supplements

Verify	Status	Supplements	Dosage	Timing	Comments
2013	ON	MagniLife Urinary Incontinence Relief		2TID	

Anticipated Scheduled Visits

December 4, 2014	Review of lab results, Physical exam, products dispensed

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ALLERGIES:
TBI

S: S:
Lab Date: 11/18/2014

Additional Notes:

11/18/2014	Remote Blood Draw
12/01/2014	Final Report sent and Fed X TBI Handbook.
12/04/2014	SKYPE CALL: Placed on Depakote after 20+ years for migraines and not seizures. Wrestless leg syndrome.

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI

Additional Files to Handbook or email to patient if a follow-up office visit.

	Gout		PLAC Test		Estrogen Dominance
	Polycythemia		Vitamin D Deficiency		Metabolic Syndrome.
XX	Traumatic Brain Injury		TPO - Thyroiditis		PSA-Low Testosterone

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Case History:6

48 y/o Female (VS): **Motor Vehicle Accident with Flip and Roll.**				
History	MVA w/o LOC. Flip and Roll			
Symptoms	Depression Labile.	Agitation	Irritability	Cognitive Deficit.
Medication	None			
Diagnoses	Hyper-Prolactinemia	Hypo-Vitaminosis D	Low free Testosterone	
Treatment	Secretropin	ECPv w/2% Testosterone	DHEA 25mg QHS	Progesterone 100mg QHS
	Ultranutrient	Cognitive Aminos	Zinc Citrate	Saw Palmetto
	B-Complex w/PQQ			



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ALLERGIES:

TBI

V S

Lab Date: 1/26/2015

LNMP: 12/28/2014 (29th)

Hormone Testing	Results	Range
Growth Hormone	0.19 LN	5*ng/ml
Somatomedin C (IGF-1)	204 N	> 200 ng/ml*
IGF BP-3	4900 N	>4000 ng/ml*
DHEA-S*	174.4 LN	195 ug/dl*
Estrone (E1)	38 N	< 200 pg/ml*
Estradiol (E2)	181.3 HN	pg/ml*
Progesterone	6.85 N	ng/ml*
Pregnenolone	204 N	205ng/dl*
EP Ratio	32 N	< 250
Testosterone Free*	0.15 LN	2-4 pg/ml*
Testosterone Total	24 N	44 ng/ml*
Dihydrotestosterone (DHT)	24.9 N	< 30 ng/Dl*
Sex Hormone Binding Gb*	133 HN	< 75 pg/ml*
FSH	3.3 LN	7 mIU/ml*
LH	4.2 LN	5.1 mIU/ml
Prolactin*	24.6 H	14 ng/ml*
Zinc	81 LN	95 mcg/dL*
Insulin	17.5 N	< 30mIU/L
Vitamin D3*	29 L	60 ng/dl*
TSH	1.61 N	<2.5 mcu/ml*
T3, Free	2.6 N	> 2.5 pg/ml
T4, Free	1.27 LN	> 1.5 ng/ml
rT3	160 N	80-250 pg/ml
T3/rT3 Ratio	1.625 N	>1.06
TPO	NT	<35
ACTH	19 N	35pg/ml *
Cortisol	14.7 N	< 15 ug/dl

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Doctor	Phone	ICD-10
1988	Multiple MVA w/o LOC			
2015	Low Free Testosterone	Mark L. Gordon, M.D.	818.990.1166	
2015	Hyperprolactinemia	Mark L. Gordon, M.D.	818.990.1166	
2015	Low Testosterone	Mark L. Gordon, M.D.	818.990.1166	
2015	Hypovitaminosis D	Mark L. Gordon, M.D.	818.990.1166	

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Does Testosterone Affect the Normal Menstrual Cycle? Clinical Endocrinology (1986), 24, 5 15-52 1. P. DEWIS, M. NEWMAN, W. A. RATCLIFFE* AND D. C. ANDERSON University of Manchester, Departments of Medicine and *Chemical Pathology, Hope Hospital, Safford M6 8 HD (I7 January 1986)

- Women were studied who had either severe premenstrual syndrome or loss of libido for which they were treated with **100 mg testosterone** by S.C. implantation.
- All had regular menstrual cycles for 1 month prior to implantation. Serum LH, FSH, estradiol (E2), progesterone and testosterone were measured three times per week.
- All women showed normal cyclical variation of LH, FSH, E2 and progesterone. Following implantation; No patient had any disturbance of menstrual pattern.



Normal

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ALLERGIES:

TBI

V S

Lab Date: 1/26/2015

Chemistry Profile	Result	Range				
Glucose	122 H?F	<100mg/dl				
Sodium (NA)	145	133-149 meq/L				
Potassium(K)	4.9	3.5 – 5/.5 meq/L				
Chloride (Cl)	106	96-108 meq/L				
Iron (Fe)		35-200 mcg/L				
LIVER TESTING	Normal					
SGOT	14	0- 34 U/L				
SGPT	8	< 33 U/L				
Total Protein	7.6	6 – 8.4 gm/dl				
Albumin	5.1	3.2 – 4.8 gm/dl				
Globulin	2.5	2.0 – 3.7 gm/dl				
Alkaline Phosphatase	50	30-125 U/L				
Lactose Dehydrogenase	167	80 – 225 U/L				
GGTP	12	2 – 60 mg/dl				
Total Bilirubin	0.8	0.1 – 1.2 mg/dl				
BONE, JOINTS	*Normal*					
Calcium (Ca)	10.2	8.4 – 10.8 mg/dl				
Phosphorus	NT	2.3- 5 mg/dl				
Uric Acid	2.0	2.5 – 6.8 mg/dl				
Magnesium (Mg)	2.2	1.5 – 3.0 mg/dl				
LIPIDS	*Normal*					
Triglycerides (FAT)	66	<162 mg/dl				
Cholesterol	191	< 200 mg/dl				
HDL (Good)	64	>45 mg/dl				
LDL (Bad)	114	<100 mg/dl				
Cardiovascular Risk	2.98 ☺	☺☺1/2 risk				
RENAL FUNCTION	*Normal*					
Blood Urea Nitrogen	14	6 – 25 mg/dl				
Creatinine	0.8	< 1.0 mg/dl				
GFR	86					
BLOOD COUNT	*Normal*					
ESR	1	0 – 20 mm/hr				
WBC	6.0	4.0 – 10.8 $x10^3$				
RBC	5.04	4.0 – 5.4 $x\ 10^6$				
Hemoglobin	14.7	12 – 16 gm/dl				
Hematocrit	45.5	36 – 48%				
MCV	90	80 – 99 fL				
Granulocytes	62.1	45 – 75%				
Lymphocytes	30.4	20 – 50%				
Eosinophils	1.1	0-8%				
Urine Analysis	NT	Normal				

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Millennium Health Group
Medicine for the 21st Century

ALLERGIES:

TBI

V S

Lab Date: 1/26/2015

Dear S

Welcome to the practice. In the future you will receive a comprehensive Patient Handbook that will explain in detail your labs and offer a treatment program.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; normal. DHEA-s is the precursor to Testosterone and Estrogens and is low-Normal. Estrone and estradiol are normal to high-normal for timing in your cycle with normal progesterone. Therefore, the normal Estrogen-Progesterone Ratio (EP Ratio). The neuroprotective Pregnenolone is normal. The important Free testosterone is low-normal with a normal Total Testosterone. DHT is normal with a high-normal Sex Hormone Binding protein which can bind and decrease free Testosterone. FSH and LH increase when blood levels of hormones (estrogen, testosterone) are low. When they are low it is usually because there is adequate amount of hormones in the blood or in cases of head trauma with damage to the pituitary gland. Prolactin is a marker of hypothalamic-pituitary function; High-normal. Zinc is low-normal. Insulin is normal. Vitamin D is low. Overall, your Thyroid hormone panel suggests that you are producing a normal amount of hormone. ACTH is the hormone from the brain that stimulates your adrenal glands (above the kidneys) to make Cortisol, the hormone associated with our adaptation to stress; normal.

Chemistry Profile: Was this a fasting blood sample? Blood sugar is elevated. Liver functions and markers, bone metabolism, fats and cholesterol, kidney functions, and cell counts are all within acceptable normal ranges.

Suggested Protocol #1

Verify	Status	Product	Morning	Afternoon	Evening
	Hold	Secretropin	3 pumps at bed time as directed.		
	Start	EC-Prog100mg-Test2mg	½ gram vaginally each night.		
	Start	Ultranutrient	2 caps		2 caps
	Start	DHEA 25mg			1 cap
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	B-Complex with PQQ	1 cap		1 cap
	Start	Progesterone 100mg (#60)			1 cap
Nocharge	**Start**	Saw Palmetto	2 caps		2caps
	Start	Zinc Citrate	2 caps		2 caps

Present Medication

Medication	Dosage	Timing	Comments
Xeomin/Botox			

Present Supplements

Status	Sups	Dosage	Timing	Status	Sups	Dosage	Timing
	Excedrin	500mg	PRN		B 12 Lozenges	2000-3000mg	QD
	Magnesium	200-600mg	Weekly		Women's Herbal	300mg	QD

Anticipated Scheduled Visits

	Review of lab results, Physical exam, products dispensed

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ALLERGIES:
TBI

V S

Lab Date: 1/26/2015

Additional Notes:

01/26/2015	Remote Blood Draw. 1988.1996,2001, MVA.
02/16/2015	Email report. Prepare Handbook. Arrange for a skype call.
	Skype Call:

X	**Mark L. Gordon, M.D., AAFP,ABAAM**		**Linda Hillebrand, D.O. FCOG**
	Medical Director,		Assistant Director
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		DrLinda@millenniumhealthcenters.com

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
Skype: **MLGordonTBI**

Additional Files to Handbook or email to patient if a follow-up office visit.

	Gout		PLAC Test		Estrogen Dominance
	Polycythemia		Vitamin D Deficiency		Metabolic Syndrome.
XX	Traumatic Brain Injury		TPO - Thyroiditis		PSA-Low Testosterone

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Case History:7

27 y/o Male (FJ): Motor-cross junkie.				
History	MCA w/ Coma 3 weeks	MCA w/ LOC	MCA w/ Concussion	
Symptoms	Mood swings	Depression Anxiety	Can't focus Concentration	
Medication	None			
Diagnoses	Partial GHD	Hypo-Gonadism	Hyper-Prolactinemia	Hypo-Vitaminosis D
	Hyper-Cortisolemia			
Treatment	Secretagogue	Clomid 50mg 5x/Wk	DHEA 25mg QHS	Pregnenolone 60mg QHS
	Cognitive Aminos	CO10 w/PQQ	RiboCarnQ10	Vitamin D3 5,000iu





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ALLERGIES:

TBI

FJ (27)
Lab Date: 03/02/2015

Testosterone:

Hormone Testing	Results	Range				
Growth Hormone*	0.19 LN	5ng/ml*				
Somatomedin C (IGF-1)*	147 LN	> 200 ng/ml*				
IGF BP-3*	4000 LN	>4000 ng/ml*				
DHEA-S	427.4 HN	295 ug/dl*				
Testosterone Free*	7.57 LN	14 pg/ml*				
Testosterone Total*	363 LN	690 ng/ml*				
Dihydrotestosterone (DHT)	36.9 N	< 55 ng/Dl*				
Sex Hormone Binding Gb	25 N	< 45 pg/ml*				
Estrone (E1)	12 N	< 60 pg/ml*				
Estradiol (E2)	23.7 N	<25 pg/ml*				
Progesterone	0.98 HN	0.8ng/ml*				
Pregnenolone	19 LN	110 ng/dl*				
FSH	2.3 LN	7 mIU/ml*				
LH*	8.4 HN	5.1 mIU/ml				
Prolactin**	22.7 H	14 ng/ml*				
Zinc*	71 LN	95 mcg/dL*				
Insulin	7.1 N	< 30mIU/L				
Vitamin D3*	37 LN	>60 ng/dl*				
TSH	1.32 N	<2.5 mcu/ml*				
T3, Free	3.3 N	> 2.5 pg/ml				
T4, Free*	1.16 LN	> 1.5 ng/ml				
rT3	154 N	80-250 pg/ml				
T3/rT3 Ratio	2.14 N	>1.06				
TPO	NT	<35				
ACTH	23.8 N	< 35pg/ml *				
Cortisol*	19.1 HN	< 15 ug/dl				

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Status	Doctor	Phone	ICD-10
2003	MCA w/LOC coma for 3 wks				
Multiple	MCA w/LOC				
2015	r/o Acquired GH Deficiency	3°	Mark L. Gordon, M.D.	818.990.11166	
2015	Hypogonadism	3°	Mark L. Gordon, M.D.	818.990.11166	
2015	Prolactinemia (r/o Prolactinoma-MRI)	3°	Mark L. Gordon, M.D.	818.990.11166	
2015	Hypovitaminosis D	1°	Mark L. Gordon, M.D.	818.990.11166	
2015	Hypercortisolemia	1°	Mark L. Gordon, M.D.	818.990.11166	
2015					

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Clomiphene citrate is safe and effective for long-term management of hypogonadism. BJUI. 2011. Daniel J. Moskovic , Darren J. Katz , Ardavan Akhavan , Kelly Park and John P. Mulhall Sexual & Reproductive Medicine Program, Urology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

- After 3 years of treatment evaluation with Clomiphene citrate it was found that:
- Clomiphene citrate is an effective long-term therapy for Hypogonadal patients.
- Clomid raises T levels substantially in addition to improving other manifestations of hypogonadism such as osteopenia/osteoporosis and ADAM symptoms.



Abnormal

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ALLERGIES:

TBI

FJ (27)
Lab Date: 03/02/2015

Chemistry Profile	Result	Range					
Glucose (non-fasting)	105**nf**	< 100mg/dl					
Sodium (NA)	142	133-149 meq/L					
Potassium(K)	4.3	3.5 – 5.5 meq/L					
Chloride (Cl)	100	96-108 meq/L					
Iron (Fe)	NT	35-200 mcg/L					
LIVER TESTING	Abnormal						
SGOT	27	<34 U/L					
SGPT	29	< 33 U/L					
Total Protein	7.7	6 – 8.4 gm/dl					
Albumin	5.2 H	3.2 – 4.8 gm/dl					
Globulin	2.5	2.0 – 3.7 gm/dl					
Alkaline Phosphatase	93	30-125 U/L					
Lactose Dehydrogen	221	80 – 225 U/L					
GGTP	23	2 – 60 mg/dl					
Total Bilirubin	2.2 H	0.1 – 1.2 mg/dl					
BONE, JOINTS	*Normal*						
Calcium (Ca)	10.0	8.4 – 10.8 mg/dl					
Phosphorus		2.3- 5 mg/dl					
Uric Acid	5.8	2.5 – 6.8 mg/dl					
Magnesium (Mg)	1.8	1.5 – 3.0 mg/dl					
LIPIDS	*Normal*						
Triglycerides (FAT)	99	<162 mg/dl					
Cholesterol	196	< 200 mg/dl					
HDL (Good)	62	>45 mg/dl					
LDL (Bad)	114	<100 mg/dl					
Cardiovascular Risk	3/16	¼ -½ risk ☺☺					
RENAL FUNCTION	*Normal*						
Blood Urea Nitrogen	14	6 – 25 mg/dl					
Creatinine	1.1	< 1.0 mg/dl					
GFR	85						
BLOOD COUNT	*Abnormal*						
ESR	4	0 – 20 mm/hr					
WBC	12.3 H	4.0 – 10.8 $x10^3$					
RBC	5.39	4.0 – 5.4 $x\ 10^6$					
Hemoglobin	16.2	13 – 17 gm/dl					
Hematocrit	49.3	39 – 52%					
MCV	92	80 – 99 fL					
Granulocytes	79.2 H	45 – 75%					
Lymphocytes	10.6 L	20 – 50%					
Eosinophils	2.1	0-8%					
Urine Analysis		Normal					

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ALLERGIES:

TBI

FJ (27)
Lab Date: 03/02/2015

Dear J,

Welcome to the practice. This is the preliminary part of our process, the report. It is followed by a handbook that will be sent to you by Federal express. In the meantime, we can arrange for a Skype call to review your lab results and what they mean in terms of treatment. Then we will truly begin the process.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; Low-normal pattern. DHEA-s is the precursor to Testosterone and Estrogens and is High-Normal. This is not an issue as long as there is no acne or oily skin. The important Free testosterones is low-normal with a low-normal Total Testosterone. DHT is Normal. Sex Hormone Binding is normal. Estrogens are normal with a high-normal Progesterone. This is acceptable because of the benefits of Progesterone in the brain. The neuroprotective Pregnenolone is low. FSH and LH reflect either the body's ability to make hormones from the testes/ovaries when elevated, or low with supplementation or TBI. FSH is low-normal and LH is High-normal trying to increase testosterone. Prolactin is a marker for hypothalamic-pituitary functioning; HIGH. An MRI is recommended. Zinc is low-normal. Insulin is normal. Vitamin D is low-normal. At this point the brain-thyroid system is normal. ACTH is produced by the pituitary to produce Cortisol from the adrenal glands; Cortisol is high-normal suggesting a level of increased stress (physical, emotional, mental, nutritional, and chemical).

Chemistry Profile: Blood sugar is . Eight normal liver functions and markers with one abnormal, bone metabolism, fats and cholesterol, kidney functions, and cell counts are all within acceptable normal ranges. Abnormal white cell pattern suggestive of an infection or inflammatory process with elevated total white blood cells and granulocytes (infection??). The elevated Bilirubin indicates break down of red blood cells.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	Start	Secretropin	3 pumps at bed time as directed.		
		Testosterone	Discuss		
		Clomid 50mg	Discuss		
	Start	Men's Pure Packet	1 packet		
	Start	DHEA 25mg			1 cap
	Start	Pregnenolone 30mg			2 caps
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	ADH	1 cap		1 cap
	Start	SR-CoQ10 w/ PQQ	1 cap		1 cap
	Start	RiboCarnitine-Q10	1 cap	`	1 cap

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing

Anticipated Scheduled Visits

Initial dispensing visit	Review of lab results, Physical exam, products dispensed

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ALLERGIES:
TBI

FJ (27)
Lab Date: 03/02/2015

Additional Notes:

03/02/2015	Remote Blood Draw.
03/17/2015	Final Report sent and Fed X TBI Handbook
	SKYPE CALL: Review History, laboratory results and suggested treatment protocol. Needs an MRI of the Pituitary/Brain for elevated prolactin.

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Case History:8

43 y/o Male (JD)*: No direct physical trauma mostly blast proximity.				
History	Combat Trauma Syndrome	Fall from object	MVA w/o LOC	Post-Concussion Syndrome.
Symptoms	Depression	Low Libido	Memory Deficit	
Medication	Sertraline	Modafinil		
Diagnoses	Low Free Testosterone	Hypo-Vitaminosis D		
Treatment	Testosterone CP 40mg Q3rdDay	Ultranutrient	Pregnenolone	Cognitive Aminos
	Ultra B-Complex w/ PQQ	Vitamin D3 10,000iu QAM		



QUESTION

Would you treat JD with T or CC based upon these results?

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ALLERGIES:

TBI
Veteran

J D (43)
Lab Date: 2/04/2015

Testosterone:

Hormone Testing	Results	Range
Growth Hormone	0.20 LN	5*ng/ml
Somatomedin C (IGF-1)	207 N	> 200 ng/ml*
IGF BP-3	4800 N	4000 ng/ml*
DHEA-S	298.6 N	300 ug/dl*
Testosterone Free	6.73 L	14 pg/ml*
Testosterone Total	541 LN	690 ng/ml*
Dihydrotestosterone (DHT)	51.6 HN	< 30 ng/Dl*
Sex Hormone Binding Gb	69 HN	< 45 pg/ml*
Estrone (E1)	20 N	< 60 pg/ml*
Estradiol (E2)	25.8 HN	25 pg/ml*
Progesterone	0.59 LN	0.8ng/ml*
Pregnenolone	41 LN	110ng/dl*
FSH	9.7 HN	7 mIU/ml*
LH	7.6 HN	5.1 mIU/ml
Prolactin	8.1 N	14 ng/ml*
Zinc	63 LN	95 mcg/dL*
Insulin	10.5 N	< 30mIU/L
Vitamin D3	34 LN	60 ng/dl*
TSH	1.23 N	<2.5 mcu/ml*
T3, Free	3.2 N	> 2.5 pg/ml
T4, Free	1.11 LN	> 1.5 ng/ml
rT3	139 N	80-250 pg/ml
T3/rT3 Ratio	2.3 N	>1.06
TPO	NT	<35
ACTH	22.24 N	< 35pg/ml *
Cortisol	10.1 N	< 15 ug/dl

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Status	Doctor	Phone	ICD-10
1990-94	Multiple Combat exposures				
1983	Fall from Obj w/o LOC				
1997	MVA w/o LOC				
	Post-concussion syndrome (TBI)				
	Depression				
2015	Low Free Testosterone				
2015	Hypovitaminosis D				

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Normal

Millennium Health Group
Medicine for the 21st Century

ALLERGIES:

TBI
Veteran

J D

Lab Date: 2/04/2015

Chemistry Profile	Result	Range					
Glucose	85	< 100mg/dl					
Sodium (NA)	143	133-149 meq/L					
Potassium(K)	4.5	3.5 – 5.5 meq/L					
Chloride (Cl)	25	96-108 meq/L					
Iron (Fe)		35-200 mcg/L					
LIVER TESTING	Normal						
SGOT	32	<34/42 U/L					
SGPT	36	< 33/39 U/L					
Total Protein	7.4	6 – 8.4 gm/dl					
Albumin	4.5	3.2 – 4.8 gm/dl					
Globulin	2.9	2.0 – 3.7 gm/dl					
Alkaline Phosphatase	66	30-125 U/L					
Lactose Dehydrogen	155	80 – 225 U/L					
GGTP	26	2 – 60 mg/dl					
Total Bilirubin	0.3	0.1 – 1.2 mg/dl					
BONE, JOINTS	*Normal*						
Calcium (Ca)	9.8	8.4 – 10.8 mg/dl					
Phosphorus		2.3- 5 mg/dl					
Uric Acid	3.2	2.5 – 6.8 mg/dl					
Magnesium (Mg)	2.2	1.5 – 3.0 mg/dl					
LIPIDS	*Normal*						
Triglycerides (FAT)	154	<162 mg/dl					
Cholesterol	192	< 200 mg/dl					
HDL (Good)	61	>45 mg/dl					
LDL (Bad)	100	<100 mg/dl					
Cardiovascular Risk	3.14 ☺	1/2 risk					
RENAL FUNCTION	*Normal*						
Blood Urea Nitrogen	18	6 – 25 mg/dl					
Creatinine	1.2	< 1.0 mg/dl					
GFR	70						
BLOOD COUNT	*Normal*						
ESR	5	0 – 10/20 mm/hr					
WBC	7.5	4.0 – 10.8 $x10^3$					
RBC	4.7	4.0 – 5.4 $x\ 10^6$					
Hemoglobin	14.6	13 – 17 gm/dl					
Hematocrit	43	39 – 52%					
MCV	92	80 – 99 fL					
Granulocytes	62.3	45 – 75%					
Lymphocytes	28	20 – 50%					
Eosinophils	0.8	0-8%					
Urine Analysis		Normal					

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ALLERGIES:

TBI
Veteran

J D
Lab Date: 2/04/2015

Dear David,

Welcome to the practice. This is the preliminary part of our process, the report. It is followed by a handbook that will be sent to you by Federal express. In the meantime, we can arrange for a Skype call to review your lab results and what they mean in terms of treatment. Then we will truly begin the process.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; normal pattern. DHEA-s is the precursor to Testosterone and Estrogens and is Normal. The important Free testosterones is low with a low-normal Total Testosterone(Extenze?). DHT is high-normal. Sex Hormone Binding is High-normal which can decrease available Free Testosterone. Estrone is normal with a high-normal Estradiol and low-normal progesterone. The neuroprotective Pregnenolone is low-normal. FSH and LH reflect either the body's demand to make hormones from the testes/ovaries when elevated, or low when supplementing or with TBI. Both FSH and LH are High suggesting the body's attempt to desire to increase testosterone. ncrease testosterone. Prolactin is a marker for hypothalamic-pituitary functioning; normal. Vitamin D is low-normal. At this point the brain-thyroid system is normal. ACTH is produced by the pituitary to produce Cortisol from the adrenal glands; both normal.

Chemistry Profile: Blood sugar is Normal. Liver functions and markers, bone metabolism, fats and cholesterol, kidney functions, and cell counts are all within acceptable normal ranges.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	Discuss	Testosterone C/P	0.20cc(40mg) Every 3rd day.		
	Start	Ultranutirent	2 caps		2 caps
	HOLD	DHEA 25mg	1 cap		1 cap
	Start	Pregnenolone 30mg			2 caps
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	Ultra B Complex w/ PQQ	1 cap		1 cap
	Start	Vitamin D3 10,000IU	1 cap		

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
		Sertraline	100 mg		
		Modaeinil	100 mg		

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing
		Alpha Brain		4QD			Hemp Force Protein	QD	
		T Plus		QD			Vitamins	QD	
		Extenze					T Plus (ONNIT)	QD	

Anticipated Scheduled Visits

Initial dispensing visit	Review of lab results, Physical exam, products dispensed

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Millennium Health Group
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ALLERGIES:
TBI Veteran

J D

Lab Date: 2/04/2015

Additional Notes:

02/04/2015	Remote Blood Draw
02/24/2015	Final Report sent and Fed X TBI Handbook
	SKYPE CALL:

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI

Additional Files to Handbook or email to patient if a follow-up office visit.

	Gout		PLAC Test		Estrogen Dominance
	Polycythemia		Vitamin D Deficiency		Metabolic Syndrome.
XX	Traumatic Brain Injury		TPO - Thyroiditis		PSA-Low Testosterone

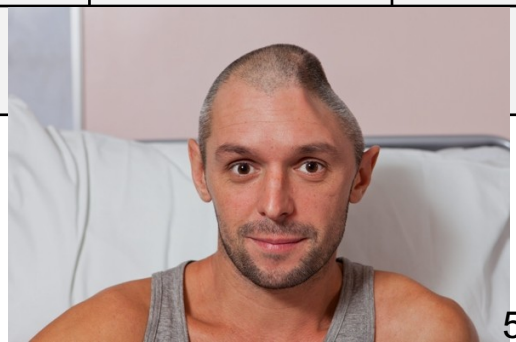
Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Case History:9

49 y/o Male (HD): Fall from 2 floor balcony to 1st floor balcony age 6.

History	Fall w/ LOC Fx Skull	Attention Deficit Disorder	Right Arm Fx from Fall	Hyper-Cholesterolemia
Symptoms	Depression	Anxiety	Attention Deficit	
Medication	Crestor 20mg	Vyvanse		
Diagnoses	AGHD	Hypo-Gonadism	Pregnenolone Steal Synd.	Hypo-Vitaminosis D
	Subclinical Hypothyroidism	Hyper-Urecemia	Hyper-Cholesterolemia	
Treatment	Secretropin	Testosterone CP 40mg Q3rdDay	DHEA 25mg QHS	Pregnenolone 60mg QHS





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ALLERGIES:

TBI

HD (48)
Lab Date: 2/20/2015

Compensatory Hypothyroidism

(Subclinical Hypothyroidism)

- TSH is linked to T4.
- TSH above median suggests that the Thyroid Gland needs more stimulation to generate the needed T4.
- Looking at the relationship of TSH-T4 can help in making a decision as to a trial of Combination therapy.

Testosterone:

Hormone Testing	Results	Range
Growth Hormone*	0.04 LN	5*ng/ml
Somatomedin C (IGF-1)*	122 LN	> 200 ng/ml*
IGF BP-3*	3100 LN	4000 ng/ml*
DHEA-S	461.9 H	245 ug/dl*
Testosterone Free*	3.43 L	14 pg/ml*
Testosterone Total*	179 L	690 ng/ml*
Dihydrotestosterone (DHT)	22.5 HN	< 30 ng/Dl*
Sex Hormone Binding Gb	32 N	< 45 pg/ml*
Estrone (E1)	12 N	< 60 pg/ml*
Estradiol (E2)	17 N	25 pg/ml*
Progesterone	1.05 HN	0.8ng/ml*
Pregnenolone	92 LN	110 ng/dl*
FSH*	3.2 LN	7 mIU/ml*
LH*	2.2 LN	5.1 mIU/ml
Prolactin	5.6 N	14 ng/ml*
Zinc	90 N	95 mcg/dL*
Insulin	19.6 N	< 30mIU/L
Vitamin D3*	28 LN	60 ng/dl*
TSH*	3.89 HN	<2.5 mcu/ml*
T3, Free*	2.4 LN	> 2.5 pg/ml
T4, Free*	1.11 LN	> 1.5 ng/ml
rT3	133 N	80-250 pg/ml
T3/rT3 Ratio	1.83 N	>1.06
TPO	NT	<35
ACTH*	1.2 N	< 35pg/ml *
Cortisol*	17.6 N	< 15 ug/dl

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Status	Doctor	Phone	ICD-10
1967	Fall – Fx Skull ?/LOC				
	ADD				
2001	Rt Arm Fx with plate				
2015	Adult GH Deficiency	1°/3°			
2015	Central Hypogonadism	3°	Mark L. Gordon, M.D.	818.990.1166	
2015	Pregnenolone Steal Syndrome		Mark L. Gordon, M.D.	818.990.1166	
2015	Hypovitaminosis D	NA	Mark L. Gordon, M.D.	818.990.1166	
2015	Subclinical Hypothyroidism	1°	Mark L. Gordon, M.D.	818.990.1166	
2015	Hyperurecemia (gout)		Mark L. Gordon, M.D.	818.990.1166	
2015	Hypercholesterolemia		Mark L. Gordon, M.D.	818.990.1166	

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Adrenocorticotropin (ACTH)- and Non-ACTH-Mediated Regulation of the Adrenal Cortex: Neural and Immune Inputs.

The Journal of Clinical Endocrinology & Metabolism 1999 . Vol. 84, No. 5 Clinical Review104.
S. R. Bornstein and GP Chrousos. Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892

- The two major peripheral limbs of the stress system are the hypothalamic-pituitary-adrenal (HPA) axis and the peripheral sympathetic nervous system.
- Central components are located in the hypothalamus and the brain stem.
- Central activation of the sympathetic neurons leads to activation of the adrenal medullae through the splanchnic nerves.
- Neurons originate in cell bodies from within the adrenal medulla may be regulated by splanchnic nerve activity.



Abnormal

Millennium Health Group
Medicine for the 21st Century

ALLERGIES:

TBI

HD (48)
Lab Date: 2/20/2015

Chemistry Profile	Result	Range				
Glucose	94	< 100mg/dl				
Sodium (NA)	143	133-149 meq/L				
Potassium(K)	4.6	3.5 – 5.5 meq/L				
Chloride (Cl)	103	96-108 meq/L				
Iron (Fe)		35-200 mcg/L				
LIVER TESTING	Normal					
SGOT	24	<34 U/L				
SGPT	8	< 33 U/L				
Total Protein	7.6	6 – 8.4 gm/dl				
Albumin	5.1	3.2 – 4.8 gm/dl				
Globulin	2.5	2.0 – 3.7 gm/dl				
Alkaline Phosphatase	64	30-125 U/L				
Lactose Dehydrogen	121	80 – 225 U/L				
GGTP	23	2 – 60 mg/dl				
Total Bilirubin	0.6	0.1 – 1.2 mg/dl				
BONE, JOINTS	*Abnorm*					
Calcium (Ca)	9.5	8.4 – 10.8 mg/dl				
Phosphorus	NT	2.3- 5 mg/dl				
Uric Acid	8.8 H	2.5 – 6.8 mg/dl				
Magnesium (Mg)	2.2	1.5 – 3.0 mg/dl				
LIPIDS	*Abnorm*					
Triglycerides (FAT)	158	<162 mg/dl				
Cholesterol	228 H	< 200 mg/dl				
HDL (Good)	49	>45 mg/dl				
LDL (Bad)	147 H	<100 mg/dl				
Cardiovascular Risk	4.6 H	2x risk				
RENAL FUNCTION	*Normal*					
Blood Urea Nitrogen	22	6 – 25 mg/dl				
Creatinine	0.9	< 1.0 mg/dl				
GFR	96					
BLOOD COUNT	*NT*					
ESR		0 – 20 mm/hr				
WBC		4.0 – 10.8 $x10^3$				
RBC		4.0 – 5.4 $x\ 10^6$				
Hemoglobin		13 – 17 gm/dl				
Hematocrit		39 – 52%				
MCV		80 – 99 fL				
Granulocytes		45 – 75%				
Lymphocytes		20 – 50%				
Eosinophils		0-8%				
Urine Analysis		Normal				

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Millennium Health Group
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ALLERGIES:

TBI

HD (48)
Lab Date: 2/20/2015

Dear DH,

Welcome to the practice. This is the preliminary part of our process, the report. It is followed by a handbook that will be sent to you by Federal express. In the meantime, we can arrange for a Skype call to review your lab results and what they mean in terms of treatment. Then we will truly begin the process.

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; Low-normal pattern. Need a Glucagon test to determine origin of this deficiency. DHEA-s is the precursor to Testosterone and Estrogens and is High-Normal. This is not an issue as long as there is no acne or oily skin. The important Free testosterones is low with a low Total Testosterone. DHT is high-nromal. Sex Hormone Binding is normal. Estrogens are normal with a high-normal progesterone. The neuroprotective Pregnenolone is low-normal. FSH and LH reflect either the body's ability to make hormones from the testes/ovaries when elevated, or low when supplementing or TBI. Both FSH and LH are low-normal with low testosterones identifying this as a Brain related deficiency. Prolactin is a marker for hypothalamic-pituitary functioning; normal. Insulin is normal. Vitamin D is low-normal. Your brain-thyroid system is normal, but your thyroid is not producing sufficient amount of thyroid hormone – T3. ACTH is produced by the pituitary to produce Cortisol from the adrenal glands; both normal.

Chemistry Profile: Blood sugar is normal . Liver functions and markers, bone metabolism, fats , and kidney functions. Cholesterol is elevated which can be due to the low thyroid and testosterone.

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	Start	Secretropin	3 pumps at bed time as directed.		
	Start	Testosterone C/P 80/20.	0.20cc every 3rd day.		
	Discuss	Armour Thyroid 30mg	1 tablet		
	Start	Ultranutrient	2 caps		2 caps
	Start	Pregnenolone 30mg			2 caps
	Start	Cognitive Aminos	2 caps	2 caps	
	Start	Ultra B-Complex w/ PQQ	1 cap		1 cap
	Start	Vitamin D3 5000IU	1 cap		

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
	OFF	Crestor	20mg		
	OFF	Vyvance	30mg		

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing
	ON	Omega	2K				Vit D3	2K	
		Multi-Vit					Multi-Mineral		

Anticipated Scheduled Visits

	Review of lab results, Physical exam, products dispensed

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ALLERGIES:

TBI

HD (48)
Lab Date: 2/20/2015

Additional Notes:

02/20/2015	Remote Blood Draw.
03/09/2015	Final Report sent and Fed X TBI Handbook.
03/12/2015	SKYPE CALL: Review History, Lab results, and treatment protocol. Consider GST in future.
	Follow-up Skype in 2-4 weeks. Start Journal.

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Case History:10

57 y/o Male (BC): Denies history of TBI				
History	Hypogonadism	AGHD	Neutropenia	
Symptoms	Hypogonadism	Low Libido	Muscular strength	Volatile moods
Medication	None			
Diagnoses	Hypogonadism By history	Low GH by history		
Treatment				



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Bee Allergy

BC
Lab Date: 08/19/2014

Testosterone 08/16/2014 .20cc (40mg) Q 3 Day.

Hormone Testing	Results	Range	7/2/13	12/6/12	11/17/11	8/26/10	3/9/10	1/7/10
Growth Hormone (GH)		5ng/ml*						
Somatomedin C (IGF-1)	267 N	> 200 ng/ml*	76 L	174.4 LN	143 LN	234 N	166 LN	150 LN
IGF Binding Protein 3	5700 N	4000 ng/ml*	5100 N	5000 N	4300 N	4900 N	4500 LN	4400 LN
DHEA-S	163.7 LN	180 ug/dl*	162.4 LN	321.9 HN	156.6 LN	164 LN	206.5 LN	288.9 H
Testosterone Free	9.66 LN	12 pg/ml*	10.42 LN	7.32 LN	9.11 LN	6.25 LN	8.5 N	33.5 LN
Testosterone Total	507 LN	690 ng/ml*	759 HN	439 LN	690 N	875 HN	971 HN	565 LN
Dihydro**t**estosterone	65.9 HN	< 62 ng/dl*	50.9 N	56.7 N	69.72 HN	76.49 HN	77.3 HN	53.8 LN
Sex Hormone Binding Gb	36 N	< 42 pg/ml*	51 HN	42 HN	53 HN	49 HN	40 N	59 H
Prostatic Specific Antigen	1.51 N	< 4.0ng/ml		1.62 N	0.78 N			0.88 N
Free PSA		>24%						0.41 N
Zinc	Retest	95 mcg/dL*	98 HN					
Estrone (E1)	13 N	<90 pg/ml*	25 N	9 N	9.52 N	18.39 N	55.9 N	89.3 H
Estradiol (E2)	20 N	<25 pg/ml*	31.4 N	61.8 HN	40.8 HN	46.8 HN	38 N	131.4 H
Insulin		< 30 mIU/L						3.0 N
Prolactin		12.5 ng/ml*						
FSH		7.1 Miu/ml						
LH		4.2 Miu/ml						
Vitamin D3		60 ng/dl*						113.3 N
TSH		<2.5 mcu/ml*	2.42 N					1.8 N
T4, Free		> 1.5 ng/ml	1.23 LN					1.38 LN
T3, Free		> 2.5 pg/ml	3.2 N					3.3 N
rT3		90-350 pg/ml	170 N					298 HN
T3/rT3 ratio		>1.06	1.88 N					1.10 N
Cortisol		< 15 ug/dl						10.0 N

**** These values represent the median or 50th percentile of the hormone.***

L = Low. LN = Low. N = Normal. HN = High Normal. H = High.

Active	Diagnosis	Doctor	Phone	ICD-9
2010	Loss of Libido	Mark L. Gordon, M.D.	818.990.1166	799.81
2005	GH Insufficiency	Mark L. Gordon, M.D.	818.990.1166	253.3
2005	Testosterone Insufficiency	Mark L. Gordon, M.D.	818.990.1166	257.20
2013	Neutropenia	Mark L. Gordon, M.D.	818.990.1166	
2013	Elevated Zinc.	Mark L. Gordon, M.D.	818.990.1166	

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Abnormal

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Bee Allergy

BC
Lab Date: 08/19/2014

Chemistry	Result	Ranges		7/2/13	12/06/12	11/17/11	2/01/11	1/07/10
Glucose		70-105mg/dl					94	96
Sodium (NA)		133-145 meq/L					141	146 H
Potassium(K)		3.5 – 5.5 meq/L					4.4	4.4
Chloride (Cl)		96-110 meq/L					103	107
Iron (Fe)		28-170 mcg/L					138	153
LIVER TESTING								
SGOT		0- 34 U/L					20	16
SGPT		0 – 35 U/L					31	18
Total Protein		6 – 8.2 gm/dl					7.0	7.2
Albumin		4.1 – 5.4 gm/dl					4.8	4.5
Globulin		2.0 – 3.7 gm/dl					2.2	2.7
Alkaline Phosphatase		30-125 U/L					86	68
Lactose Dehydrogen		80 – 225 U/L					129	108
GGTP		2 – 60 mg/dl					22	23
Total Bilirubin		0.1 – 1.2 mg/dl					0.6	0.40
BONE, JOINTS								
Calcium (Ca)		8.4 – 10.8 mg/dl					9.7	9.7
Phosphorus		2.3- 5 mg/dl					2.7	3.0
Uric Acid		3.5 – 7.2 mg/dl					3.1	5.1
Magnesium (Mg)		1.5 – 3.0 mg/dl						2.2
LIPIDS								
Triglycerides (FAT)		< 262 mg/dl					195	232
Cholesterol		< 200 mg/dl					212	243 H
HDL (Good)		>45 mg/dl					64	74
LDL (Bad)		<100 mg/dl					109	123
Cardiovascular Risk		< 4.4						3
RENAL FUNCTION								
Blood Urea Nitrogen		6 – 25 mg/dl					17	18
Creatinine		< 1.2 mg/dl					1.0	1.1
BLOOD COUNT								
ESR	3.0	0 – 10 mm/hr		5	<1	3	1	4
WBC	4.60	4.0 – 10.8 x10^3		5.9	5.8	5.9	6.7	6.7
RBC	6.04	4.3 – 6.1 x 10^6		5.76	5.94	5.97	6.39 H	5.62
Hemoglobin	16.5	13 – 17 gm/dl		15.1	15.4	15.3	16.7	14.8
Hematocrit	51.0	39 – 52%		48.5	50.7	48.7	51.3	45.5
MCV	84.4	80 – 99 fL		84.2	85.4	81.6*	80.3	81.0
Granulocytes	47.6	45 – 75%		51.4	23.6 L	49.5	56.1	57.8
Lymphocytes	37.3	20 – 50%		37.3	42.4	38.2	30.9	32.1
Eosinophils	4.0	< 5 %		3.8	4.9	5.9 H		
Urine Analysis		Normal						UricA

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Bee Allergy

BC
Lab Date: 08/19/2014

Dear Claudio,

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; normal patterns. DHEA-s is the precursor to Testosterone and Estrogens and is low-Normal. The important Free testosterones and Total Testosterone are low-normal. DHT is high-normal. (Restart SP1) Sex Hormone Binding is normal. PSA for the prostate is normal. Estrogens are normal.

If you are only using the Testosterone and not replacing DHEA and Pregnenolone it can alter your libido and Neurobehavior.

On your next laboratory testing, I will suggest our new comprehensive lab panel 3426 it looks at primary and secondary hormones as well as insulin, Vitamin D, and prolactin.

Chemistry Profile: Your white blood cells Granulocytes are now normal with a lower zinc level.

Please verify your program and fax any corrections to (818) 990-2841

Verify	Status	Products	Morning	Afternoon	Evening
	ON	Secretropin			
	ON	Testosterone Cypionate	.25cc (40mg) Q 3 Day		
	RESTART	Saw Palmetto Plus	1 cap		1 cap
	RESTART	Ultranutrient	2 Caps		2 Caps
	RESTART	DHEA 25mg			2 Cap
	RESTART	Pregnenolone 30mg			1 Cap
	~~OFF~~	~~Cognitive Aminos~~	~~2 caps~~	~~2 caps~~	
	ON	Zinc Citrate	1 caps		1 caps
	RESTART	Vitamin D3 5000 IU	1 cap		
	~~OFF~~	~~Melatonin 0.5mg~~			~~1-6 Caps~~
	~~OFF~~	~~B12 500ug~~	~~3 times a week~~		
	~~OFF~~	~~7 Keto -DHEA~~			~~1 Cap~~
	~~OFF~~	~~EPA/DHA~~	~~1 cap~~	~~1 cap~~	~~1 cap~~
	~~OFF~~	~~Clomid~~	~~1 Tab 5 times a week~~		
	ON	HCG	200 IU 3 times a week		

Present Medication

Status	Medication	Dosage	Timing	Comments

Please call to make your appointment (818) 990-1166

June 2015	Panel 3624, CBC

Mark L. Gordon, M.D., 16661 Ventura Blvd., Suite 716. Encino, California 91436. (818) 990-1166



Millennium Health Group
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Bee Allergy

BC
Lab Date: 08/19/2014

Additional Notes

01/07/2010	Initial Office visit. Consult and labs
1/26/2010	Email Lab result without Zinc (pending). Make an appointment to start program.
03/09/2010	OV with labs
03/18/2010	Final report. No changes.
04/27/2010	OV with labs.
02/01/2011	OV with Labs
02/14/2011	Phone: Reviewed lab results.
02/15/2011	Email final report.
04/26/2011	OV with Labs
05/04/2011	Email report.
11/17/2011	OV with Labs
11/29/2011	Email Final report.
12/06/2012	CPX with Labs
12/13/2012	Email sent. Repeat PSA in January with parameters. Add CBC? MISC TEST??
02/14/2013	OV With Labs
02/22/2013	Email labs. Stop Zinc. Check copper supplies.
07/02/2013	OV with labs
07/15/2013	Email final report.
08/19/2014	OV with labs
09/01/2014	Email final report. Schedule a call or skype to address your results and program. Need to restart a number of the supplements that you have stopped.

X	**Mark L. Gordon, M.D., AAFP,ABAAM**		
	Medical Director,		
	Millennium Health Group		
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com



Case History:TX1

Treatment

48 y/o Male (HB): **Called to verify he was not using any Anabolic Steroids..**				
History	NFL x 3 seasons	Concussions w/o LOC	Post concussion Syndrome	
Symptoms	Chronic bilateral Knee pain	Depression	Agitation and Irritability	Argumentative
Medication	T Cypionate 200mg/week	NSAIDs		
Diagnoses	Arthralgia- knees	Mood Disorder	Post concussion syndrome	
Treatment	Testosterone CP 40mg Q3rdDay	DHEA 25mg	Zinc Citrate 30mg BID	Quercetin 500mg BID





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HB
Lab Date: 10/07/2014

Testosterone: 10/05/2014 0.5cc QW

Hormone Testing	Results	Range				06/10/2014
Growth Hormone		5ng/ml*				0.05 L
Somatomedin C (IGF-1)	226 N	> 200 ng/ml*				197 LN
IGF BP-3	4400 N	>4000 ng/ml*				5300 N
DHEA-S	387.8 HN	145 ug/dl*				138.3 LN
Testosterone Free	34.71 H	14 pg/ml*				15.78 HN
Testosterone Total	1262 H	690 ng/ml*				556 LN
Dihydrotestosterone (DHT)*	88 HN	< 30 ng/Dl*				52 HN
Sex Hormone Binding Gb	25 N	< 45 pg/ml*				15 N
Estrone (E1)	6.0 N	< 60 pg/ml*				27 N
Estradiol (E2)**	24.7 HN	25 pg/ml*				39.8 HN
Progesterone**		0.8ng/ml*				0.32 N
Pregnenolone		205ng/dl*				626 H
FSH**		7 mIU/ml*				3.2 LN
LH**		5.1 mIU/ml*				2.2 LN
Prolactin		14 ng/ml*				7.9 N
Zinc		95 mcg/dL*				NT
Insulin		< 30mIU/L				14.8 N
Vitamin D3**		60 ng/dl*				30 LN
TSH		<2.5 mcu/ml*				1.6 N
T3, Free		> 2.5 pg/ml				3.6 N
T4, Free		> 1.5 ng/ml				1.27 LN
rT3		80-250 pg/ml				160 HN
T3/rT3 Ratio		>1.06				2.25 N
TPO		<35				NT
ACTH		< 35pg/ml *				38.9 HN
Cortisol		< 15 ug/dl				9.3 N

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Doctor	Phone	ICD-10
	Multiple Concussions			
	Post-concussion Syndrome			
	Hypogonadism by History			
2014	Elevated Estrogen	Mark L. Gordon, MD	818.990.1166	
2014	Hypovitaminosis D	Mark L. Gordon, MD	818.990.1166	
2014	Hypercholesterolemia	Mark L. Gordon, MD	818.990.1166	
2014	Allergies (Eosinophils)	Mark L. Gordon, MD	818.990.1166	
2014	Right Shift – Viral Infection	Mark L. Gordon, MD	818.990.1166	

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Abnormal To Normal

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HB
Lab Date: 10/07/2014

Chemistry Profile	Result	Range				06/10/2014
Glucose		<100mg/dl				101 H
Sodium (NA)		133-149 meq/L				137
Potassium(K)		3.5 – 5.5 meq/L				4.2
Chloride (Cl)		96-108 meq/L				103
Iron (Fe)		35-200 mcg/L				87
LIVER TESTING						Normal
SGOT		0- 34 U/L				20
SGPT		< 33 U/L				29
Total Protein		6 – 8.4 gm/dl				7.4
Albumin		3.2 – 4.8 gm/dl				4.4
Globulin		2.0 – 3.7 gm/dl				3.0
Alkaline Phosphatase		30-125 U/L				73
Lactose Dehydrogenase		80 – 225 U/L				149
GGTP		2 – 60 mg/dl				117
Total Bilirubin		0.1 – 1.2 mg/dl				1.1
BONE, JOINTS						*Normal*
Calcium (Ca)		8.4 – 10.8 mg/dl				9.1
Phosphorus		2.3- 5 mg/dl				4.3
Uric Acid		2.5 – 6.8 mg/dl				7.3H
Magnesium (Mg)		1.5 – 3.0 mg/dl				2.6
LIPIDS						*Abnormal*
Triglycerides (FAT)		<162 mg/dl				95
Cholesterol		< 200 mg/dl				285 H
HDL (Good)		>45 mg/dl				79
LDL (Bad)		<100 mg/dl				187
Cardiovascular Risk		1/2 risk				3.6
RENAL FUNCTION						*Normal*
Blood Urea Nitrogen		6 – 25 mg/dl				18
Creatinine		< 1.0 mg/dl				1.3
BLOOD COUNT						*Abnormal*
ESR	7	0 – 10 mm/hr				10
WBC	4.8	4.0 – 10.8 x10^3				3.8 L
RBC	5.29	4.0 – 5.4 x 10^6				5.38
Hemoglobin	16.4	13 – 18 gm/dl				16.4
Hematocrit	47.5	38 – 52%				50
MCV	89.7	80 – 99 fL				93
Granulocytes	50.9	45 – 75%				31 L
Lymphocytes	35.0	20 – 50%				51H
Eosinophils	5.3H	0-5%				7 H
Urine Analysis		Normal				UA

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Millennium Health Group
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HB
Lab Date: 10/07/2014

Dear BH,

Hormone Profile: **GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; normal patterns. DHEA-s is the precursor to Testosterone and Estrogens and is high-Normal. This is not an issue unless you have oily skin and acne. The benefits of DHEA/DHEA-s in the brain and for the heart are impressive. The important free testosterone is high with a HIGH Total Testosterone. DHT is high and can cause hair loss, enlargement of prostate and shrinkage of testicles. Sex Hormone Binding is normal. Estradiol is high-normal with normal Estrone.**

Chemistry Profile: Cell count is normal except for the Allergy cells being elevated. How are your allergies??

Please verify your program and send corrections to reception@millenniumhealthcenters.com or 818-990-2841

Verify	Status	Product	Morning	Afternoon	Evening
X	Change	Testosterone CP	Start 0.20cc (40mg) every 3rd day: I x x I x x I x x I		
	ON	Zinc Citrate	2 caps		2 caps
	ON	Men's Pure Packet	1 packet		
	ON	DHEA 25mg			1 cap
	ON	Quercetin 250mg	2 caps		2 caps
	ON	Cognitive Aminos	2 caps	2 caps	
	ON	RiboCarnitine-Q10	1 cap		1 cap
	ON	Mineral 650	1		1 cap
	ON	Glucosamine MSM	2 caps		2 caps
10/07/2014	ON	7-Keto DHEA			1 cap

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
7/2014	OFF	Testosterone C	200mg	Weekly	

Present Supplements

Verify	Status	Supp	Dosage	Timing	Verify	Status	Supp	Dosage	Timing

Anticipated Scheduled Visits

January 2015	P1520, Vitamin D, PSA



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HB

Lab Date: 10/07/2014

Additional Notes:

06/10/2014	Office Blood Draw.
06/19/2014	Q: Patient had significant improvement in knees ("150%") better and feels he is losing weight.
06/23/2014	Final Report sent and Fed X TBI Handbook
06/24/2014	OV. Pt exposed to children with URI. No anabolic steroids or any hormones in the past.
10/07/2014	Office Visit: With Labs
10/11/2014	Emailed preliminary comments
10/13/2014	Email final report
10/30/2014	Skype or Phone. Reviewed labs and protocol. Patient doing well. Knees are good, in gym working out more physical.

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com

SKYPE: MLGordonTBI



Case History:TX2

Treatment

38 y/o Male (RJ)*: A Brit with soccer brawls in the past.				
History	Concussions w/o LOC	Post Concussion Syndrome		
Symptoms	Muscular weakness	Fatigue		
Medication	Crestor 20mg			
Diagnoses	Hypogonadism	Compensatory Hypothyroidism	Elevated rT3 Low T3 Synd.	Hypo-Vitaminosis D
Treatment	Testosterone CP 40mg Q3rdDay	DHEA 25mg QSH	Pregnenolone 30mg QHS	Cognitive Aminos
	Vitamin D3 5,000iu QDay			



Special Case

Patient started GH 2iu a day.

1.GH/IGF-1 increases the

Conversion of T4 to T3.

2. TRH is regulated by T4 levels.

3. Low T4 increased TSH.

(Check Selenium/Iodine)

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RJ
Lab Date: 3/19/2015

Testosterone: 03/17/2015 0.15cc (30mg) Q3D.

Hormone Testing	Results	Ranges	08/28/14	2/13/14	12/19/13	11/8/13
Growth Hormone		5*ng/ml	3.65 LN		0.2 L	
Somatomedin C (IGF-1)	260 N	> 200 ng/ml*	404 N	311 N	221 N	271 N
IGF Binding Protein 3	5700 N	>4000 ng/ml*	6500 N	5100 N	4700 N	5100 N
DHEA-S	351.5 HN	250 ug/dl*	489.6 H	421.6 HN	482.7 H	68.3 L
Testosterone Free	7.7 LN	14 pg/ml*	14.67 N	21.93 HN	14.18 N	7.89 LN
Testosterone Total	375 LN	690 ng/ml*	676 N	752 HN	547 LN	383 LN
Dihydrotestosterone	24.9 N	< 55 ng/Dl*	39.4 N	28 N	45.2 N	13.4 LN
Sex Hormone Binding Gb	28 N	< 42 pg/ml*	31 N	24 N	27 N	34 N
PSA	0.697 N	< 4.0ng/ml				
Estrone (E1)	6 N	< 90 pg/ml*	18 N	28 N	13 N	14 N
Estradiol (E2)	6.3 N	< 25.1 pg/ml*	17.7 N	17.8 N	22.2 N	<5 N
Progesterone		0.8ng/ml*	1.73 HN		1.72 HN	
Pregnenolone		205ng/dl*	341 HN		559 H	
FSH		7 mIU/ml*	0.1 LN		0.6 L	
LH		5.1 mIU/ml	<0.1 LN		<0.1 L	
Prolactin		14 ng/ml*	7.5 N		14.2 N	
Zinc		95 mcg/dL*	136 H			
Insulin		< 30mIU/L	6.8 N			
Vitamin D3		>60 ng/dl*	70 N		45 LN	
TSH	3.28 HN	<2.5 mcu/ml*	5.88 H		3.88 HN	
T3, Free	3.4 N	> 2.5 pg/ml	3.7 N		3.7 N	
T4, Free	1.15 LN	> 1.5 ng/ml	0.76 LN		1.44 LN	
rT3	203 HN	80-250 pg/ml	100 N		180 HN	
T3/rT3 Ratio	1.67 N	>1.06	3.7 N		2.05 N	
TPO		<35				
ACTH		< 35pg/ml *	16.65		18.65 N	
Cortisol		< 15 ug/dl	14.9 HN		14.5 HN	

** These values represent the median or 50th percentile of the hormone range.*

L = Low. LN = Low. N = Normal. HN = High Normal. H = High.

Active	Diagnosis	Doctor	Phone	ICD-10
2013	Hypogonadism	Mark L. Gordon M.D.	(818) 990-1166	257.20
2013	Partial Hypothyroidism 1°	Mark L. Gordon M.D.	(818) 990-1166	

Mark L. Gordon, M.D., 16661 Ventura Blvd., Suite 716. Encino, California 91436. (818) 990-1166

Please stand and give your opinion on these issues!

The interaction between growth hormone and the thyroid axis in hypopituitary patients.

Clinical Endocrinology (2011) 74, 281–288Lucy Ann Behan, John P. Monson† and Amar Agha. Academic Departments of Endocrinology, Beaumont Hospital, Dublin, Ireland and St Bartholomew's Hospital, London, England.



- In adult hypopituitary patients, GH replacement has been reported to unmask central hypothyroidism in 36–47% of apparently Euthyroidism patients.
- Alterations in the hypothalamo-pituitary-thyroid axis have been reported following GH administration in both adults and children with and without growth hormone deficiency.
- Reductions in serum (fT4), increased (T3) with or without a reduction in serum TSH secretion have been reported following GH replacement. Inconsistencies exist.

Dehydroepiandrosterone replacement reduces growth hormone dose requirement in female hypopituitary patients on GH replacement. Clin Endocrinol (Oxf). 2006; 65(5):673-80,Brooke AM; Centre for Clinical Endocrinology, William Harvey Research Institute, St. Bartholomew's Hospital, QMUL, London, UK.



- DHEA replacement in female patients lead to a 20% reduction in the dose of GH for a constant serum IGF-I.
- This was maintained for 12 months and there was a significant fall in serum IGF-I two months after withdrawal of DHEA.
- Therefore, take at night and not in the morning to enhance GH production.



Normal

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RJ
Lab Date: 3/19/2015

Chemistry	Result	Range			08/24/14	02/13/14	11/8/13
Glucose (NF)	118nf	<100mg/dl			98	127 H	92
Sodium (NA)	145	133-149 meq/L			141	137	142
Potassium (K)	4.2	3.5 – 5.5 meq/L			4.3	4.2	3.8
Chloride (Cl)	97	96-108 meq/L			103	101	100
Iron (Fe)	116	30-160 mcg/L			135	63	
LIVER TESTING	Normal				Abnorm	Normal	Normal
SGOT	25	0- 33 U/L			35 H	27	24
SGPT	39	0 – 43 U/L			61 H	47	49
Total Protein	7.1	6 – 8.4 gm/dl			7.0	7	7.4
Albumin	4.7	4.1 – 5.4 gm/dl			4.6	4.6	5.1
Globulin	2.4	2.0 – 3.7 gm/dl			2.4	2.4	2.3
Alkaline Phosphatase	79	30-125 U/L			77	65	47
Lactose Dehydrogenase	108	80 – 225 U/L			133	128	250
GGTP	31	2 – 60 mg/dl			32	45	53
Total Bilirubin	0.9	0.1 – 1.2 mg/dl			0.8	0.5	0.9
BONE, JOINTS	*Normal*				*Normal*	*Normal*	*Normal*
Calcium (Ca)	9.0	8.4 – 10.8 mg/dl			9.5	10.2	10
Phosphorus	3.5	2.3- 5 mg/dl			3.9	3.6	
Uric Acid	4.8	3.5 – 7.2 mg/dl			5.1	4.3	7.8
Magnesium (Mg)	2.2	1.5 – 3.0 mg/dl			2.5		2.3
LIPIDS	*Normal*				*Abnorm*		
Triglycerides (FAT)	56	< 162 mg/dl			81	221 H	141
Cholesterol	258 H	< 200 mg/dl			273 H	268 H	292 H
HDL (Good)	56	>45 mg/dl			63	61	68
LDL (Bad)	191	<100 mg/dl			194	163 H	196
Cardiovascular Risk	4.6	1 Risk ⊗			4.3	4.3 ☺	4.29
RENAL FUNCTION	*Normal*				*Normal*	*Normal*	*Normal*
Blood Urea Nitrogen	15	6 – 25 mg/dl			19	19	20
Creatinine	1.2	< 1.2 mg/dl			1.1	1.2	1
BLOOD COUNT	*Normal*				*Normal*	*Normal*	*Borderline*
ESR	4	0 – 10 mm/hr			5	4	1
WBC	5.7	4.0 – 10.8 $x10^3$			5.2	7.4	13.7
RBC	4.91	4.3 – 6.1 $x 10^6$			5.2	5.15	4.8
Hemoglobin	15.1	13 – 17 gm/dl			15.8	15.6	14.8
Hematocrit	43.7	39 – 52%			46.2	45.7	47.4
MCV	89	80 – 99 fL			88.8	88.7	99 H
Granulocytes	46.6	45 – 75%			42	59.5	
Lymphocytes	12.1	20 – 50%			46	27.7	
Eosinophils	3.4	<5%			2	1.7	
Urine Analysis	N/Dehyd	Normal			Abnor		

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RJ
Lab Date: 3/19/2015

Dear JR,

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; .normal patterns. Supplementation? DHEA-s is the precursor to Testosterone and Estrogens and is High-Normal. This is not an issue as long as there is no acne or oily skin. The important Free testosterones is low-normal as is the Total Testosterone. DHT is normal as is the Sex Hormone Binding Globulin. If DHT was elevated it would cause hair loss and thinning. PSA from the prostate is NORMAL. Estrogens are normal. At this point the brain-thyroid system has changed from your GH use. This is transient where the higher levels of GH/IGF-1 are causing the T4 to rapidly convert to T3. Lower levels of T4 cause TSH to increase. There has been an improvement since last testing. (reduced rhGH?).

Chemistry Profile: Blood sugar is normal for a non-fasting test (up to 140-145mg%). Liver functions and markers, bone metabolism, fats, kidney functions, and cell counts are all within acceptable normal ranges. Cholesterol is elevated but not inconsistent with your prior levels. Suggest that we do an LP-6 to make sure that the inflammatory markers for heart disease are low!! (LP-6 suggested with next labs).

Urine Analysis: More water needed. Some Urate crystals present. More water.

Suggested Protocol: **Please verify your program and fax any corrections to (818) 990-2841.**

Verify	Status	Products	Morning	Afternoon	Evening
	ON	Testosterone Cypionate	.150cc (30mg) every third day.		
	ON	Men's Pack	1 pack		
	ON	DHEA 25mg			1 Cap
	ON	Pregnenolone			1 Cap
	Hold	Cognitive Aminos	2 caps	2 caps	
	Change	Zinc Citrate	2 caps		
	ON	Vitamin D3 5000 IU	1 cap		

Present Medication

Status	Medication	Dosage	Timing	Comments
Rec	Crestor	10mg	Daily	Consideration if diet and exercise fail.

Present Supplements

Status	Supplement	Dosage	Timing	Status	Supplement	Dosage	Timing

Please call to make your appointment (818) 990-1166

September 2015	LP-6
March 2016	P3426. P1449. PSA.

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RJ
Lab Date: 3/19/2015

Additional Notes: ☐ **TBI** ☐ **Out of Town**

11/08/2013	Remote Blood Draw
11/15/2013	Email Final report.
12/19/2013	OV with labs
01/03/2013	Report: No changes indicated at this juncture. Repeat labs in February.
02/13/2014	OV with labs
02/20/2014	Phone: Review.
8/28/2014	OV with labs
09/11/2014	Email final report schedule Skype.
	Skype
03/19/2015	OV with Labs
03/26/2015	Email final lab. Offer Skype or phone if review requested.
04/09/2015	SKYPE follow-up: Discussed Thyroid. Needs UFCT-SCAN.

X	**Mark L. Gordon, M.D., AAFP,ABAAM**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
Skype: MLGordonTBI



Case History:TX3

Treatment

54 y/o Female (MK): **Neurotrauma from fall.**				
History	Blunt Head Trauma w/o LOC	MVA w/o LOC	1° Ovarian Failure	
Symptoms	Depression w/ Panic Attacks	Angry and Mean	Insomnia – Sleep deprivation	
Medication	Paxil 20mg	Provera	Premarin	
Diagnoses	Adult GH Deficiency	Hypogonadism 1° ovarian failure	Hypo-Vitaminosis D	
Treatment				



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ALLERGIES:

TBI

MK (54)
Lab Date: 01/20/2015

LNMP: 2010 -

Hormone Testing	Results	Range	08/05/14	05/08/14	03/20/14
Growth Hormone	0.76 LN	5ng/ml*			**0.03 LN**
Somatomedin C (IGF-1)	212 N	> 200 ng/ml*			**116 LN**
IGF BP-3	3950 LN	>4000 ng/ml*			**2750 LN**
DHEA-S	237 HN	195 ug/dl*			76 LN
Estrone (E1)	27.0 N	< 200 pg/ml*			187 N
Estradiol (E2)	96 N	90 pg/ml*			238 HN
Progesterone	3.86 LN	5-7 ng/ml*			.26 L
Pregnenolone	78 LN	100 ng/dl*			46 L
EP Ratio	31.8 N	< 250			1634 H
Testosterone Free	2.13 N	2-4 pg/ml*			<0.01 L
Testosterone Total	43 N	<44 ng/ml*			7.3L
Dihydrotestosterone (DHT)	27.3 N	< 30 ng/Dl*			12 LN
Sex Hormone Binding Gb	56 N	< 75 pg/ml*			146 H
FSH	2.4 LN	7 mIU/ml*			47 H
LH	1.01 LN	5.1 mIU/ml			63 H
Prolactin	8.4 N	14 ng/ml*			8.0 N
Zinc	81 N	95 mcg/dL*			59 LN
Insulin	7.2Nf	< 30mIU/L			9.7 Nf
Vitamin D3	73 N	>60 ng/dl*			34 LN
TSH	2.56 HN	<2.5 mcu/ml*			3.88 HN
T3, Free	3.1 N	> 2.5 pg/ml			2.4 LN
T4, Free	1.44 N	> 1.5 ng/ml			1.12 LN
rT3	132 N	80-250 pg/ml			214 HN
T3/rT3 Ratio	2.32 N	>1.06			1.12 N
TPO	NT	<35			NT
ACTH	12.0	35pg/ml *			11.8 N
Cortisol	7.86	< 15 ug/dl			2.94 LN

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

Active	Diagnosis	Doctor	Phone	ICD-10
2010	Anxiety with Panic			
2010	Depression			
2010	Decreased libido			
2014	Adult GH Deficiency	Mark L. Gordon, M.D.	818-990-1166	
2014	Primary Ovarian Failure	Mark L. Gordon, M.D.	818-990-1166	
2014	Elevated EP Ratio	Mark L. Gordon, M.D.	818-990-1166	
2014	Hypogonadism	Mark L. Gordon, M.D.	818-990-1166	
2014	Hypovitaminosis D	Mark L. Gordon, M.D.	818-990-1166	
2014	Subclinical Hypothyroidism	Mark L. Gordon, M.D.	818-990-1166	
2014	Adrenal Fatigue/Insufficiency	Mark L. Gordon, M.D.	818-990-1166	
2014	Pregnenolone Steal Syndrome	Mark L. Gordon, M.D.	818-990-1166	
2014	Eosinophilia	Mark L. Gordon, M.D.	818-990-1166	

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MK (56)
Lab Date: 01/20/2015

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; normal. DHEA-s is the precursor to Testosterone and Estrogens and is Normal. Estrogens and progesterone are normal with a normal Estrogen Progesterone Ratio (EP Ratio). The neuroprotective Pregnenolone is normal. The important free testosterone is normal as is the Total Testosterone. DHT and Sex Hormone Binding protein are normal. FSH and LH reflect the brains regulation of the sex hormones and they are elevated meaning that the body is trying to get your body to produce more DHEA, Estrogens, Testosterone and Progesterone. This pattern is seen in Primary Ovarian Failure when the ovaries stop making hormones or if surgical menopause was induced. Vitamin D is normal. Overall, your Thyroid hormone panel suggests that you are producing a normal amount of hormone to run your body. ACTH is the hormone from the brain that stimulates your adrenal glands (above the kidneys) to make Cortisol, the hormone associated with our adaptation to stress. These are normal.

Chemistry Profile:

Suggested Program

Verify	Status	Product	Morning	Afternoon	Evening
	ON	Secretropin	3 pumps at bed time as directed.		
	ON	EC-Prog-Test 1mg	½ gram vaginally each night.		
	ON	Progesterone 100mg			1 cap
	ON	AT 30mg	1 tablet		
	ON	Women's Pure Packet	1 packet		
	ON	DHEA 25mg			1 cap
	ON	Pregnenolone 30mg/cap			2 caps
	ON	Cognitive Aminos	2 caps	2 caps	
	ON	AD1 – Adrenal Support	1 cap		1 cap
	ON	Ultra B w/ PQQ	1 cap		1 cap

Present Medication

Status	Medication	Dosage	Timing	Comments
OFF	Paxil	20	BID	
OFF	Premarin	0.625	QD	
OFF	Provera		QD	

Present Supplements

Status	Supplement	Dosage	Timing	Status	Supplement	Dosage	Timing

Anticipated Scheduled Visits

September 2015	P1521, CBC. Add Thyroid and Adrenal.

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MK (56)
Lab Date: 01/20/2015

Additional Notes:

03/20/2014	In Office Blood Draw. PTT 0.15cc (30mg).
03/24/2014	Phone: Response was a 7/10.
03/31/2014	Email report. Prepare Handbook. Arrange for a skype/call
04/03/2014	Skype Call: Review history, laboratory report and suggested protocol #1.
04/17/2014	Phone: Patient notes some improvement in sleep and mood. Libido picking up.
05/04/2014	Questionnaire – improvements.
05/08/2014	In Office Blood Draw. Patient doing better.
05/19/2014	Email final report. Arrange for Skype/Call.
05/26/2014	Phone: reviewed lab results, protocol and lowered testosterone.
07/xx/2014	Questionnaire – improvements.
08/05/2014	In Office Blood Draw. Patient doing better.
08/xx/2014	Email final report. Arrange for Skype/Call.
08/xx/2014	Phone: reviewed lab results, protocol
09/xx/2014	Questionnaire – improvements.
01/20/2014	In Office Blood Draw. Patient continues to do well.
02/xx/2015	Email final report.
02/xx/2015	Phone: reviewed lab results, protocol. Patient to continue on protocol. Repeat labs in 6 months then to annual protocol.
03/xx/2015	Questionnaire status quo.
09/??/2015	Labs pending.

X	**Mark L. Gordon, M.D., AAFP,ABAAM**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
Skype: **MLGordonTBI**



Case History:TX4

Treatment

32 y/o Male (PM): Blunt Head Trauma				
History	Age 6 Fall from balcony w/LOC	Post Concussion Syndrome	Depression Anxiety	MVA w/o LOC
Symptoms	Fatigue	Mood Swings Depression/Anxiety	Insomnia	Low Libido
Medication	Mary Jane			
Diagnoses	Hypogonadism 3°	Insulin Ω DM Hyperinsulinemia		
Treatment				



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ALLERGIES:

TBI

PM
Lab Date: 09/24/2015

CLOMID: Q3D

Hormone Testing	Results	Range			7/14/15	03/10/15	01/15/15
Growth Hormone		5ng/ml*					0.17 LN
Somatomedin C (IGF-1)	193 LN	> 200 ng/ml*			169.0 LN	199 LN	304 N
IGF BP-3	4000 N	4000 ng/ml*			4200 N	4600 N	4300 N
DHEA-S	408.1 HN	245 ug/dl*			454.7 H	449.6 H	477.2 H
Testosterone Free*±	18.37 HN	14 pg/ml*			11.54 N	15.31 HN	6.86 LN
Testosterone Total*	873 HN	690 ng/ml*			679 N	759 HN	367 L
Dihydrotestosterone (DHT)	36.8 N	< 55 ng/Dl*			29.0 N	40.3 N	24 N
Sex Hormone Binding Gb	36 N	< 45 pg/ml*			43 N	36 N	32 N
Estrone (E1)	10 N	< 60 pg/ml*			12.0 N	16 N	<1.0 N
Estradiol (E2)	36.6 HN	25 pg/ml*			37.6 HN	47 HN	15 N
Progesterone		0.8ng/ml*					1.13 HN
Pregnenolone		110 ng/dl*					72 LN
FSH		7 mIU/ml*					3.0 LN
LH*	11.5 HN	5.1 mIU/ml			3.8 LN	8.8 H	4.2 LN
Prolactin		14 ng/ml*					6.5 N
Zinc*		95 mcg/dL*					101 HN
Insulin*	6.2 N	< 25 mIU/L			3.9 N		58.9 H
Vitamin D3*		60 ng/dl*					38 LN
TSH		<2.5 mcu/ml*					1.2 N
T3, Free		> 2.5 pg/ml					3.5 N
T4, Free		> 1.5 ng/ml					1.43 LN
rT3		80-250 pg/ml					210 HN
T3/rT3 Ratio		>1.06					1.66 N
TPO		<35					NT
ACTH		< 35pg/ml *					12.23 N
Cortisol*		< 15 ug/dl			16.1 HN	28.3 H	21.5 H

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High-Normal. H = High

High DHEA-s and Low Free Testosterone:

WHY??

Heavy Metal Toxicity = Hg affects the CYP17A1 Enzyme system.

Elevated Insulin in a 32yo. Metabolic Syndrome?

Active	Diagnosis	Doctor	Phone	ICD-10
1990	Fall w/LOC <24 hrs			
1990	Post Conscussional Syndrome			
1990	Depression			
2013	MVA? Multiple lateral impact.			
	Sports related TBI			
2015	Hypogonadism - Central	Mark L. Gordon, MD	818.990.1166	
2015	Hypovitaminosis D	Mark L. Gordon, MD	818.990.1166	
2015	Hypercortisolemia	Mark L. Gordon, MD	818.990.1166	
2015	Hyperinsulinemia	Mark L. Gordon, MD	818.990.1166	
2015	Metabolic Syndrome	Mark L. Gordon, MD	818.990.1166	

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Low Testosterone In Men May Be A Diabetes Risk Factor

Journal Diabetes Care, Feb **2007.** Elizabeth Selvin. Johns Hopkins Bloomberg School of Public Health in Baltimore



- After the influence of age, race and obesity was factored in, **men with the lowest levels of testosterone were four times (4x) more likely to have diabetes than men with the highest levels.**

Testosterone and Sex Hormone–Binding Globulin Predict the Metabolic Syndrome and Diabetes in Middle-Aged Men

. *Diabetes Care* 27:1036-1041, 2004. David E. Laaksonen, MD, PHD, MPH1, Leo Niskanen, MD, PHD, Tomi-Pekka Tuomainen, MD, Veli-Pekka Valkonen, MD, Riitta Salonen, MD, PHD, and Jukka T. Salonen, MD, PHD, MSCPH, Department of Medicine, Kuopio University Hospital, Kuopio, Finland.



- Low total (T) and SHBG levels independently predict development of the Metabolic Syndrome and diabetes in middle-aged men.
- Hypogonadism is an early marker for disturbances in insulin and glucose metabolism that may progress to the metabolic syndrome or diabetes.



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ALLERGIES:

TBI

PM
Lab Date: 09/24/2015

Dear Michael,

Based upon these results you are good regarless of your increased physical activities and related injuries. This treatment does nothing to stop injuries!!

Hormone Profile: GH stimulates the liver to produce IGF-1 and IGF-BP-3; measuring these three gives us a basic look at the functioning of the pituitary and liver; almost normal pattern. DHEA-s is the precursor to Testosterone and Estrogens and continues High-Normal. This is not an issue as long as there is no acne or oily skin. The important Free testosterones is now high-normal with a high-normal Total Testosterone on 50mg Clomid Q3D Protocol. LH is now high-normal your testicular response is normal testosterone. DHT is normal. Sex Hormone Binding is normal. Estrone is normal with a lower but High-Normal Estradiol (E2) due to the continued impressive increase in testosterone.

Chemistry Profile:

Please verify your protocol and send any corrections to 818-990-2841 or reception@millenniumhealthcenters.com

Verify	Status	Product	Morning	Afternoon	Evening
	ON	Clomid 50mg	Q3rd day. C xx C xx C xx C		
	ON	Ultranutrient	2 caps		2 caps
	ON	Pregnenolone 30mg			1 caps
	ON	Cognitive Aminos	2 caps	2 caps	
Stop	**OFF**	Adrenal support (AD1)	1 cap		1 cap
	ON	Chromate (ITF)	1 cap		1 cap
	ON	Ultra B-complex w/ PQQ	1 cap		1 cap
	ON	Vitamin D 10,000IU	1 cap		
	ON	B-12 Hydroxycobalamin 500mcg	½ cc		
	On	Zinc Citrate	1 cap`		1 cap
New	**NC**	Glucosamine Mix	1 cap		1 cap

Present Medication

Verify	Status	Medication	Dosage	Timing	Comments
	OFF	Medical Marijuana			1 gram a week for sleep

Present Supplements

Verify	Status	Sups	Dosage	Timing	Verify	Status	Sups	Dosage	Timing

Follow-up and Laboratory Procedures

March 2016	1520 and LH

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166

Nutritional factors influencing the glucose/insulin system: chromium.

Journal of the American College of Nutrition. Volume 16, Issue 5, 1997. R A Anderson pages 404-410



- Chromium (Cr) improves the glucose/insulin system in subjects with hypoglycemia, hyperglycemia, diabetes and hyperlipidemia with no detectable effects on control subjects.
- Chromium improves insulin binding, insulin receptor number, insulin internalization, beta cell sensitivity and insulin receptor enzymes with overall increases in insulin sensitivity.



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PM
Lab Date: 09/24/2015

Additional Notes:

01/15/2015	Blood Draw. PTT 60mg with PTTQ. Good response.
01/26/2015	Final Report sent and Fed X TBI Handbook.
01/29/2015	SKYPE CALL: Review of labs and treatment protocol. Start Clomid. Hold Testosterone.
03/10/2015	In Office: Labs 1520, LH, Cortisol.
03/17/2015	Email final report. Will add Insulin to next labs.
03/19/2015	SKYPE CALL: Review labs and adjustments to treatment protocol.
04/03/2015	MPQ received and commented on.
07/14/2015	In office blood draw. Review of protocol and recults. Patient condition improved.
07/23/2015	Email lab report. Continue Clomid 4 days a week. Stop AD1. Insulin normal. Skype follow-up 30 minutes.
8/10/2015	In Office: (±) Patient was off Clomid 50 for 2 weeks prior to testing.
09/24/2015	In Office Blood Draw.
10/01/2015	Email final report. Arrange for 15 minute skype
10/05/2015	Skype/Call: Reviewed labs and protocol.

X	**Mark L. Gordon, M.D.**		
	Medical Director,		
	Millennium Health Group		Millennium Health Group
	gordonmd@millenniumhealthcenters.com		

You can email appointment and order requests to:
Front Desk: reception@millenniumhealthcenters.com
Secretropin: http://www.secretropinrx.com
SKYPE: MLGordonTBI



Case History: TX5

Treatment

45 y/o Female (WA): Prolonged Surgery.				
History	Sub-Total Hysterectomy			
Symptoms	Fatigue	Irritability	Lost Libido	Weight Gain
Medication	None			
Diagnoses	Surgical Menopause	Hormonal Disorder Testosterone	Climacteric Syndrome	Macrocytic Anemia
Treatment				



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ALLERGIES:

WA
Lab Date: 04/25/2013

TSH Index1 = 2.03

TSH Index2 = 2.86

LNMP: 2008 Surgical Menopause

Hormone Profile	Results	Ranges		10/11/12	7/19/12
Somatomedin C (IGF-1)	275 LN	> 200ng/ml		158 LN	132 LN
IGF Binding Protein 3	6000 N	>4000 ng/ml*		6700 N	5300 N
DHEA-S	217.1 HN	140 ug/dl		663.6 H	206.8
Estrone (E1)*	157 N	< 200 pg/ml*		75.3 N	20.9 N
Estradiol (E2)**	185.3 HN	90 pg/ml*		138.6 N	23.5 LN
Progesterone	4.94 N	13 ng/ml		3.10 LN	0.12 L
EP Ratio	69 N	< 250		69	370
Testosterone Total	28 N	44 ng/dl*		85 H	18 LN
Testosterone Free**	0.24 L	3-4 pg/ml		1.27 LN	0.17 L
Dihydrotestosterone	12.1 N	<30 ng/dl		21.9 N	8.1 N
SHBG	81 HN	<75 nmol/L*		47 N	58 N
Zinc		95 mcg/dL*			
Insulin		< 30mIU/L			
Homocysteine		< 10umol/L			
C-Reactive Protein		< 1.2 mg/dl			
PLAC		< 200 ng/ml			
Vitamin D3		60ng/ml*			
TSH**	2.74 HN	<2.5 mcu/ml			1.93 N
T3, Free	2.9 N	> 2.5 pg/ml			2.9 N
T4, Free**	0.94 LN	> 1.5 ng/ml			1.04 LN
rT3	160 N	90-350 pg/ml			183 N
T3/rT3 Ratio	1.81 N	> 1.06			1.58 N
TPO	21.9 N	<35 IU/ml			
Cortisol		< 15 ug/dl *			

* The IDEAL RANGE is at the 50th percentile of optimal. Treatment is geared to 50th – 75th percentile.

L = Low. LN = Low-Normal. N =Normal. HN = High Normal. H = High

Active	Diagnosis	Doctor	Phone	ICD-9
2008	Hysterectomy			256.20
2012	Macrocytosis (B12 deficiency)	Dr. Mark L. Gordon MD	(818) 990-1166	289.89
2012	Testosterone Deficiency	Dr. Mark L. Gordon MD	(818) 990-1166	
2012	Low Progesterone	Dr. Mark L. Gordon MD	(818) 990-1166	
2013	Thyroid (T4-T3 conversion)	Dr. Mark L. Gordon MD	(818) 990-1166	

Mark L. Gordon, MD. 16661 Ventura Blvd., Ste 716. Encino, California 91436. (818) 990-1166



Normal

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Chemistry Profile	Result	Ranges						7/19/12
Glucose	91	80-120mg/dl						85
Sodium (NA)	135	133-149 meq/L						139
Potassium(K)	4.2	3.5 – 5/.5 meq/L						3.9
Chloride (Cl)	99	96-108 meq/L						101
Iron (Fe)	142	35-200 mcg/L						
LIVER TESTING								
SGOT	24	0- 34 U/L						26
SGPT	38 H	10 – 35 U/L						29
Total Protein	7.6	6 – 8.4 gm/dl						7.4
Albumin	4.4	4.1 – 5.4 gm/dl						4.6
Globulin	3.2	2.0 – 3.7 gm/dl						2.8
Alkaline Phosphatase	76	30-125 U/L						54
Lactose Dehydrogen	171	80 – 225 U/L						173
GGTP	87 H	2 – 60 mg/dl						73 H
Total Bilirubin	0.6	0.1 – 1.2 mg/dl						0.4
BONE, JOINTS								
Calcium (Ca)	9.7	8.4 – 10.8 mg/dl						9.6
Phosphorus	3.9	2.3- 5 mg/dl						
Uric Acid	4.3	2.5 – 6.8 mg/dl						4.4
Magnesium (Mg)	2.3	1.5 – 3.0 mg/dl						2
LIPIDS								
Triglycerides (FAT)	238 H	<162 mg/dl						185 H
Cholesterol	267 H	< 200 mg/dl						291 H
HDL (Good)	89	>45 mg/dl						70
LDL (Bad)	130 H	<100 mg/dl						184 H
Cardiovascular Risk	3.0	< 4.4						4.1 ☺
RENAL FUNCTION								
Blood Urea Nitrogen	17	6 – 25 mg/dl						14
Creatinine	0.9	< 1.0 mg/dl						0.6
BLOOD COUNT								
ESR	7.0	0 – 20 mm/hr						1
WBC	8	4.0 – 10.8 x10^3						7.6
RBC	5.12	4.0 – 5.4 x 10^6						4.25
Hemoglobin	16.3 H	12 – 16 gm/dl						14.9
Hematocrit	50.9 H	36 – 48%						44
MCV	99.5 H	80 – 99 fL						104 H
Granulocytes	65	45 – 75%						66.2
Lymphocytes	23.7	20 – 50%						24.7
Eosinophils	1.1	0-8%						3
Urine Analysis		Normal						

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ALLERGIES:

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Dear AW,

Stop all fats, fried foods, grease…..

Hormone Profile: IGF-1 and IGFBP-3 are markers of growth hormone production and use; IGF-1 is low. DHEA-s is the precursor to testosterones and estrogens and is now high-normal. This level is still not an issue unless you have side-effects of oily shin, acne, thinning of hair. Estrogens are now in the normal and high-normal (E1) range with an increase in progesterone. The ratio of estrogens to progesterone is optimal. Free testosterone is down again. This is more important that the total testosterone. DHT is normal with a high-normal SHBG which can bind up the free Testosterone. This can be due to the higher level of E1-Estrone.

Chemistry Profile: Blood Sugar is normal. Minerals are normal. Two of the 9 liver markers are up, Alcohol, Tylenol, some medications. Bone markers are normal. Fats, cholesterol, and LDL-c are elevated with a good cardio-risk based upon high Good HDL-c. Kidney functions are normal. Blood count shows an elevation in red cell markers from low B12 and elevation in Hematocrit (Testosterone??).

Urine Analysis: Need more water!

Please verify your program and email/fax corrections to 818-990-2841

Verify	Status	Product	Morning	Afternoon	Evening
	On	Secretropin	3 sprays at bedtime		
	ON	EstroCream with 2mgTest	(E2:0.2mg, E3:2.0mg, Prog:100mg, T:2mg) per gram .		
	ON	Women's Ultra Pack	1 packet a day.		
	ON	Pregnenolone 30mg			1 cap
	ON	DHEA 25mg	1 cap		1 cap
	ON	Cognitive Aminos	2 caps	2 caps	
	ON	Vitamin D3	1 cap		

Present Medication

Medication	Dosage	Timing	Comments
B12	500IU	TID	MCV 99.
Toprimax	25mg	Qam	90 day program
Phentermine	15mg	Qam	90 Day Program.

Present Supplements

Status	Supplement	Dosage	Timing	Status	Supplement	Dosage	Timing

Anticipated Scheduled Visits

8 week follow up	CBC.

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Additional Notes:

07/19/2012	Initial Office visit. Consult and labs
07/27/2012	Email final report.
10/11/2012	OV with labs
10/22/2012	Email final report.
04/25/2013	OV with labs
05/06/2013	Email REPORT. Need to discuss RED Cell mass. Cholesterol and fats. Live markers.

X	Mark L. Gordon, M.D., AAFP,ABAAM		Linda Hillebrand, D.O. FCOG
	Medical Director,		Assistant Director
	Millennium Health Group		Millennium Health Group
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Summary

1. Comprehensive Neurosteroid and Neuroactive Steroid assessments.
2. Interpretation using the Median Method and treating the patient and not the numbers.
3. Use of an age appropriate means to achieve the Median levels in all the NS and NAS.
4. Follow-up labs to documents the improvement in the numbers while monitoring the patient's response with the MPQ.