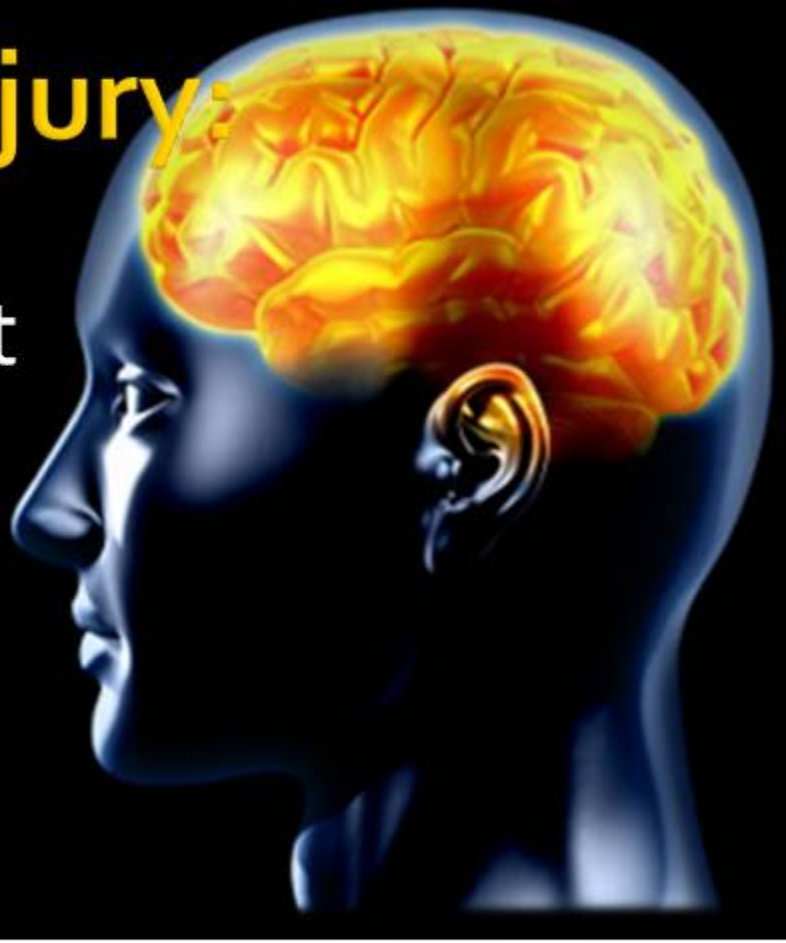
Traumatic Brain Injury:

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.

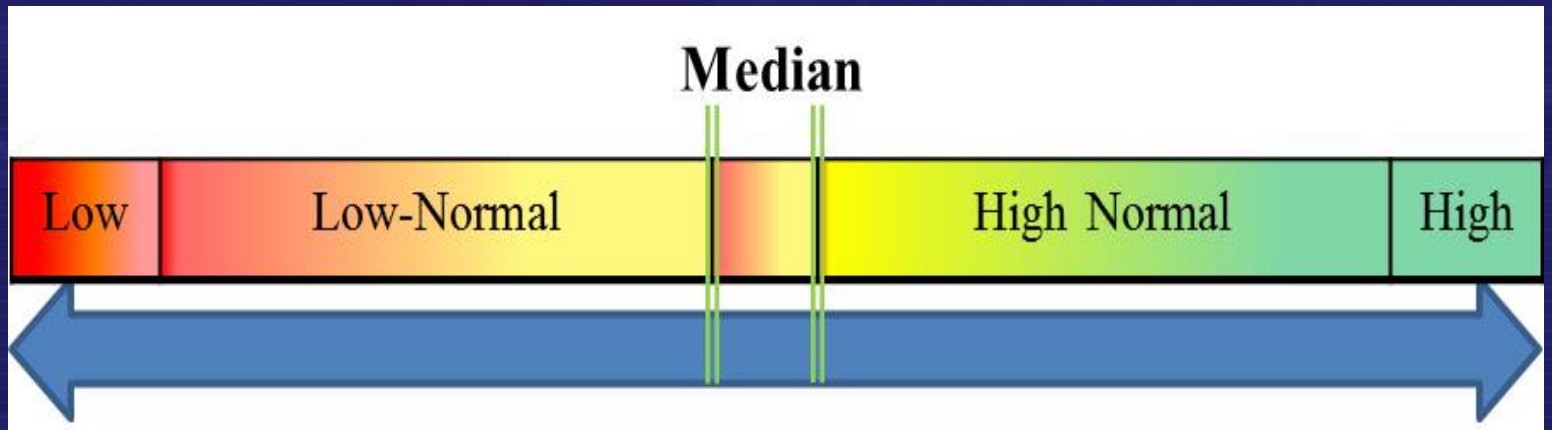


Figure 6.1 Optimal results with optimal treatment. Using treatment protocols to achieve a homeostatic balance so that each hormone hovers around its median range. Although this might be viewed as arbitrary, the concept of Homeostasis, a dynamic process, would place each hormone with points of its median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

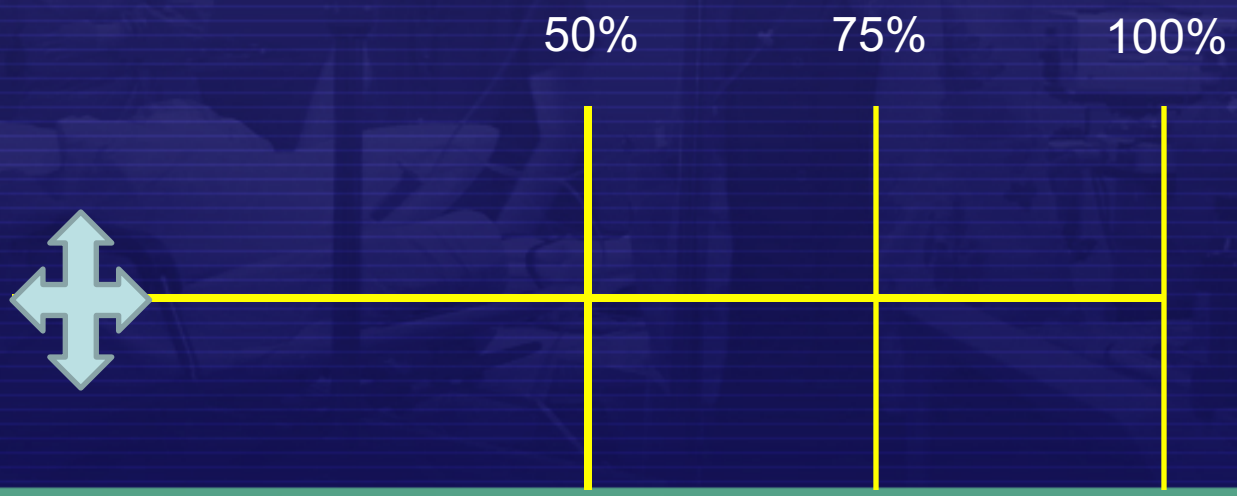
Hormone	Median M	Median F	Hormone	Median M	Median F
DHEA-s	200 ug/dL	277 ug/dL	Growth Hormone	5.0 ng/ml	5.0 ng/ml
T-Testosterone	690 ng/ml	44 ng/ml	IGF-1	>200 ng/ml	>200 ng/ml
F-Testosterone	14 pg/ml	2-4 pg/ml	IGFBP-3	4000 ng/ml	4000 ng/ml
DHT	< 52 ng/dl	< 30 ng/ml	TSH	2.5 mcu/ml	2.5 mcu/ml
SHBG	45 pg/ml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

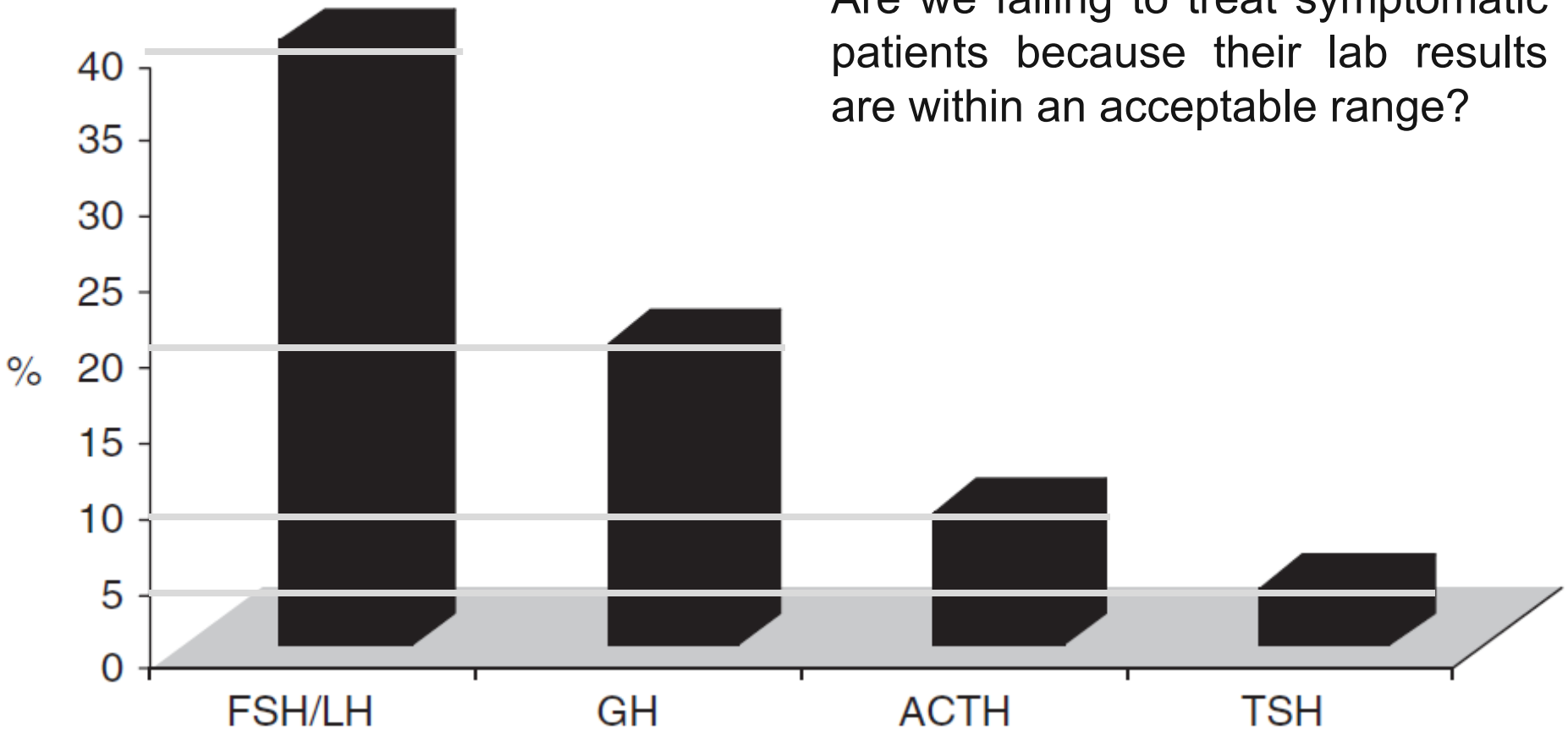


Pituitary functions in the acute phase of traumatic brain injury: Are they related to severity of the injury or mortality?

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.

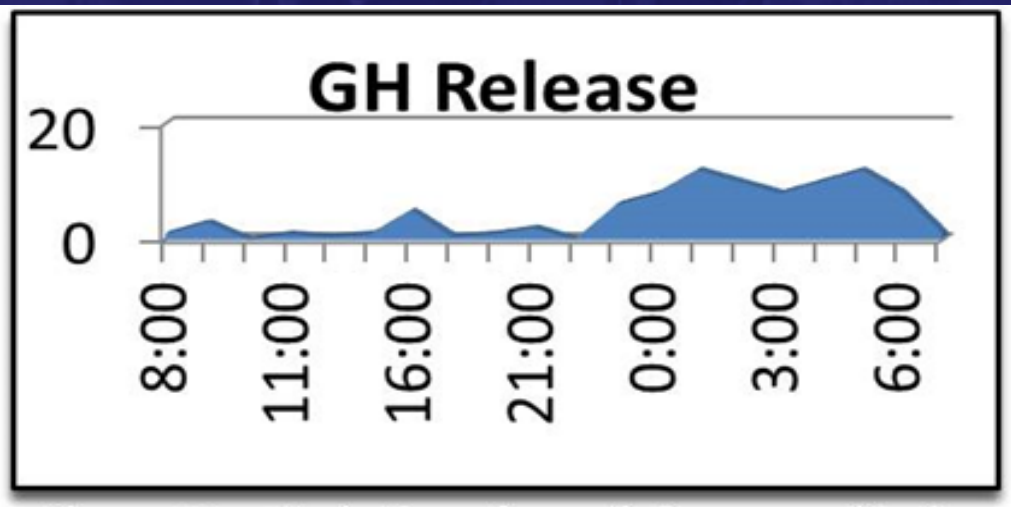
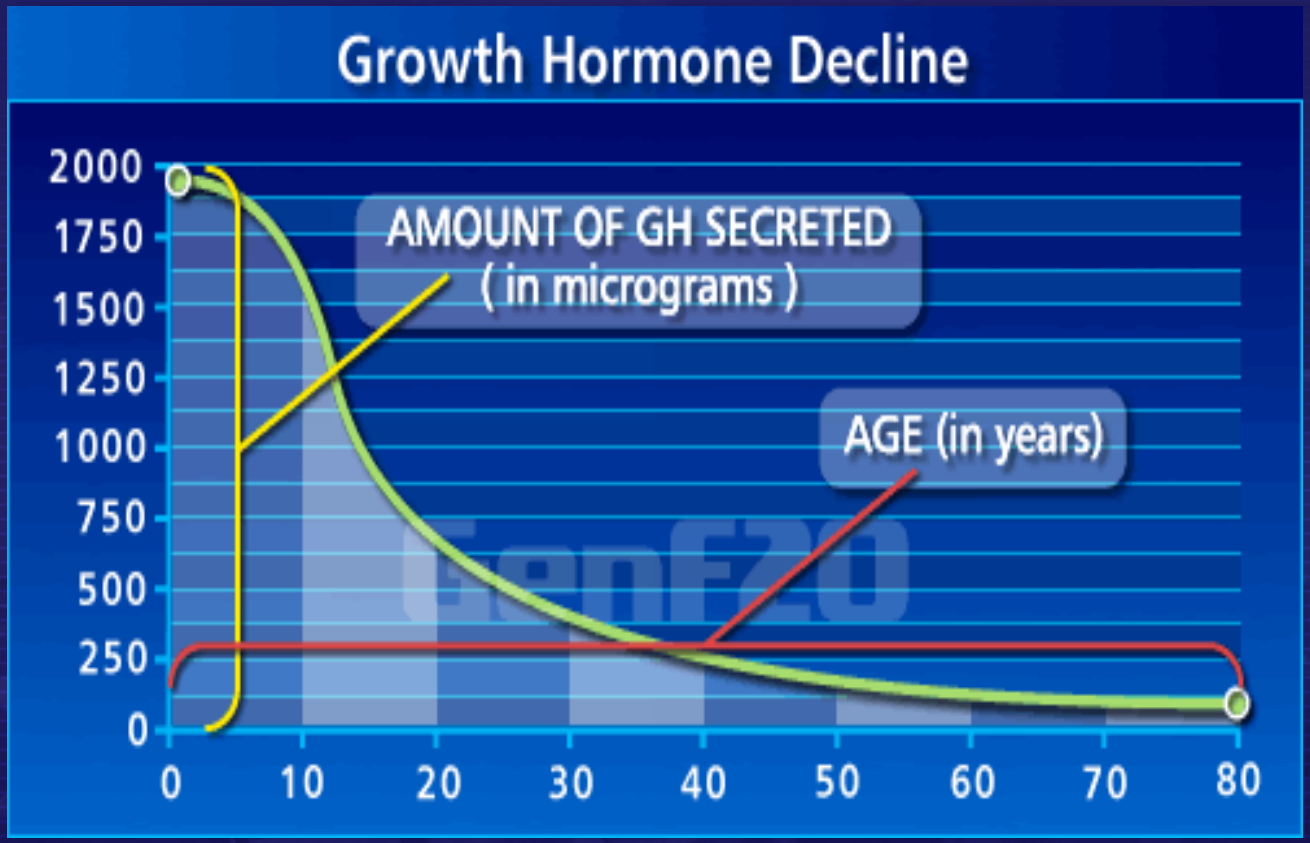


Figure 6.1: Production of growth hormone with the majority of GH released from 8pm to 4am with minor pulses throughout the day.

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.

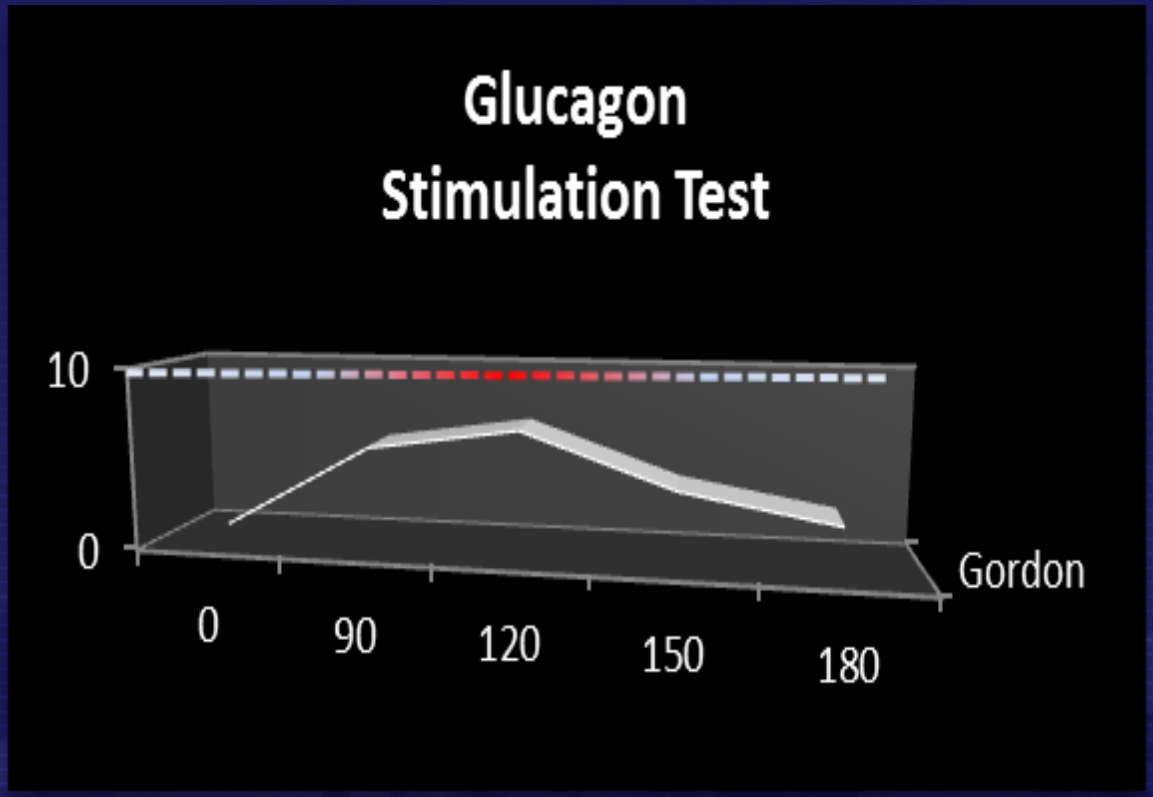
Case 1c

- 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.

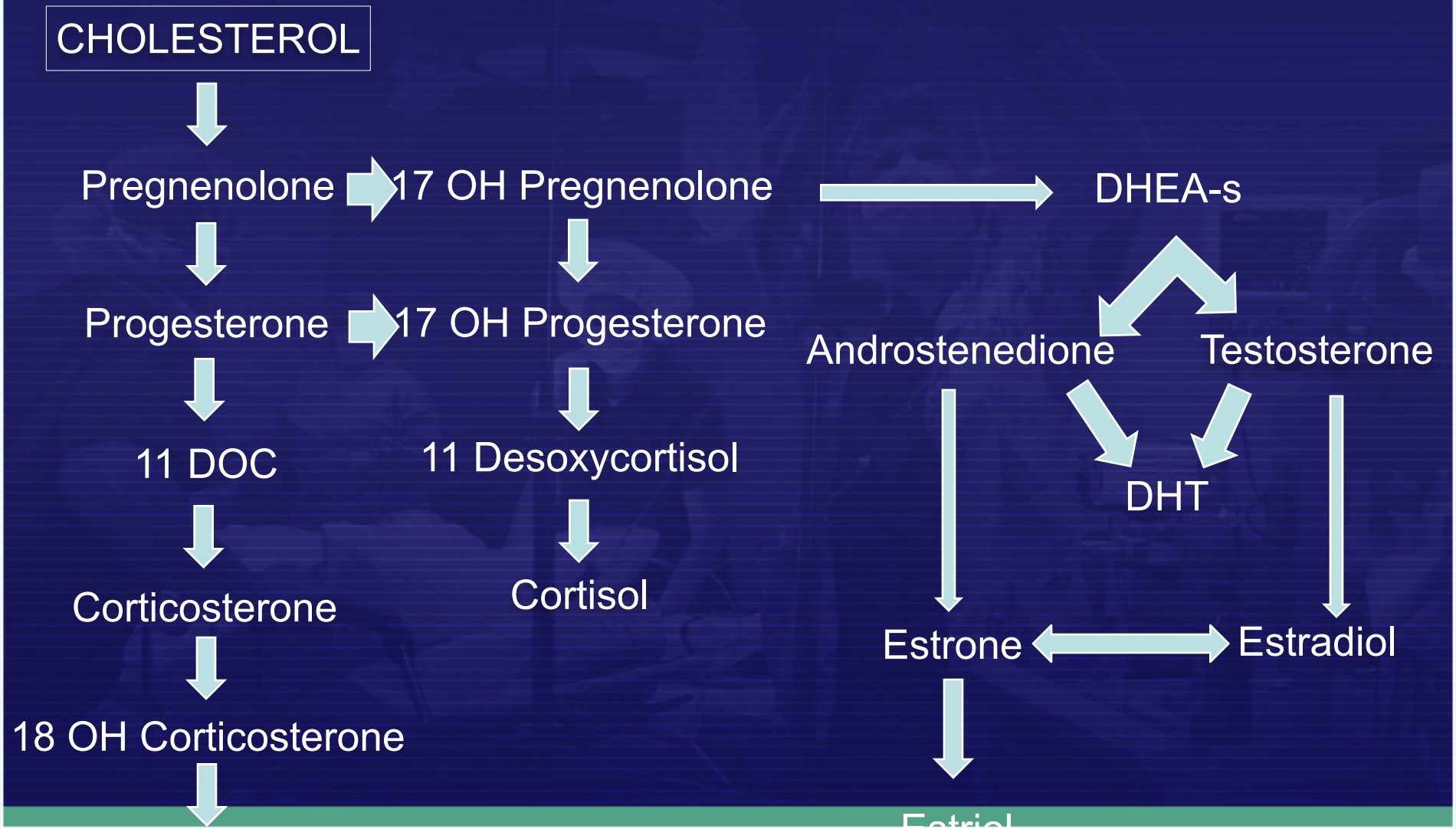
The BP-3 is abo **(1)** that during the night an ample a e liver's production of BP-3, **(2)** that high estrogen level or (4) inflammati

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

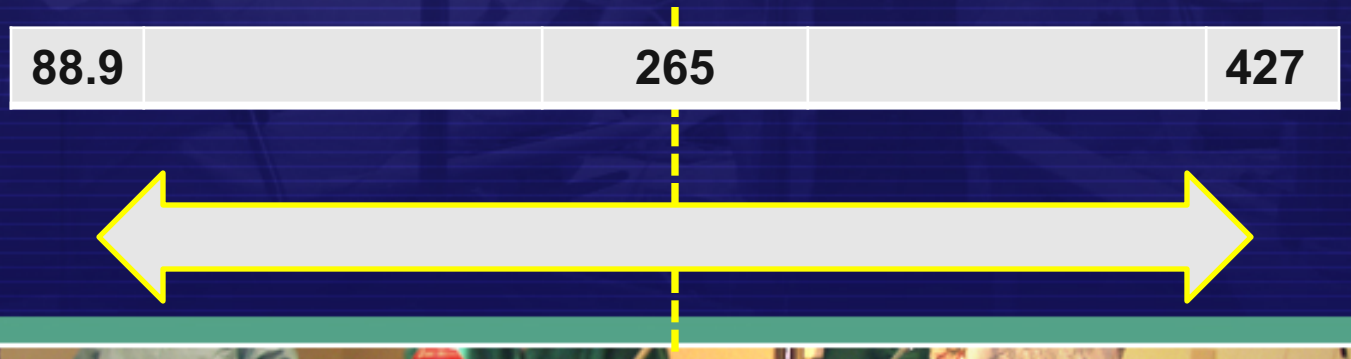
Hormone Cascade



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

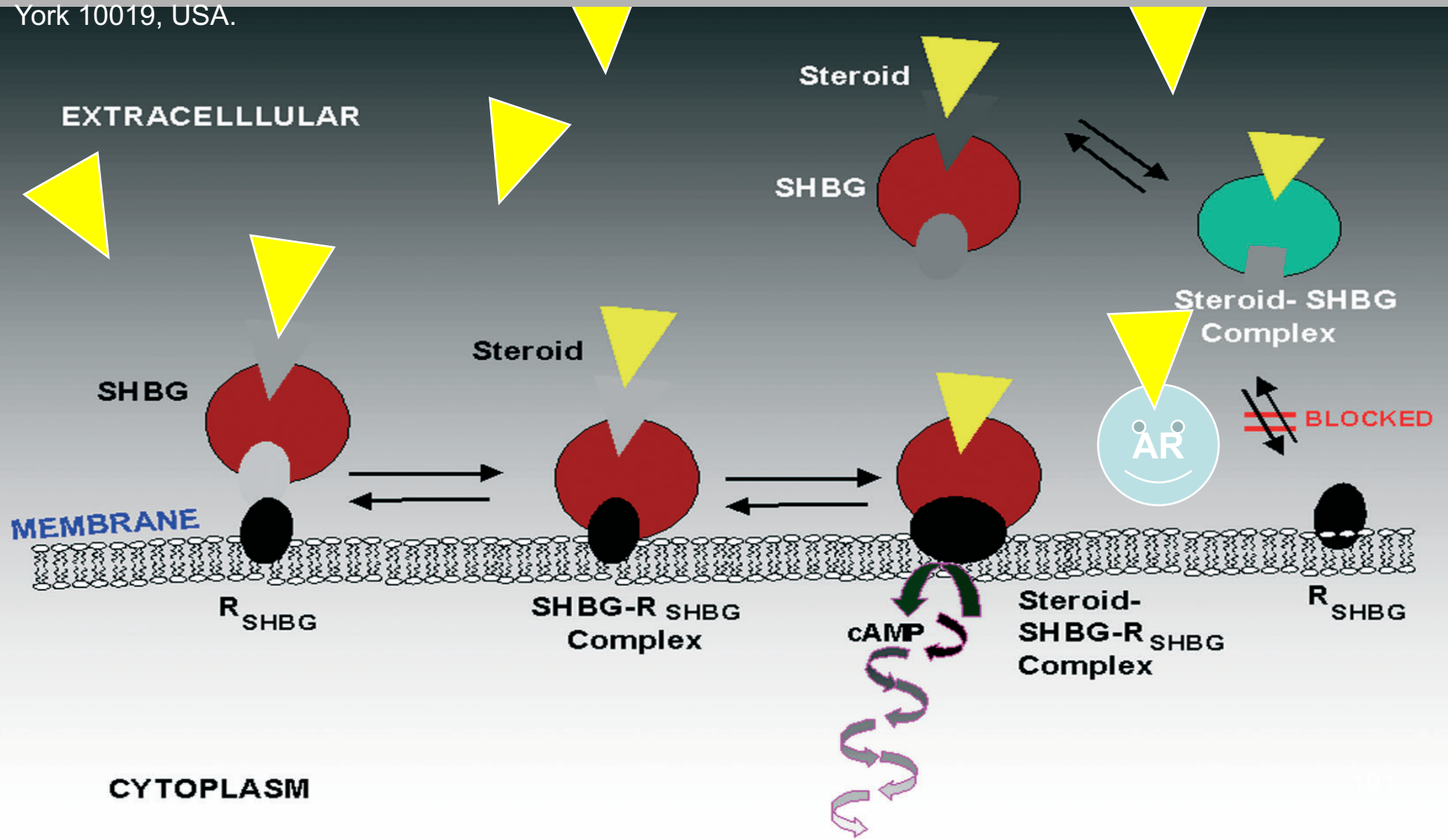
Table 2. Conditions and Medications Associated With Alterations in SHBG*[4]

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.

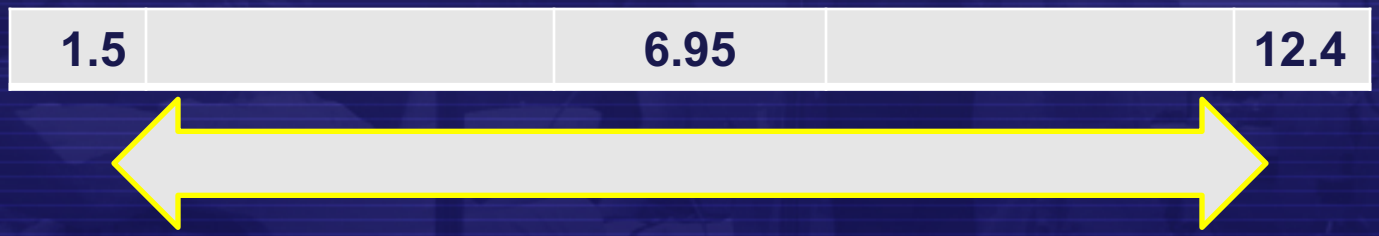
Luteinizing Hormone

- **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)

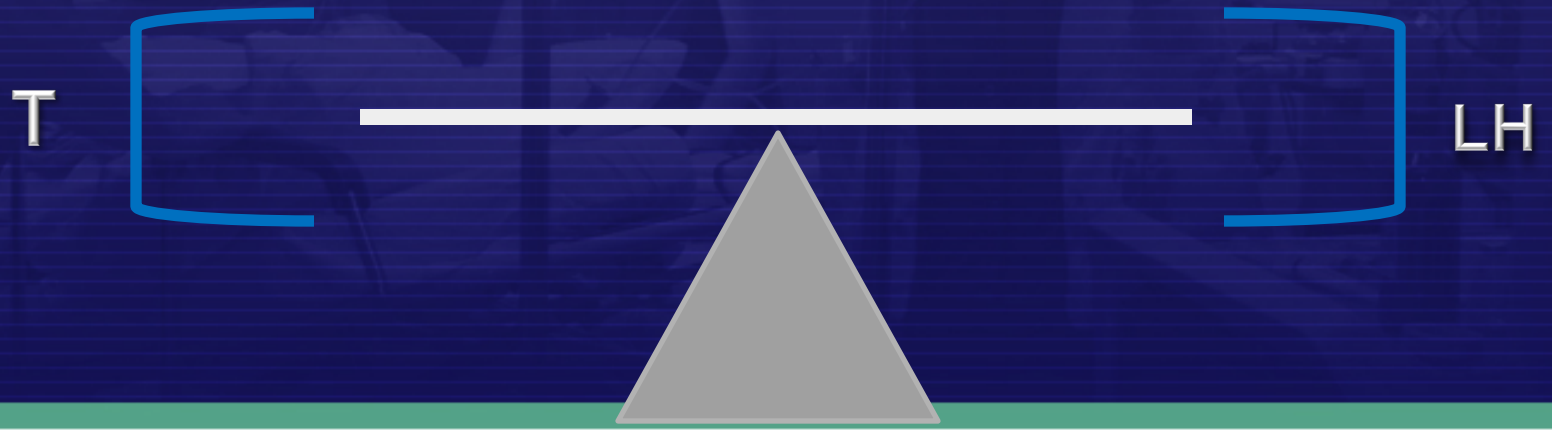


Testosterone Summary-1

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.

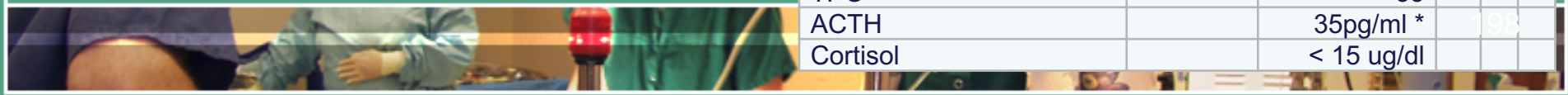
Male Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	23 L	245 ug/dl*
Estrone (E1)	2.37 N	< 60 pg/ml*
Estradiol (E2)	5.60 N	<25 pg/ml*
Progesterone	0.65 LN	0.8 ng/ml*
Pregnenolone	27 LN	110 ng/dl*
EP Ratio		< 250
Testosterone Free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

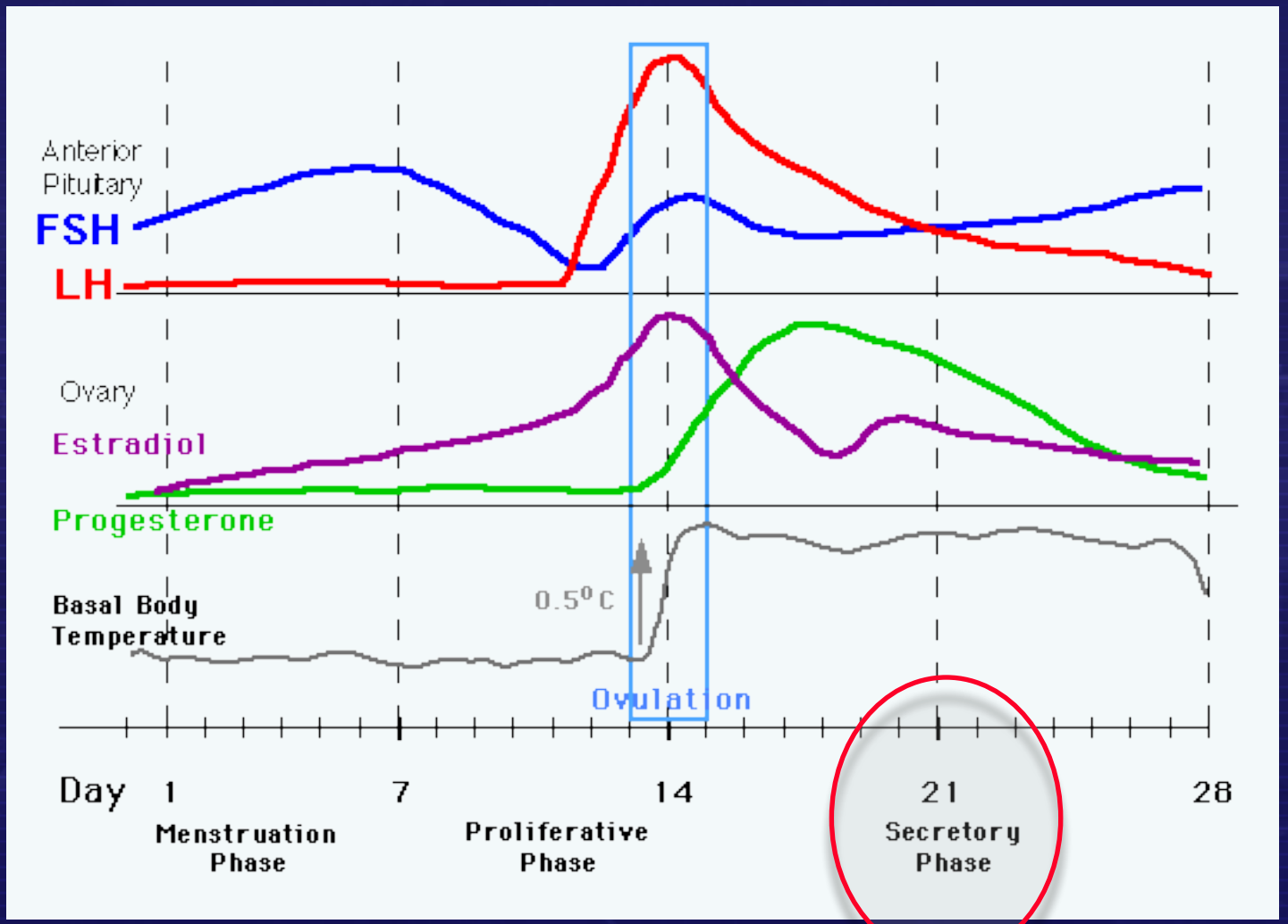
Estradiol (E2)

- 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.

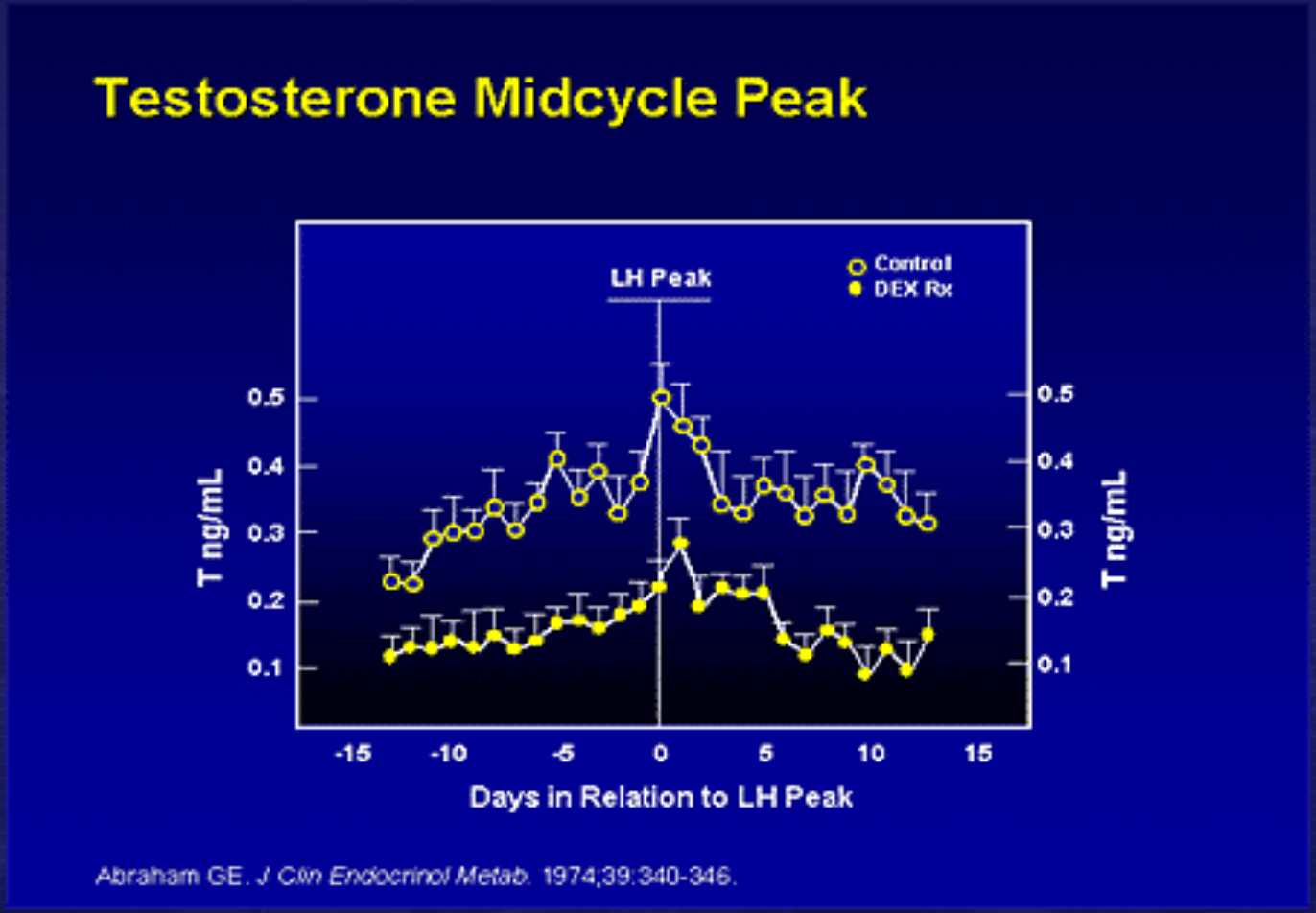
Summary for Estrogens

- 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

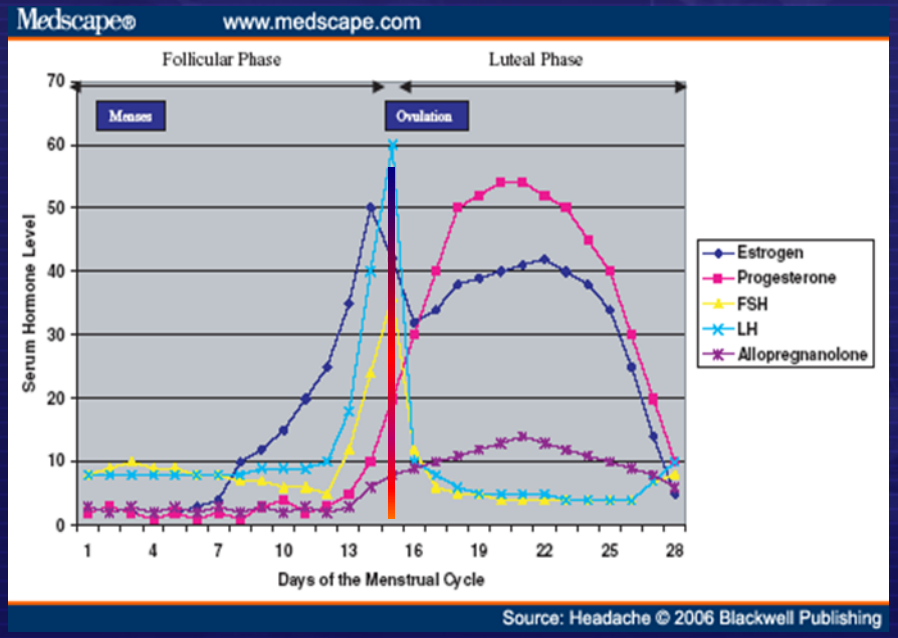
Symptoms	< 250	250- 1000	1000-5000	> 5000
Head Aches/ Migraines	Intermittent	Mild	Moderate	Severe
Sleep Issues	Intermittent	Mild	Moderate	Severe
Sleep Deprivation	NP	Intermittent	Mild	Moderate
Bloating	NP	NP	Mild	Moderate
Mood Swings/Irritability	NP	Mild	Moderate	Severe
Anxiety	NP	Intermittent	Mild	Severe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

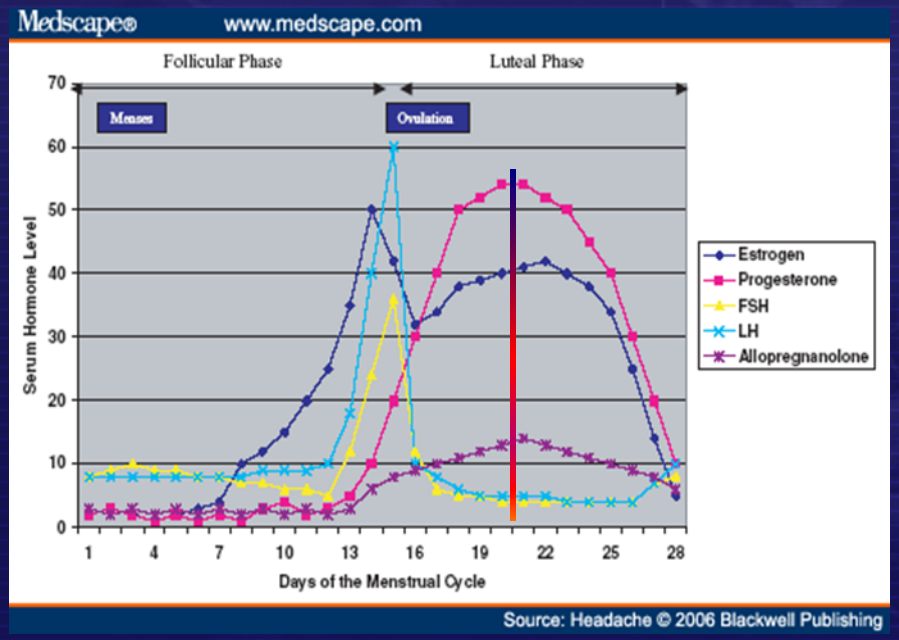


Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	143 L	195 ug/dl*
Estrone (E1)*	36 N	< 200 pg/ml*
Estradiol (E2)*	187.3 HN	90 pg/ml*
Progesterone*	1.17 LN	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio*	190 N	< 250
Testosterone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



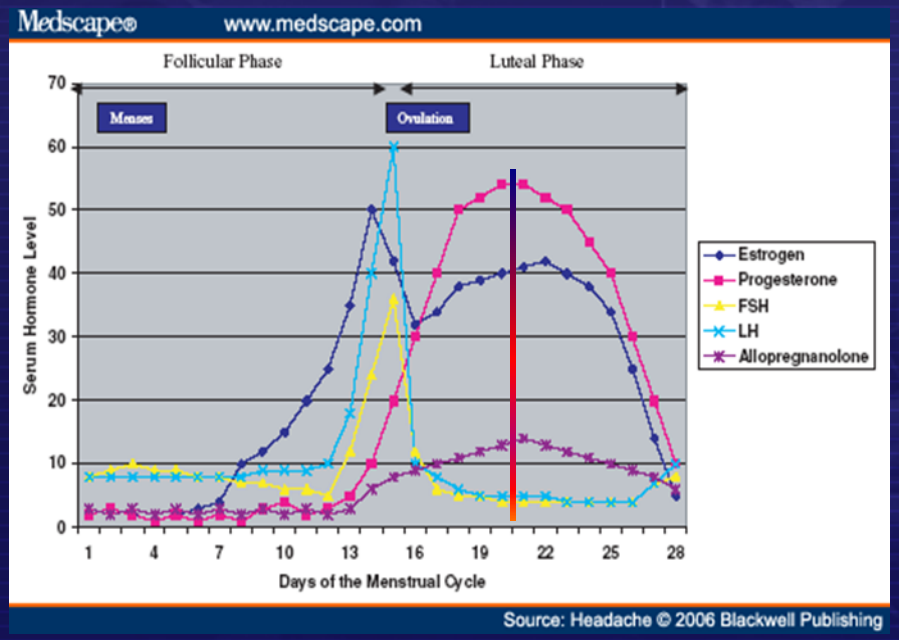
Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml*
IGF BP-3		>4000 ng/ml*
DHEA-S	121 LN	195 ug/dl*
Estrone (E1)*	8 N	< 200 pg/ml*
Estradiol (E2)*	68 LN	90 pg/ml*
Progesterone*	9.7 HN	5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio*	6.6 N	< 250
Testosterone Free*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

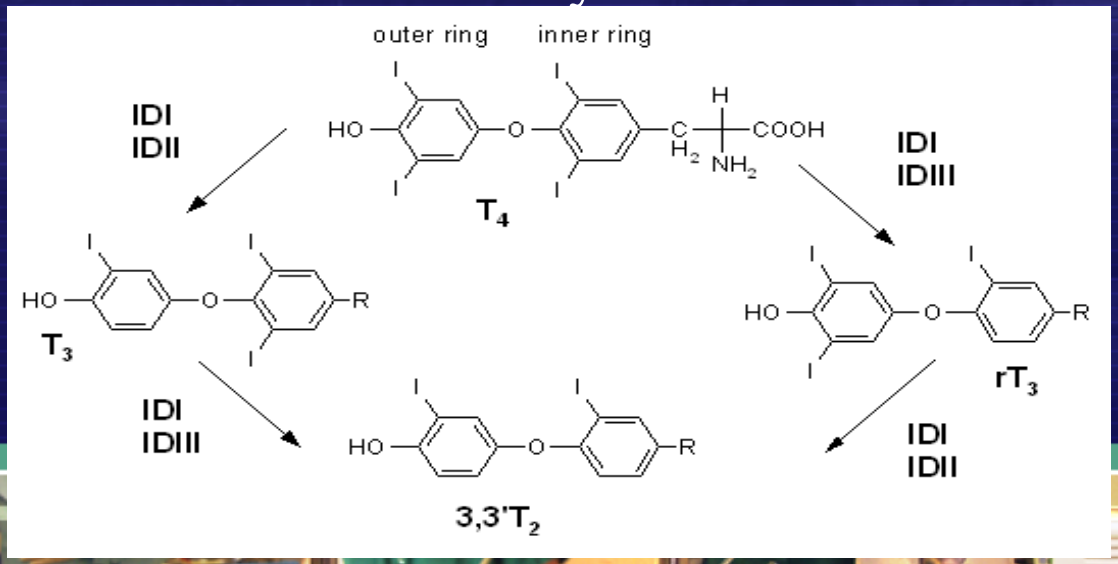
- Reference range: 1.3 – 4.6 pg/ml
- Median: 2.95 pg/ml

- 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

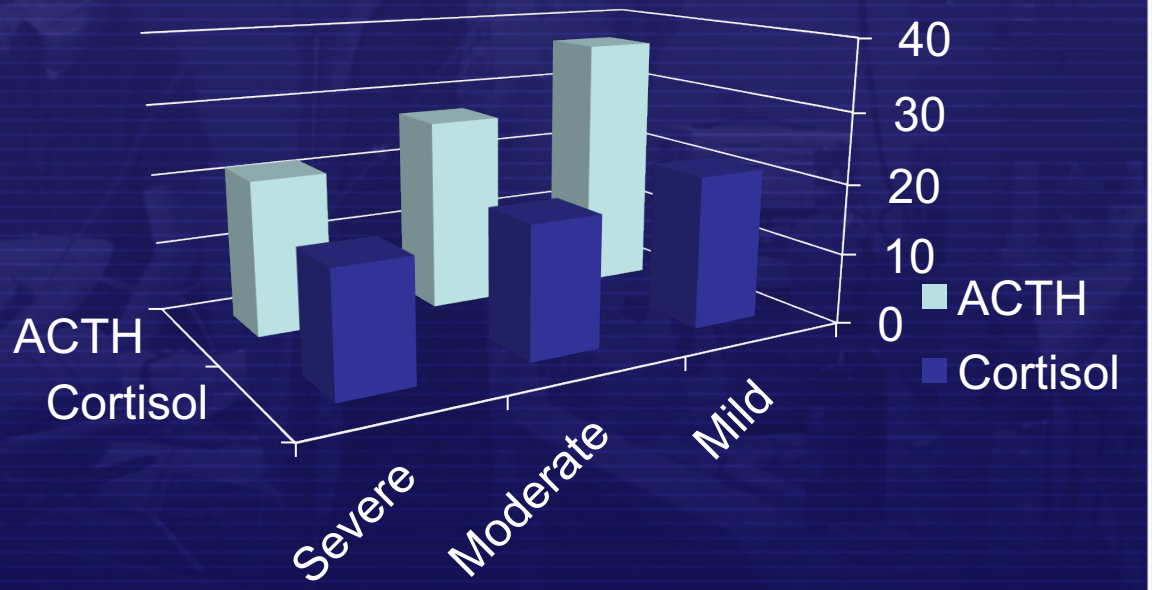
Cortisol

- 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.

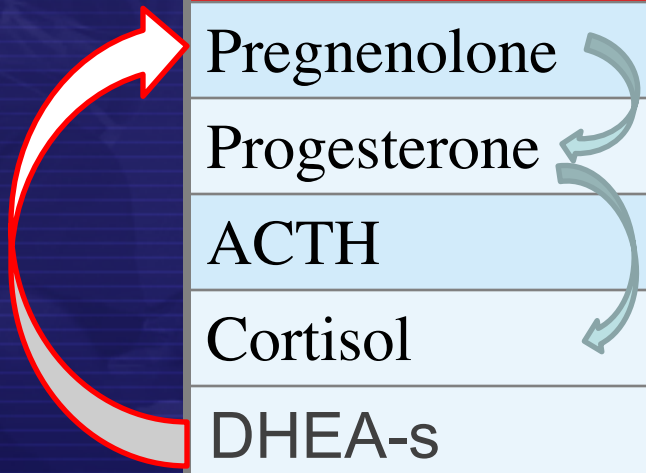
Two peripheral systems for the regulation of Cortisol:

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.

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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. -