

# TEST REPORT

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# D2021 03 17 876 U

Ordering Provider:  
Getuwell

Samples Received  
03/17/2021

Report Date  
03/18/2021

Samples Collected  
Urine - 03/15/21 05:30  
Urine - 03/15/21 07:30  
Urine - 03/15/21 18:00  
Urine - 03/15/21 22:00

Patient Name: NeuroAdvanced w-Diurnal  
Patient Phone Number: 555 555 5555

<b>Gender</b> Male	<b>Height</b> 5 ft 11 in	<b>Waist</b> 30 in
<b>DOB</b> 5/17/1997 (23 yrs)	<b>Weight</b> 160 lb	<b>BMI</b> 22.3

TEST NAME	RESULTS   03/15/21	RANGE
<b>Urinary Inhibitory Neurotransmitters</b>		
Tryptophan	14082 H	2633-12688 µg/g Cr (Optimal 3970-8450)
Serotonin	72.6	47.6-140.3 µg/g Cr (Optimal 61.0-103.2)
5-HIAA	3857	2205-11816 µg/g Cr (Optimal 2988-5850)
GABA	341	167-463 µg/g Cr (Optimal 193-367)
Glycine	56	41-295 mg/g Cr (Optimal 61-159)
Taurine	4.2 L	7.1-293.1 mg/g Cr (24.5-134.1)
<b>Urinary Excitatory Neurotransmitters</b>		
Glutamate	1436	1213-4246 µg/g Cr (Optimal 1515-2710)
Glutamine	38	27-106 mg/g Cr (Optimal 37-71)
Histidine	63.8	10.8-98.9 mg/g Cr (Optimal 19.7-58.4)
Histamine	25.4	3.6-44.3 µg/g Cr (Optimal 5.2-15.3)
N-Methylhistamine	285 H	59-195 µg/g Cr (Optimal 79-140)
PEA	4.3	3.6-38.8 µg/g Cr (Optimal 5.3-16.1)
Tyrosine	5240	3128-15548 µg/g Cr (Optimal 4790-10278)
Tyramine	353	187-910 µg/g Cr (Optimal 279-588)
Dopamine	132	103-282 µg/g Cr (Optimal 144-240)
DOPAC	658	495-2456 µg/g Cr (Optimal 658-1449)
HVA	6122	3025-9654 µg/g Cr (Optimal 3737-7048)

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The above results and comments are for informational purposes only and are not to be construed as medical advice. Please consult your healthcare practitioner for diagnosis and treatment.



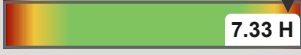








*David T. Zava*

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Laboratory Director

*Alison McAllister, ND*

Alison McAllister, ND.  
(Ordering Provider unless otherwise specified on page 1)

TEST NAME	RESULTS   03/15/21	RANGE
<b>Urinary Excitatory Neurotransmitters</b>		
Norepinephrine (pooled)	21.8	10.0-35.7 µg/g Cr (Optimal 15.0-28.1)
Normetanephrine	18.1	13.4-44.8 µg/g Cr (Optimal 17.9-31.7)
Epinephrine (pooled)	3.3	0.8-6.2 µg/g Cr (Optimal 1.4-4.2)
Ratio: Norepi/Epi	6.6	2.9-25.2 (Optimal 5.2-13.7)
VMA	2849	1996-5939 µg/g Cr (Optimal 2580-4766)
<b>Urinary Inflammatory Markers</b>		
Kynurenine	1462	108-1641 µg/g Cr (Optimal 257-960)
Kynurenic Acid	916	437-1719 µg/g Cr (Optimal 639-1200)
3-Hydroxykynurenine	1227 H	80-822 µg/g Cr (Optimal 147-467)
Xanthurenic Acid	1308	450-2175 µg/g Cr (694-1510)
<b>Urinary Free Diurnal Cortisol</b>		
Free Cortisol	57.28 H	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	9.54 L	23.4-68.9 µg/g Cr (2nd Morning)
Free Cortisol	10.51	6.0-19.2 µg/g Cr (Evening)
Free Cortisol	4.13	2.6-8.4 µg/g Cr (Night)
<b>Urinary Free Diurnal Cortisone</b>		
Free Cortisone	234.25 H	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	53.48 L	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	66.8	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	25.99	15.5-44.7 µg/g Cr (Night)
<b>Urinary Diurnal Melatonin MT6s</b>		
Melatonin	6.14 L	10.1-26.0 µg/g Cr (1st Morning)
Melatonin	5.79 L	6.0-17.0 µg/g Cr (2nd Morning)
Melatonin	1.69	0.5-3.6 µg/g Cr (Evening)
Melatonin	1.7	1.3-8.4 µg/g Cr (Night)
<b>Urinary Diurnal Norepinephrine</b>		
Norepinephrine	40.6 H	9.4-22.0 µg/g Cr (1st Morning)
Norepinephrine	22.74	12.6-38.2 µg/g Cr (2nd Morning)

TEST NAME	RESULTS   03/15/21	RANGE
<b>Urinary Diurnal Norepinephrine</b>		
Norepinephrine	 51.42 H	21.1-42.9 µg/g Cr (Evening)
Norepinephrine	 29.77	16.9-38.8 µg/g Cr (Night)
<b>Urinary Diurnal Epinephrine</b>		
Epinephrine	 7.33 H	0.5-1.5 µg/g Cr (1st Morning)
Epinephrine	 1.24	0.7-6.1 µg/g Cr (2nd Morning)
Epinephrine	 6.96	2.3-8.1 µg/g Cr (Evening)
Epinephrine	 4.12	1.2-4.2 µg/g Cr (Night)
<b>Urinary Creatinine</b>		
Creatinine (pooled)	 0.92	0.3-2.0 mg/mL
Creatinine	 0.34	0.3-2.0 mg/mL (1st morning)
Creatinine	 1.54	0.3-2.0 mg/mL (2nd morning)
Creatinine	 0.56	0.3-2.0 mg/mL (Evening)
Creatinine	 1.24	0.3-2.0 mg/mL (Night)

<dl = Less than the detectable limit of the lab. N/A = Not applicable; 1 or more values used in this calculation is less than the detectable limit. H = High. L = Low.

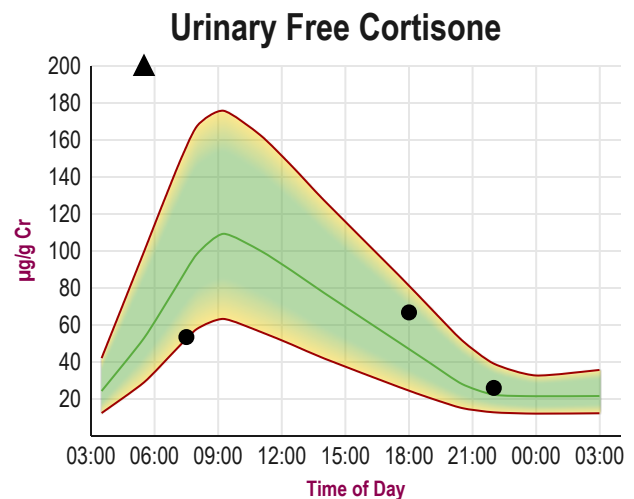
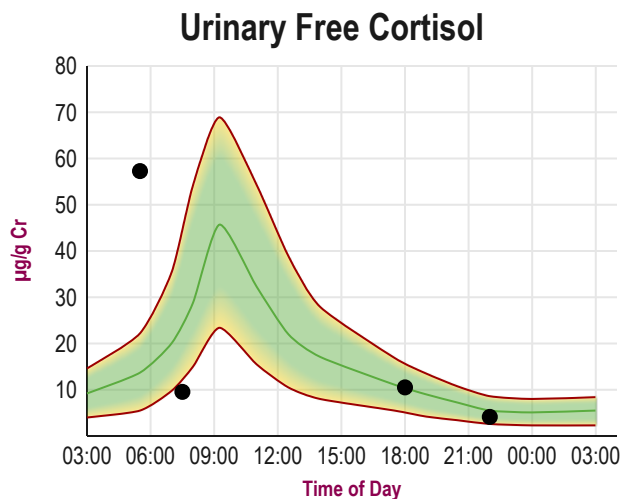
**Therapies**

BID topical Clobex (clobetasol propionate) (Pharmaceutical) (7 Hours Last Used)

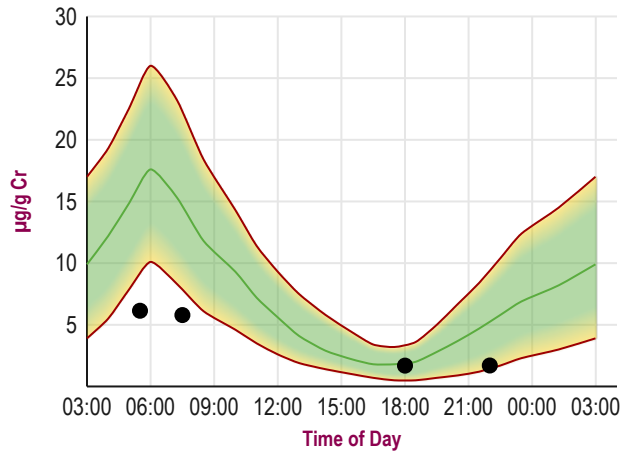
**Graphs**

**Disclaimer:** Graphs below represent averages for healthy individuals not using hormones. Supplementation ranges may be higher. Please see supplementation ranges and lab comments if results are higher or lower than expected.

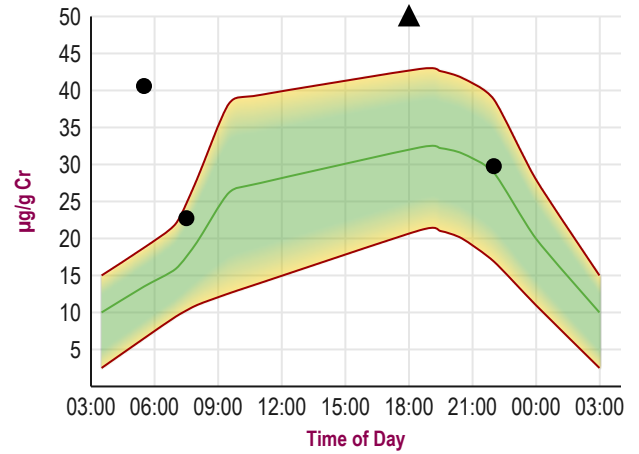
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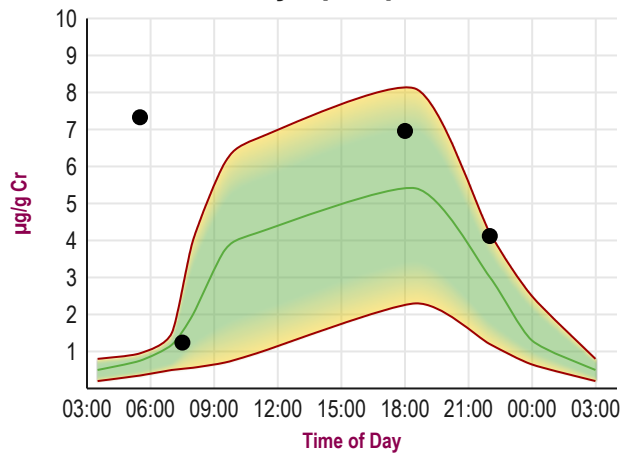
### Urinary Melatonin (MT6s)



### Urinary Norepinephrine

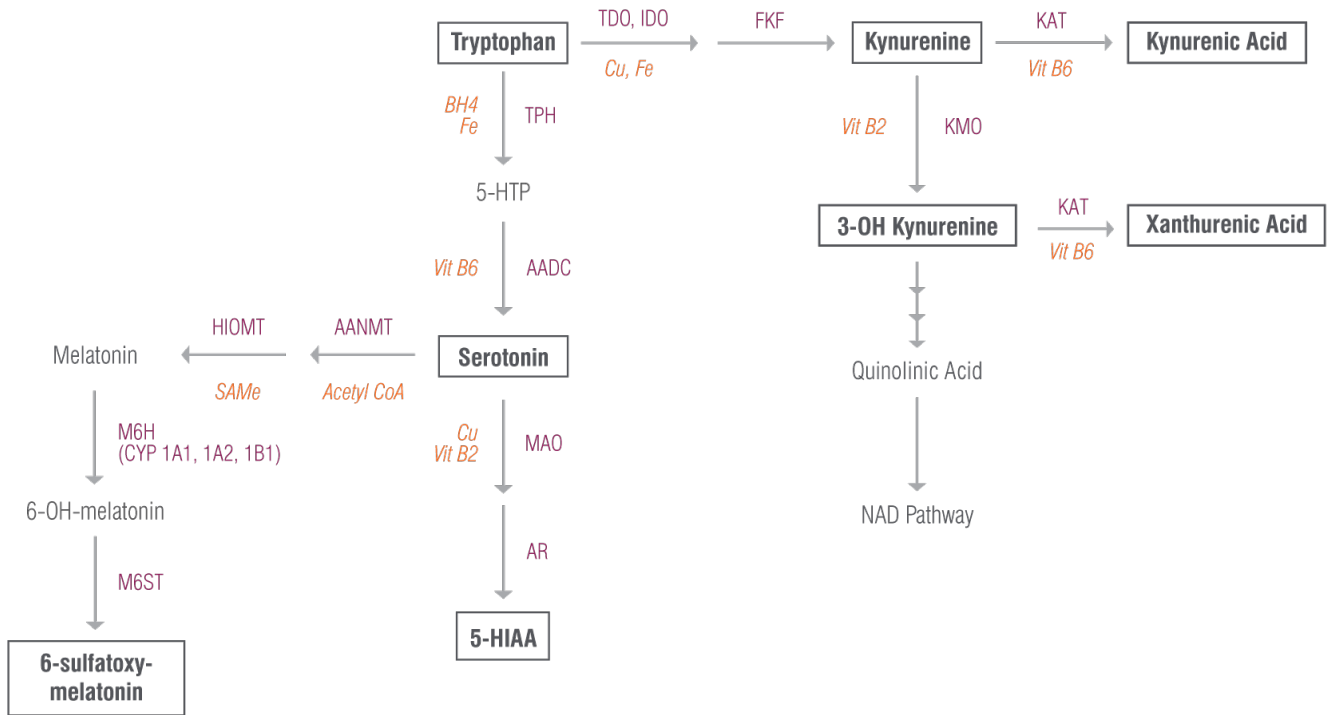


### Urinary Epinephrine

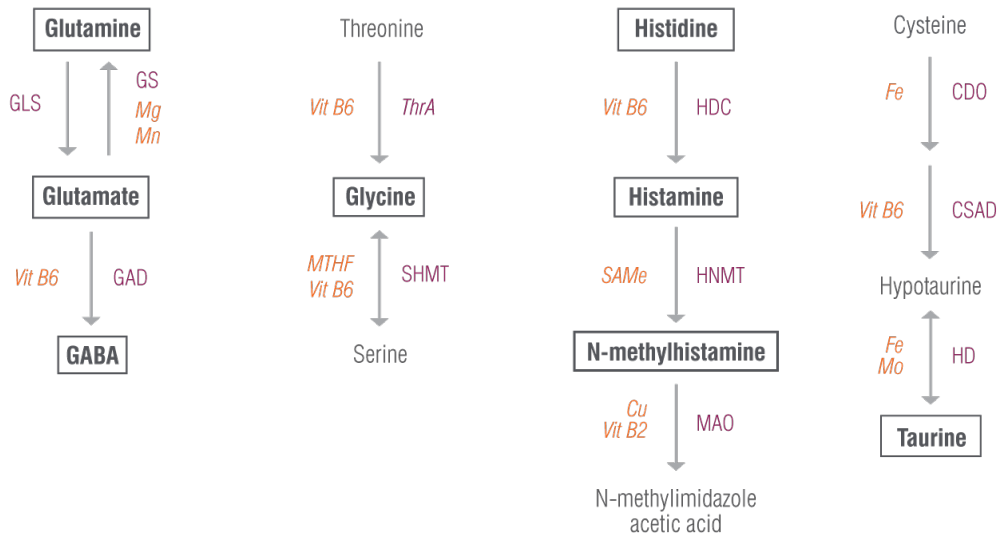


# Neurotransmitter Cascades

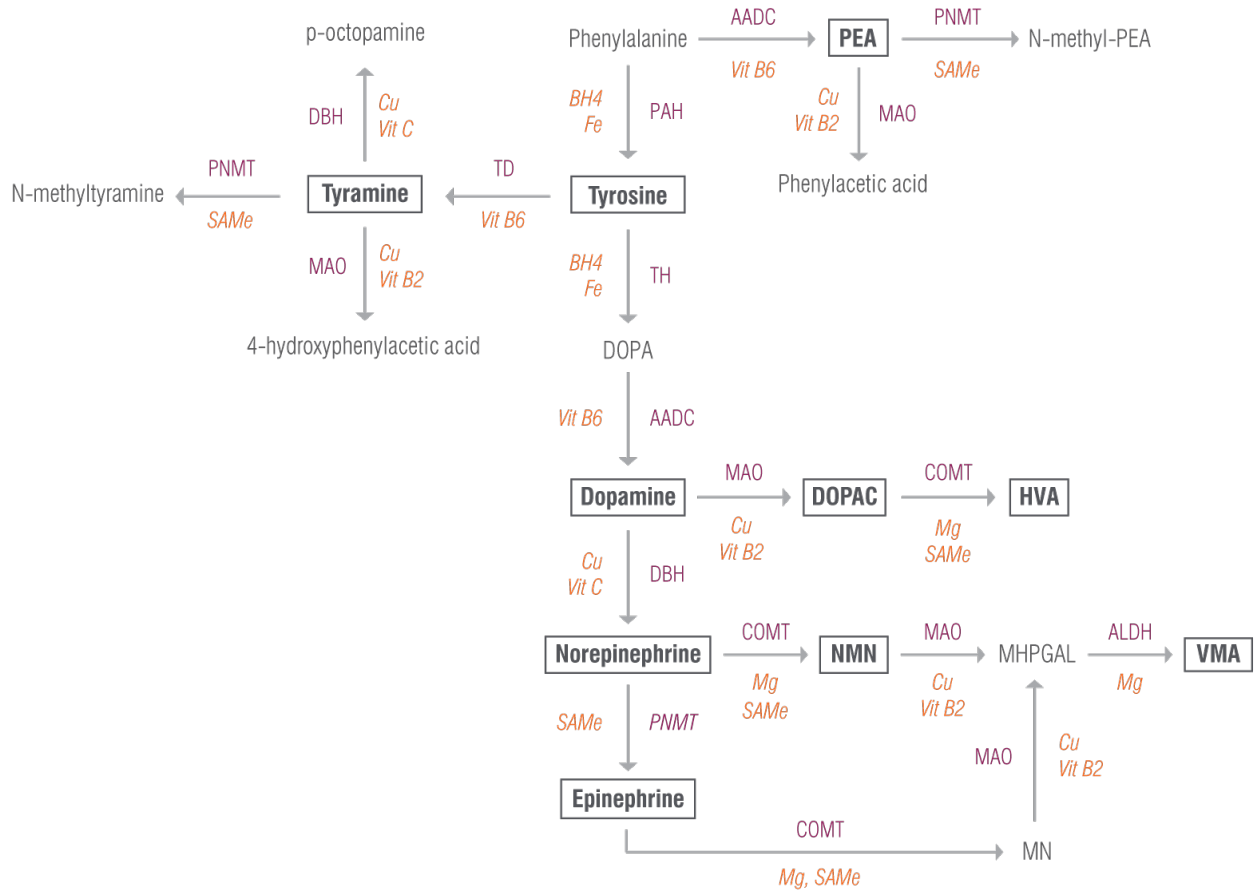
## Tryptophan & Metabolites



## Glutamate/GABA, Glycine, Histamine & Taurine



## Catecholamines & Metabolites



## Abbreviations & Key

Neurotransmitters & Metabolites:

<b>HVA</b>	homovanillic acid
<b>NMN</b>	normetanephrine
<b>PEA</b>	phenethylamine
<b>VMA</b>	vanillylmandelic acid
<b>5-HIAA</b>	5-hydroxyindole 3-acetic acid

Cofactors:

<b>BH4</b>	tetrahydrobiopterin
<b>Cu</b>	copper
<b>Fe</b>	iron
<b>Mg</b>	magnesium
<b>Mn</b>	manganese
<b>Mo</b>	molybdenum
<b>MTHF</b>	methyltetrahydrofolate
<b>SAmE</b>	S-adenosyl methionine

Enzymes:

<b>AADC</b>	aromatic L-amino acid decarboxylase
<b>AANMT</b>	arylalkylamine N-methyltransferase
<b>ALDH</b>	aldehyde dehydrogenase
<b>AR</b>	aldehyde reductase
<b>CDO</b>	cysteine dioxygenase
<b>COMT</b>	catechol-O-methyltransferase

<b>CSAD</b>	cysteinesulfonic acid decarboxylase
<b>DBH</b>	dopamine beta hydroxylase
<b>FKF</b>	N-Formyl kynurenine formamidase
<b>GAD</b>	glutamate decarboxylase
<b>GLS</b>	glutaminase
<b>GS</b>	glutamine synthetase
<b>HD</b>	hypotaurine dehydrogenase
<b>HDC</b>	histidine decarboxylase
<b>HIOMT</b>	hydroxyindole-O-methyltransferase
<b>HNMT</b>	histamine N-methyltransferase
<b>IDO</b>	indoleamine 2,3-dioxygenase
<b>KAT</b>	kynurenine aminotransferase
<b>KMO</b>	kynurenine hydroxylase/monooxygenase
<b>MAO</b>	monoamine oxidase
<b>M6H</b>	melatonin 6 hydroxylase
<b>M6ST</b>	melatonin 6 sulfotransferase
<b>PAH</b>	phenylalanine hydroxylase
<b>PNMT</b>	phenylethanolamine N-methyltransferase
<b>SHMT</b>	serine hydroxymethyltransferase
<b>TD</b>	tyrosine decarboxylase
<b>TDO</b>	tryptophan 2,3-dioxygenase
<b>TH</b>	tyrosine hydroxylase
<b>ThrA</b>	threonine aldolase
<b>TPH</b>	tryptophan hydroxylase

**Disclaimer:** Symptom Categories below show percent of symptoms self-reported by the patient compared to total available symptoms for each category. For detailed information on category breakdowns, go to [www.zrtlab.com/patient-symptoms](http://www.zrtlab.com/patient-symptoms).

SYMPTOM CATEGORIES		RESULTS   03/15/21
Estrogen / Progesterone Deficiency	12%	
Estrogen Dominance / Progesterone Deficiency	3%	
Low Androgens (DHEA/Testosterone)	17%	
High Androgens (DHEA/Testosterone)	44%	
Low Cortisol	20%	
High Cortisol	28%	
Hypometabolism	21%	
Metabolic Syndrome	7%	

SYMPTOM CHECKLIST	MILD	MODERATE	SEVERE
Acne			
ADD/ADHD			
Addictive Behaviors			
Aggressive Behavior			
Allergies			
Anxious			
Apathy			
Autism Spectrum Disorder			
Blood Pressure High			
Blood Pressure Low			
Blood Sugar Low			
Body Temperature Cold			
Bone Loss			
Burned Out Feeling			
Chemical Sensitivity			
Cholesterol High			
Constipation			
Depressed			
Developmental Delays			
Dizzy Spells			
Eating Disorders			
Erections Decreased			
Fatigue - Evening			
Fatigue - Mental			
Fatigue - Morning			
Flexibility Decreased			
Forgetfulness			
Goiter			
Hair - Dry or Brittle			
Hair or Skin Oily			
Headaches			
Hearing Loss			
Heart Palpitations			
Hoarseness			
Hot Flashes			
Infertility			
Irritable			
Joint Pain			
Libido Decreased			
Mania			

SYMPTOM CHECKLIST	MILD	MODERATE	SEVERE
Mental Sharpness Decreased	██████████		
Muscle Size Decreased	██		
Muscle Soreness	██		
Nails Breaking or Brittle	██		
Neck or Back Pain	██		
Nervous	██████████		
Night Sweats	██		
Numbness - Feet or Hands	██		
OCD	██		
Panic Attacks	██████████		
Prostate Cancer	██		
Prostate Problems	██		
Pulse Rate Slow	██		
Rapid Aging	██		
Rapid Heartbeat	██		
Ringing In Ears	██		
Skin Thinning	██		
Sleeping Difficulty	██████████		
Stamina Decreased	██████████		
Stress	██████████		
Sugar Cravings	██		
Sweating Decreased	██		
Swelling or Puffy Eyes/Face	██		
Triglycerides Elevated	BLANK		
Urinary Urge Increased	██		
Urine Flow Decreased	██		
Weight Gain - Breast or Hips	██		
Weight Gain - Waist	██		

## Lab Comments

### INHIBITORY NEUROTRANSMITTERS

#### TRYPTOPHAN

Tryptophan is high likely due to supplementation. The essential amino acid tryptophan originates in diet and serves as a constituent of proteins and a precursor to neurotransmitters. Only a fraction of tryptophan is used by the GI tract, the vast majority of this amino acid enters portal circulation and undergoes liver metabolism. The remaining tryptophan pool, together with its liver degradation products, is distributed to peripheral circulation and transported to tissues such as the brain, heart, and skeletal muscle. Tryptophan not taken up by the upper GI tract is metabolized by resident microbiota.

Tryptophan is a substrate for two important biosynthetic pathways relevant to the inflammatory neuropsychiatric interface: the generation of the neurotransmitter serotonin and therefore hormone melatonin, and the formation of kynurenine derivatives and therefore niacin (vitamin B3). Tryptophan hydroxylase initiates the two-step conversion to serotonin, a process that requires tetrahydrobiopterin (BH4), iron and vitamin B6. Approximately 5-10% of tryptophan is converted to serotonin. Tryptophan dioxygenase and indoleamine 2,3-dioxygenase are the enzymes responsible for tryptophan's conversion to kynurenine in a copper and iron-dependent manner. In fact, upward of 90-95% of tryptophan is metabolized to the kynurenine pathway, and upregulation of this pathway may be a hallmark of neuroinflammation.

Research shows that tryptophan is high with tryptophan supplementation (Michael, Drummond et al. 1964) and in some individuals with a high protein diet (Poesen, Mutsaers et al. 2015). Clinically, high tryptophan is associated with headaches (Curto, Lionetto et al. 2015) and selective serotonin reuptake inhibitor treatment (Mackay, Forrest et al. 2009).

**TREATMENT CONSIDERATIONS:** discontinue tryptophan supplementation if side effects are bothersome, these include blurred vision, dizziness, fatigue, nausea, stomach pain, vomiting, diarrhea and loss of appetite.

#### SEROTONIN

Serotonin is within reference range. Serotonin has calming effects and contributes to the feelings of well-being. Serotonin elevates mood, decreases anxiety, appetite, and libido, improves sleep and memory, eases depression, and helps regulate body temperature. Most of serotonin in the human body is produced in the gastrointestinal tract, where it stimulates gut motility.

#### 5-HIAA



5-hydroxyindoleacetic acid (5-HIAA) is within reference range. 5-HIAA is the primary metabolite of serotonin via the actions of monoamine oxidase and aldehyde dehydrogenase enzymes.

#### GABA

GABA is within the reference range. The brain's major inhibitory neurotransmitter GABA functions as the off switch in the brain. GABA is essential to limiting excitation so that input signals are balanced and not overdone. GABA prevents anxiety, improves mood, promotes sleep, lowers blood pressure, acts as a muscle relaxant, aids in formation and storage of fear memories, increases insulin secretion and decreases blood glucose levels.

#### GLYCINE

Glycine is lower than the optimal range, which may be due to depression (self-reported). Although research on urinary levels of glycine is scarce, levels of glycine in blood are lower in depressed individuals than in controls (Altamura, et. al. 1995).

Glycine is a neurotransmitter and a simple, nonessential (can be made in the body) amino acid that plays a role in the production of DNA, phospholipids, collagen, creatine, heme and glutathione. Glycine serves as an anti-inflammatory agent, calms aggression, improves sleep quality, stabilizes blood sugar, improves metabolic parameters and modulates excitatory signals in the brain. Low levels may be indicative of chronically increased demand for tetrahydrofolate (active folic acid) production, for which glycine serves as a precursor. Additional research studies show that urinary glycine levels are reduced after intense exercise (Corsetti, et. al. 2016), and in patients with rheumatoid arthritis (Jones, et. al. 2005), or hypometabolic disorders, such as hypothyroidism (Friedrich, et. al. 2017), obesity (Ahmad, et. al. 2016), and diabetes (Sasaki, et. al. 1988).

**THERAPEUTIC CONSIDERATIONS:** Glycine supplementation, vitamin B6, serine and MTHF may all support optimal glycine levels.

#### TAURINE

Taurine is lower than the reference range. Taurine is a semi-essential or conditionally essential sulfur-containing amino acid and an inhibitory (calming) neurotransmitter. Taurine improves sleep, relieves anxiety, alleviates fatigue, aids with metabolism and digestion, and promotes glucose control and electrolyte balance.

The main source of taurine is diet (highest in shellfish and poultry (dark meat)). Taurine protects healthy cells and tissues, functions as a potent antioxidant to reduce oxidative stress, mitigates mitochondrial and endoplasmic reticulum stress, inhibits lipid peroxidation, improves energy metabolism, regulates gene expression, and participates in detoxification, calcium homeostasis and osmoregulation processes. By fulfilling all these functions, taurine is therefore protective in cardiovascular health, improves lean body mass and exercise performance. With regard to brain health, taurine serves a neuroprotective role, promotes neural development in embryonic and adult brain tissues, and is an important factor in neurogenesis.

Research shows that taurine excretion is low specifically with vegetarian or vegan diets (Rana and Sanders 1986) and with low protein diets in general (Turner, Brum et al. 1964). Low taurine levels are implicated in diabetes (Sak, Erdenen et al. 2019), hypertension (Sak, Erdenen et al. 2019) and breast cancer (El Agouza, Eissa et al. 2011).

**THERAPEUTIC CONSIDERATIONS:** taurine is found in most types of meat, shellfish, and fish - increasing intake of these foods may help restore normal taurine levels. Additionally, taurine supplementation is considered safe and can be tolerated up to 3 g per day without adverse effects.

#### EXCITATORY NEUROTRANSMITTERS

##### GLUTAMATE

Glutamate is low-normal (< 20th percentile). The brain's major excitatory neurotransmitter glutamate functions as the "on" switch in the brain. Glutamate regulates appetite, thinking, increases gut motility, optimizes learning, modulates memory, improves libido, and decreases sleep. Low urinary glutamate levels have been reported in patients with migraines (Ragginer et al., 2012). Clinically, lower glutamate levels may contribute to agitation, depression, chronic fatigue, lack of concentration, low energy levels, and sleep difficulties.

**THERAPEUTIC CONSIDERATIONS:** L-glutamine may be beneficial to restore glutamate to normal values.

##### GLUTAMINE

Glutamine is within range. Glutamine is an essential and the most abundant free amino acid in the human body. Glutamine provides fuel for rapidly dividing cells (lymphocytes, enterocytes and epithelial cells of the intestines), helps balance ammonia levels in the body, improves immune system function, contributes to biosynthesis of proteins, amino acids, nucleic acids and glutathione, and protects intestinal lining. Additionally, glutamine increases glutamate and GABA levels in the brain and in the body.

##### HISTIDINE

Histidine is high-normal (>80th percentile), likely due to supplementation or recent dietary intake. Histidine is a semi-essential amino acid that gives rise to the neurotransmitter histamine. Histidine protects neurons, assists with making new blood cells, reduces inflammation and oxidative stress, helps with tissue repair and growth. Histidine also helps ameliorate fatigue, promotes clear thinking and concentration, reduces appetite, decreases anxiety, improves sleep and glucose homeostasis.

Research shows that histidine excretion is high with histidine administration (Du, Sun et al. 2017), in histidinemia (Auerbach, DiGeorge et al. 1962), and in diabetic nephropathy (Shao, Lu et al. 2020).

**THERAPEUTIC CONSIDERATIONS:** because high histamine has not been linked to adverse symptoms, no therapy is thought to be needed.

#### HISTAMINE

Histamine is above the optimal range, which may be due to allergies (self-reported). Research shows that individuals with gastrointestinal food allergies have higher urinary histamine levels (Raithel, et. al. 2015). This study showed that histamine was elevated in both IgE- and non-IgE food allergy types during consumption of offending foods, but not during the hypoallergenic diet.

This individual concurrently reports having ADHD. Literature suggests that some individuals with ADHD may have food sensitivities, and when present in diet, these foods could exacerbate symptoms of the disorder. Restriction/elimination diets, excluding artificial food coloring and excess sugar from diet have been shown by multiple studies to improve symptoms of hyperactivity and inattentiveness (Nigg and Holton, 2014).

Histamine plays a dual role in the body as a neurotransmitter and a modulator of the immune system that has anti-pain properties, plays a neuroprotective role in the brain, and contributes to optimal maintenance of cognition and memory. Histamine stimulates wakefulness and decreases sleep, stimulates gastric acid production, increases metabolism, suppresses appetite, and prevents weight gain. Histamine is a potent vasodilator and a pro-inflammatory agent. Additional research studies show that urinary histamine is elevated in patients with flushing disorder (Myers et al., 1981), cystitis (el-Mansoury et al., 1994), polycythemia (Horakova et al., 1977), and pregnancy (Harrison et al., 1974). Clinically, high histamine levels are implicated in depression, headaches, sensitivity to chemicals, and sleep difficulties.

**THERAPEUTIC CONSIDERATIONS:** Beneficial therapeutic strategies to reduce histamine levels may involve antihistamines and/or a low histamine diet. High histamine foods include but are not limited to beer, champagne, aged cheeses, eggplant, canned fish, fermented meat, red and white wine, sauerkraut, and spinach (Maintz and Novak, 2007), however individual food sensitivities ought to be considered as well. Additionally, flavonoids (green tea extract, quercetin, grape seed extract, ginkgo biloba, citrus bioflavonoids, bilberry extract, hawthorn extract) may be beneficial to ease the symptoms of high histamine (Murray et al., 2005).

#### N-METHYLHISTAMINE

N-Methylhistamine is high. N-Methylhistamine is a major metabolite of the neurotransmitter histamine. Research shows that N-methylhistamine excretion is elevated with high protein diet (Keyzer, Breukelman et al. 10/1984), in gastrointestinal food allergies (Raithel, Hagel et al. 2015), in irritable bowel disease (Winterkamp, Weidenhiller et al. 2002), in colitis (Schwab, Hahn et al. 2003), in histidinemia (Imamura, Watanabe et al. 1984), in chronic urticaria (Patel and Divekar 2017), in angioedema (Patel and Divekar 2017), and with interstitial cystitis (el-Mansoury, Boucher et al. 8/1994).

**THERAPEUTIC CONSIDERATIONS:** evaluation for food allergy sources may be warranted.

#### PEA

Phenethylamine or PEA is below the optimal range. Low PEA may contribute to fatigue, depression and decreased attention span. PEA acts as a "neuro-amplifier" - increasing the actions of dopamine (for wellbeing and feeling pleasure), norepinephrine (the brain's stimulant for wakefulness, alertness and higher performance), acetylcholine (for improving memory and mental activity), and serotonin (for better mood emotion and impulse control) (Paterson, et. al. 1990).

Recently, PEA has been recognized as a biomarker in ADHD and research shows that urinary levels of PEA are low in patients with ADHD (Irsfeld, et. al. 2013). Patients whose symptoms improve in response to treatment, typically show higher PEA levels than patients who do not experience an improvement in the condition.

Additionally, low PEA has been implicated in a number of psychological disorders, such as depression (Sabelli and Mosnaim, 1974), eating disorders (bulimia nervosa) (Davis et al., 1994), inattentiveness (Faraone et al., 2014), Parkinson's disease (Wolf and Mosnaim, 1983), and Tourette's syndrome (Bornstein et al., 1990)

**THERAPEUTIC CONSIDERATIONS:** when PEA is low, supplementation with vitamin B6 (cofactor) and phenylalanine (precursor) to promote biosynthesis may be beneficial. Exercise helps increase PEA levels (Szabo, et a. 2001). Additionally, curcumin and passionflower, botanical MAO inhibitors, may help by preventing rapid PEA metabolism.

#### TYROSINE

Tyrosine is within range. Tyrosine is obtained from diet (sesame seeds, cheese, soy, meat, nuts and fish) or synthesized in the body from the amino acid phenylalanine. Tyrosine serves as a constituent of proteins and gives rise to neurotransmitters, like dopamine, norepinephrine and epinephrine; and the trace-amine tyramine. Additionally, in the thyroid gland, tyrosine can also be iodinated to give rise to thyroid hormones. Tyrosine enhances cognitive performance, energy, and alertness, and improves memory after sleep deprivation. Tyrosine also prevents the depletion of central and peripheral catecholamines (dopamine, norepinephrine, epinephrine) induced by acute stress, thereby eliciting protective effects on behavioral and cardiovascular parameters in the body.

#### TYRAMINE

Tyramine is within range. Tyramine is a trace amine derived from the amino acid tyrosine that is found naturally in food. Specifically, tyramine is found in aged, fermented cured or spoiled food where microbes with decarboxylase enzymes convert tyrosine to tyramine. These foods include aged cheeses, smoked fish, cured meats, wine, and some types of beer. In sensitive individuals, eating high amount of tyramine can trigger migraines and increase blood pressure.

**DOPAMINE**

Dopamine is low-normal (<20th percentile). Dopamine improves attention, focus, and motivation, helps with decision making, modulates movement control, promotes lactation, increases blood pressure, urine output and sodium excretion, and allows for feelings of reward and pleasure. Additionally, the quest for dopamine stimulation plays a central role in the etiology of addiction. Dopamine also serves as the parent precursor to norepinephrine and epinephrine. Research shows that urinary dopamine levels are reduced in patients with Alzheimer's disease (Liu et al., 2011), anorexia nervosa (Van Binsbergen et al., 1991), anxiety with depression (Field et al., 2010), fibromyalgia (Riva et al., 2012), and periodic limb movement disorder (Cohrs et al., 2004). Clinically, low dopamine is also implicated in apathy, cravings, fatigue, impulse control issues, increased sensitivity to pain, low libido, low mood, memory issues, sleep disturbances, and weight control issues.

**THERAPEUTIC CONSIDERATIONS:** Supplementation with precursors (tyrosine or L-DOPA) and/or cofactors (iron, vitamin B6, tetrahydrofolate) to promote biosynthesis may be beneficial.

**DOPAC**

DOPAC is low-normal (<20th percentile). DOPAC is the primary metabolite of dopamine formed via the actions of monoamine oxidase. Research shows that DOPAC is reduced in the urine of patients with Alzheimer's disease (Liu et al., 2011). Lower than optimal levels suggest that dopamine and its upstream precursors L-Dopa or tyrosine may be insufficient. DOPAC may also be lower due to MAO genetic SNPs which can slow down this enzyme or insufficient vitamin B2 or copper levels. Evaluate this level in combination with dopamine, but also 5HIAA (the serotonin metabolite) since it also uses the MAO enzyme.

**THERAPEUTIC CONSIDERATIONS:** Consider supplementing with the building blocks of dopamine (tyrosine and/or l-dopa). L-dopa is found naturally in the herb mucuna as well as supporting nutritional co-factors used with MAO enzymes.

**HVA**

Homovanillic acid (HVA) is within reference range. HVA is a dopamine metabolite.

**NOREPINEPHRINE**

Norepinephrine is within reference range. Norepinephrine functions both as a neurotransmitter and a hormone, participating in the body's "fight or flight" response. Norepinephrine increases alertness, focuses attention, fine-tunes vigilance, increases blood pressure, heart rate, and blood sugar, reduces digestive activity, pain, and sleep, prevents bladder emptying, and regulates body temperature. Norepinephrine is very similar in structure and physiological effects to epinephrine. The adrenal gland produces approximately 20% of the total output with 80% produced by the sympathetic nerve fibers.

**NORMETANEPHRINE**

Normetanephrine is within reference range. Normetanephrine is a norepinephrine metabolite formed via the actions of catechol-O-methyl (COMT) transferase enzyme in response to stress.

**EPINEPHRINE**

Epinephrine is within reference range. Epinephrine, also called adrenaline, functions both as a neurotransmitter and a hormone, participating in the body's fight or flight response. Epinephrine increases alertness, focuses attention, fine-tunes vigilance, increases blood pressure, heart rate, and blood glucose, reduces digestive activity, pain and sleep, prevents bladder emptying, and regulates body temperature.

**VMA**

Vanillylmandelic acid (VMA) is within reference range. VMA is a norepinephrine and epinephrine metabolite formed via the actions of monoamine oxidase, catechol-O-methyl transferase (COMT), and aldehyde dehydrogenase.

**INFLAMMATORY MARKERS****KYNURENINE**

Kynurenine is high-normal (>80th percentile). Kynurenine is a central metabolite of the amino acid tryptophan with vasodilatory properties. Kynurenine is utilized by the body in the production of niacin (vitamin B3), eventually leading to the formation of NAD<sup>+</sup>, which plays a pivotal role in energy metabolism, gene expression, cell death and regulation of calcium homeostasis. More than 90% of the body's tryptophan is metabolized to the kynurenine pathway.

Kynurenine is synthesized by the enzyme tryptophan dioxygenase, which is expressed primarily but not exclusively in the liver, and indoleamine 2,3-dioxygenase, which is made in many tissues in response to immune activation by interferons and cytokines, or free radicals. In the brain, approximately ~40% of kynurenine is produced locally, whereas the rest is absorbed from the blood.

Kynurenine degradation generates a series of neuroprotective and neurotoxic compounds that can activate or inhibit N-methyl-d-aspartate (NMDA) glutamate receptors (see kynurenic acid and 3-OH kynurenine). Upregulation of this pathway may be a hallmark of neuroinflammation and is associated with certain disorders.

Research shows that kynurenine is high with tryptophan administration (Michael, Drummond et al. 1964), hydrocortisone treatment (Rose and Braidman 1971), metabolic syndrome (Oh, Seo et al. 2017), with major coronary events (Pedersen, Svingen et al. 9/2013), and in women in pregnancy (Rose and Braidman 1971). High kynurenine levels have been implicated in disorders like Irritable Bowel Syndrome (Fitzgerald, Cassidy Eugene et al. 2008), lupus (Akesson, Pettersson et al. 2018), Crohn's disease (Gupta, Thaker et al. 2012), and Alzheimer's Disease (Chatterjee, Goozee et al. 2018). Additionally, caffeine (Orlikov and Ryzov 1991) and regular black tea (Gostner, Becker et al. 2015) consumption can elevate kynurenine levels as well.

TREATMENT CONSIDERATIONS: reduction of inflammation through diet and supplementation may be beneficial. Glutathione support and modulation of the NMDA receptor (e.g. magnesium) may help reduce symptoms.

#### KYNURENIC ACID

Kynurenic acid is within range. Kynurenic acid is a neuroactive metabolite produced from kynurenine. Kynurenine is formed from tryptophan via the enzyme tryptophan dioxygenase and indoleamine 2,3-dioxygenase; and metabolized along two independent pathways to produce kynurenic acid via aminotransferases and 3-OH kynurenine.

Kynurenic acid (unless in excess amounts) is regarded to have a neuroprotective role because it inhibits the N-methyl-d-aspartate (NMDA) glutamate receptor, reduces the neurotransmitter glutamate release and thereby prevents excitotoxicity.

#### 3-HYDROXYKYNURENINE

3-Hydroxykynurenine is high. 3-Hydroxy Kynurenine (3-OH Kynurenine) is a metabolic intermediate of the kynurenine pathway, one of the major metabolites of tryptophan degradation. Kynurenine is transformed into 3-OH Kynurenine, which acts as a N-methyl-d-aspartate (NMDA) glutamate receptor agonist and has been demonstrated to exert neurotoxic effects.

Neurotoxicity elicited by 3-OH Kynurenine appears to be also related to generation of oxidative stress produced by reactive radical species, formed as a result of auto-oxidation. Additionally, 3-OH Kynurenine gives rise to neurotoxic metabolites, such as quinolinic acid, which activate the NMDA receptor, induce lipid peroxidation and promote oxidative stress.

Research shows that urinary levels of 3-OH Kynurenine are high with hydrocortisone treatment (Rose and Braidman 1971) and in women in pregnancy (Rose and Braidman 1971). High 3-OH Kynurenine is implicated in vitamin B6 deficiency (Theofylaktopoulos, Ulvik et al. 2014) and Alzheimer's disease (Schwarz, Guillemin et al. 2013).

TREATMENT CONSIDERATIONS: consider glutathione support and antioxidant support to prevent the oxidative stress produced by 3-hydroxykynurenine. Consider B6 supplementation (under 200 mg/day for safety).

#### XANTHURENIC ACID

Xanthurenic acid is within range. Xanthurenic acid is a metabolite of the kynurenine pathway, formed directly from 3-OH Kynurenine, and serves as an indirect marker of vitamin B6 status.

#### URINARY FREE CORTISOL (F) AND CORTISONE (E)

Urinary free cortisol (F) and cortisone (E) are NOT following a normal circadian rhythm and levels are outside the expected reference ranges, particularly in the first two morning voids. F and E are very high in the first morning void, but drop precipitously in the second void but begin to recover to normal reference ranges in the evening and at night before bed. This individual has reported use of a synthetic glucocorticoid, commonly used topically for treating skin conditions associated with inflammation. Synthetic glucocorticoids that enter the systemic circulation suppress endogenous cortisol synthesis by negative feedback to the hypothalamic-pituitary-adrenal axis and lower ACTH/cortisol synthesis. The negative feedback is transient and may result in a rebound with higher synthesis of cortisol several hours afterward. Low second morning cortisol likely results from use of the synthetic glucocorticoid after collecting the first morning void. As seen in these results cortisol recovers to expected levels in the evening and at night before bed. A high F and E in the first morning void suggests that levels are high during sleep at night or rise rapidly just before waking (possible rebound from evening use of the synthetic glucocorticoid).

Overall, these results indicate that endogenous cortisol synthesis is high and is somewhat amplified by use of the topical synthetic glucocorticoid. Self-reported symptoms (e.g. excessive stress, fatigue, depression, irritability, decreased mental sharpness, weight gain most in the waist (belly fat), are consistent with overall high cortisol exposure.

While a normal daily adrenal output of cortisol is essential to maintain normal metabolic activity, help regulate steady state glucose levels (important for brain function and energy production), and optimize immune function, excessive levels of glucocorticoids (natural and synthetic) can have the opposite effect over time. For information about strategies to support adrenal health and reduce stress(ors) that can lead to excess or deficient cortisol synthesis, the following books are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "The Role of Stress and the HPA Axis in Chronic Disease Management" by Thomas Williams, PhD.

#### MELATONIN METABOLITE 6-SULFATOXYMELATONIN (MT6s)

The melatonin metabolite 6-sulfatoxymelatonin (MT6s) is not following a normal circadian rhythm. MT6s should be at its highest level in the first morning void, which is reflective of the dark period (night), but instead is low. Lower MT6s in the first morning void may reflect work during a night shift or staying up at night with excessive lighting (e.g. watching television). Some sleep (benzodiazepines, barbituates), pain (ibuprofen, opiates) and blood pressure medications (beta blockers like propranolol) are known to interfere with melatonin production and secretion and lower the circulating and excreted (MT6s) urinary levels of melatonin. Use of any of these medications at night before bed would result in a lower melatonin in the first morning void. The second morning void in this individual is also lower than the reference range. MT6s begins to rise thereafter in the evening and is within normal reference range at night before bed.

In a healthy individual the circadian rhythm of melatonin is inversely related to circulating levels of adrenal cortisol levels, i.e. melatonin rises with darkness and peaks about 2-3 am, while cortisol falls to its lowest level at this time of day. With morning and onset of light exposure, melatonin



drops rapidly and cortisol rises, peaking to its highest level about 30 min to 1 hr after waking (referred to as a Cortisol Awakening Response-CAR). By mid-afternoon (evening void) with maximal light exposure melatonin reaches a nadir. It then gradually begins to rise again with nightfall and less light exposure, while cortisol continues to rise. Cortisol and melatonin reach their nadir and peak, respectively, about 2-3 am. Melatonin synthesis by the pineal gland is controlled by light exposure, while cortisol synthesis is controlled by the hypothalamic-pituitary axis in response to stressors. While melatonin and cortisol have opposing circadian rhythms neither hormone directly and acutely controls the synthesis of the other.

Melatonin is known to have many different beneficial effects in the body. For an excellent review of melatonin's many benefits please read: Pandi-Perumal et.al. Melatonin, Nature's most versatile biological signal. FEBS 273: 2813-2838, 2006. Melatonin has multiple roles in maintaining health. It helps slow the aging process, is a potent anti-oxidant, regulates the immune system, inhibits formation and growth of tumors such as breast and prostate cancers, and helps regulate the synthesis of the sex-hormones estradiol and progesterone (melatonin increases progesterone, decreases estrogens by inhibiting aromatase, and down-regulates cellular estrogen receptors, which diminishes response of estrogen-sensitive tissues to estrogens). Low melatonin is also thought to contribute to obesity in people with insomnia or those who do night shift work.

Because of its established role in the regulation of the circadian rhythm, treatment with exogenous melatonin has been found useful in people with circadian rhythm sleep disorders, such as delayed sleep phase disorder, jet lag, shift worker disorder, and the non-24-hour sleep-wake disorder most commonly found in totally blind individuals; however, its utility for the treatment of insomnia is not established and remains controversial.

If melatonin is taken as a supplement (available OTC) to correct low levels or treat a condition, the timing and dosage are important to its effectiveness, especially as a sleep aid. Response to supplemental melatonin can be very individual. For optimal benefit it is best to work with a health care provider familiar with melatonin dosage and timing. Excessive dosing can result in spillover of melatonin into daylight hours, excessive sleepiness during the day, and disruption of the normal melatonin-cortisol circadian rhythms.

For more general information about melatonin please see: <http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html>

#### DIURNAL EPINEPHRINE

Epinephrine is elevated during the night (1st morning), but returns to normal range in the morning (2nd sample), and remains within normal ranges throughout the day (evening collection) and at night (evening/night sample) before bed. The pooled sample is within range, but the diurnal results are more accurate for true epinephrine status. Epinephrine, also called adrenaline, functions both as a neurotransmitter and a hormone, participating in the body's "fight or flight" response. Epinephrine increases alertness, focuses attention, fine-tunes vigilance, increases blood pressure, heart rate, and blood glucose, reduces digestive activity, pain and sleep, prevents bladder emptying, and regulates body temperature. It is commonly triggered by stress, fear, blood sugar irregularities or anxiety.

Research shows that urinary epinephrine levels are increased in patients with attention deficit disorder (Faraone et al., 2014), anxiety and depression (Hughes et al., 2004), bipolar disorder (Koslow et al., 1983), hyperglycemia (Troisi et al., 1991), hyperinsulinemia (Troisi et al., 1991), obstructive sleep apnea (Kheirandish-Gozal et al., 2013), post-traumatic stress disorder (Yehuda et al., 1992), and stress (Holzman et al., 2009; Fujiwara et al., 2004). Fluctuating levels throughout the day have been commonly associated with an inverse relationship with cortisol (e.g. high epi when cortisol is low).

**THERAPEUTIC CONSIDERATIONS:** Because epinephrine is almost exclusively from the adrenal glands, treatments geared to support normal adrenal function and calm the sympathetic nervous system may be beneficial. Supplements such as adrenal adaptogens, B vitamins, essential fatty acids, vitamin C, as well as stress management, blood sugar balance and sleep support may be helpful.

Creatinine is within range throughout the day reflecting normal concentration of urine.

Creatinine levels reflect urine concentration.

Low values suggest overly dilute urine; High values suggest overly concentrated urine.

Extreme low or high values may be induced by kidney or other metabolic disorders, but most values will be due to inadequate hydration (high creatinine) or excessive water intake in the several hours prior to testing (low creatinine). Creatinine is used to adjust the lab results for kidney function. No samples were refused due to quality issues.

#### INHIBITORY NEUROTRANSMITTERS

##### TRYPTOPHAN

Tryptophan is high likely due to supplementation. The essential amino acid tryptophan originates in diet and serves as a constituent of proteins and a precursor to neurotransmitters. Only a fraction of tryptophan is used by the GI tract, the vast majority of this amino acid enters portal circulation and undergoes liver metabolism. The remaining tryptophan pool, together with its liver degradation products, is distributed to peripheral circulation and transported to tissues such as the brain, heart, and skeletal muscle. Tryptophan not taken up by the upper GI tract is metabolized by resident microbiota.

Tryptophan is a substrate for two important biosynthetic pathways relevant to the inflammatory neuropsychiatric interface: the generation of the neurotransmitter serotonin and therefore hormone melatonin, and the formation of kynurenine derivatives and therefore niacin (vitamin B3).

Tryptophan hydroxylase initiates the two-step conversion to serotonin, a process that requires tetrahydrobiopterin (BH4), iron and vitamin B6. Approximately 5-10% of tryptophan is converted to serotonin. Tryptophan dioxygenase and indoleamine 2,3-dioxygenase are the enzymes responsible for tryptophan's conversion to kynurenine in a copper and iron-dependent manner. In fact, upward of 90-95% of tryptophan is metabolized to the kynurenine pathway, and upregulation of this pathway may be a hallmark of neuroinflammation.

Research shows that tryptophan is high with tryptophan supplementation (Michael, Drummond et al. 1964) and in some individuals with a high protein diet (Poesen, Mutsaers et al. 2015). Clinically, high tryptophan is associated with headaches (Curto, Lionetto et al. 2015) and selective serotonin reuptake inhibitor treatment (Mackay, Forrest et al. 2009).

**TREATMENT CONSIDERATIONS:** discontinue tryptophan supplementation if side effects are bothersome, these include blurred vision, dizziness, fatigue, nausea, stomach pain, vomiting, diarrhea and loss of appetite.

#### SEROTONIN

Serotonin is within reference range. Serotonin has calming effects and contributes to the feelings of well-being. Serotonin elevates mood, decreases anxiety, appetite, and libido, improves sleep and memory, eases depression, and helps regulate body temperature. Most of serotonin in the human body is produced in the gastrointestinal tract, where it stimulates gut motility.

#### 5-HIAA

5-hydroxyindoleacetic acid (5-HIAA) is within reference range. 5-HIAA is the primary metabolite of serotonin via the actions of monoamine oxidase and aldehyde dehydrogenase enzymes.

#### GABA

GABA is within the reference range. The brain's major inhibitory neurotransmitter GABA functions as the off switch in the brain. GABA is essential to limiting excitation so that input signals are balanced and not overdone. GABA prevents anxiety, improves mood, promotes sleep, lowers blood pressure, acts as a muscle relaxant, aids in formation and storage of fear memories, increases insulin secretion and decreases blood glucose levels.

#### GLYCINE

Glycine is lower than the reference range. Glycine is a neurotransmitter and a simple, nonessential (can be made in the body) amino acid that plays a role in the production of DNA, phospholipids, collagen, creatine, heme and glutathione. Glycine serves as an anti-inflammatory agent, calms aggression, improves sleep quality, stabilizes blood sugar, improves metabolic parameters and modulates excitatory signals in the brain. Low levels may be indicative of chronically increased demand for tetrahydrofolate (active folic acid) production, for which glycine serves as a precursor. Research shows that glycine levels are reduced after intense exercise (Corsetti, et. al. 2016) and in patients with rheumatoid arthritis (Jones, et. al. 2005), hypometabolism, such as hypothyroidism (Friedrich, et. al. 2017), obesity (Ahmad, et. al. 2016), and diabetes (Sasaki, et. al. 1988).

**THERAPEUTIC CONSIDERATIONS:** Glycine supplementation has been shown to improve metabolic response - such as cholesterol parameters and insulin sensitivity, reduce blood pressure, and aid with decreasing the levels of hemoglobin A1C and pro-inflammatory cytokines (Diaz-Flores, et. al. 2013; Perez-Torres, et. al. 2017). Additionally, vitamin B6, serine support, and MTHF may all support the production of glycine.

#### TAURINE

Taurine is lower than the reference range. Taurine is a semi-essential or conditionally essential sulfur-containing amino acid and an inhibitory (calming) neurotransmitter. Taurine improves sleep, relieves anxiety, alleviates fatigue, aids with metabolism and digestion, and promotes glucose control and electrolyte balance.

The main source of taurine is diet (highest in shellfish and poultry (dark meat)). Taurine protects healthy cells and tissues, functions as a potent antioxidant to reduce oxidative stress, mitigates mitochondrial and endoplasmic reticulum stress, inhibits lipid peroxidation, improves energy metabolism, regulates gene expression, and participates in detoxification, calcium homeostasis and osmoregulation processes. By fulfilling all these functions, taurine is therefore protective in cardiovascular health, improves lean body mass and exercise performance. With regard to brain health, taurine serves a neuroprotective role, promotes neural development in embryonic and adult brain tissues, and is an important factor in neurogenesis.

Research shows that taurine excretion is low specifically with vegetarian or vegan diets (Rana and Sanders 1986) and with low protein diets in general (Turner, Brum et al. 1964). Low taurine levels are implicated in diabetes (Sak, Erdenen et al. 2019), hypertension (Sak, Erdenen et al. 2019) and breast cancer (El Agouza, Eissa et al. 2011).

**THERAPEUTIC CONSIDERATIONS:** taurine is found in most types of meat, shellfish, and fish - increasing intake of these foods may help restore normal taurine levels. Additionally, taurine supplementation is considered safe and can be tolerated up to 3 g per day without adverse effects.

#### EXCITATORY NEUROTRANSMITTERS

##### GLUTAMATE

Glutamate is low-normal (< 20th percentile). The brain's major excitatory neurotransmitter glutamate functions as the "on" switch in the brain. Glutamate regulates appetite, thinking, increases gut motility, optimizes learning, modulates memory, improves libido, and decreases sleep. Low urinary glutamate levels have been reported in patients with migraines (Ragginer et al., 2012). Clinically, lower glutamate levels may contribute

to agitation, depression, chronic fatigue, lack of concentration, low energy levels, and sleep difficulties.

THERAPEUTIC CONSIDERATIONS:: L-glutamine may be beneficial to restore glutamate to normal values.

#### GLUTAMINE

Glutamine is lower than the reference range. Glutamine is an essential and should be the most abundant free amino acid in the human body. Glutamine provides fuel for rapidly dividing cells (lymphocytes, enterocytes and epithelial cells of the intestines), helps balance ammonia levels in the body, improves immune system function, contributes to biosynthesis of proteins, amino acids, nucleic acids and glutathione, and protects intestinal lining. Additionally, glutamine increases glutamate and GABA levels in the brain and in the body. Although the body usually makes enough glutamine to meet all its needs, extreme stress (e.g., strenuous exercise, persistent stress, or injury) can increase the demand for glutamine beyond the amount naturally manufactured. Research on urinary low glutamine levels is scarce, however low circulating glutamine levels are reported after intense exercise (Keast, Arstein et al. 1995), in overtraining syndrome (Rowbottom, Keast et al. 1996), in diabetes (Liu, Zheng et al. 2019), depression (Umehara, Numata et al. 2017), and in autism spectrum disorder (Rolf, Haarmann et al. 1993, Moreno-Fuenmayor, Borjas et al. 1996). Low glutamine levels are associated with high oxidative stress (Pietzner, Kaul et al. 2017).

THERAPEUTIC CONSIDERATIONS: consider supplementation with glutamine which comes in capsules or powder. Glutamine is a fairly bland tasting amino acid and easily goes into smoothies. Glutamine is also high in chicken, fish, cabbage, spinach, dairy, tofu and lentils among many over foods.

#### HISTIDINE

Histidine is low. Histidine is a semi-essential amino acid that gives rise to the neurotransmitter histamine. Histidine protects neurons, assists with making new blood cells, reduces inflammation and oxidative stress, helps with tissue repair and growth. Histidine also helps ameliorate fatigue, promotes clear thinking and concentration, reduces appetite, decreases anxiety, improves sleep and glucose homeostasis. Research shows that urinary levels of histidine are low in in folate deficiency (Cooperman and Lopez 2002). Low histidine levels are also implicated in obesity (Niu, Feng et al. 2012), fatigue with MS (Loy, Fling et al. 2019), rheumatoid arthritis (Gerber 1975), obstructive pulmonary disease (Diao, Labaki et al. 2019), and chronic kidney disease (Watanabe, Suliman et al. 2008).

THERAPEUTIC CONSIDERATIONS: dosages of histidine up to 4 g/day have shown no negative side effects and have been associated with general improvements. Meat, fish, eggs, soy, and beans are all high in histidine.

#### HISTAMINE

Histamine is high-normal (>80th percentile). Histamine is both a neurotransmitter and a modulator of the immune system that has anti-pain properties, plays a neuroprotective role in the brain, and contributes to optimal maintenance of cognition and memory. Histamine stimulates wakefulness and decreases sleep, stimulates gastric acid production, increases metabolism, suppresses appetite, and prevents weight gain. Histamine is a potent vasodilator and a pro-inflammatory agent. Research shows that urinary histamine is high in patients with burns (Johansson et al., 2012), flushing disorder (Myers et al., 1981), food allergies (Raithel et al., 2015), cystitis (el-Mansoury et al., 1994), polycythemia (Horakova et al., 1977), and pregnancy (Harrison et al., 1974). Clinically, high histamine levels are implicated in allergies, depression, headaches, migraines, OCD, schizophrenia, sensitivity to chemicals, and sleep difficulties.

THERAPEUTIC CONSIDERATIONS: Therapeutic strategies to reduce histamine levels may involve antihistamines and a low histamine diet. High histamine foods include but are not limited to beer, champagne, aged cheeses, eggplant, canned fish, fermented meat, red and white wine, sauerkraut, and spinach (Maintz and Novak, 2007). Additionally, flavonoids (green tea extract, quercetin, grape seed extract, ginkgo biloba, citrus bioflavonoids, bilberry extract, hawthorn extract) may be beneficial to ease the symptoms of high histamine (Murray et al., 2005).

#### N-METHYLHISTAMINE

N-Methylhistamine is high. N-Methylhistamine is a major metabolite of the neurotransmitter histamine. Research shows that N-methylhistamine excretion is elevated with high protein diet (Keyzer, Breukelman et al. 10/1984), in gastrointestinal food allergies (Raithel, Hagel et al. 2015), in irritable bowel disease (Winterkamp, Weidenhiller et al. 2002), in colitis (Schwab, Hahn et al. 2003), in histidinemia (Imamura, Watanabe et al. 1984), in chronic urticaria (Patel and Divekar 2017), in angioedema (Patel and Divekar 2017), and with interstitial cystitis (el-Mansoury, Boucher et al. 8/1994).

THERAPEUTIC CONSIDERATIONS: evaluation for food allergy sources may be warranted.

#### PEA

PEA is low-normal (< 20th percentile). PEA, also known as phenethylamine, promotes energy, elevates mood, and regulates attention. Low urinary PEA levels are detected in patients with autism (Kusaga et al., 2002), ADHD, (Kusaga et al., 2002; Baker et al., 1991; Irsfeld et al., 2013), depression (Sabelli and Mosnaim, 1974), eating disorders (bulimia nervosa) (Davis et al., 1994), inattentiveness (Faraone et al., 2014), Parkinson's disease (Wolf and Mosnaim, 1983), and Tourette's syndrome (Bornstein et al., 1990). Clinically, low PEA is suspected to contribute to inability to concentrate, memory issues, and weight control difficulties.

THERAPEUTIC CONSIDERATIONS: Supplementation with PEA, phenylalanine, and cofactors (e.g. B6) that aid with PEA metabolism may be helpful to increase PEA levels. Additionally, beans, chocolate, cocoa nibs, eggs, Korean natto, and peas are food sources of PEA.

**TYROSINE**

Tyrosine is within range. Tyrosine is obtained from diet (sesame seeds, cheese, soy, meat, nuts and fish) or synthesized in the body from the amino acid phenylalanine. Tyrosine serves as a constituent of proteins and gives rise to neurotransmitters, like dopamine, norepinephrine and epinephrine; and the trace-amine tyramine. Additionally, in the thyroid gland, tyrosine can also be iodinated to give rise to thyroid hormones. Tyrosine enhances cognitive performance, energy, and alertness, and improves memory after sleep deprivation. Tyrosine also prevents the depletion of central and peripheral catecholamines (dopamine, norepinephrine, epinephrine) induced by acute stress, thereby eliciting protective effects on behavioral and cardiovascular parameters in the body.

**TYRAMINE**

Tyramine is within range. Tyramine is a trace amine derived from the amino acid tyrosine that is found naturally in food. Specifically, tyramine is found in aged, fermented cured or spoiled food where microbes with decarboxylase enzymes convert tyrosine to tyramine. These foods include aged cheeses, smoked fish, cured meats, wine, and some types of beer. In sensitive individuals, eating high amount of tyramine can trigger migraines and increase blood pressure.

**DOPAMINE**

Dopamine is low-normal (<20th percentile). Dopamine improves attention, focus, and motivation, helps with decision making, modulates movement control, promotes lactation, increases blood pressure, urine output and sodium excretion, and allows for feelings of reward and pleasure. Additionally, the quest for dopamine stimulation plays a central role in the etiology of addiction. Dopamine also serves as the parent precursor to norepinephrine and epinephrine. Research shows that urinary dopamine levels are reduced in patients with Alzheimer's disease (Liu et al., 2011), anorexia nervosa (Van Binsbergen et al., 1991), anxiety with depression (Field et al., 2010), fibromyalgia (Riva et al., 2012), and periodic limb movement disorder (Cohrs et al., 2004). Clinically, low dopamine is also implicated in apathy, cravings, fatigue, impulse control issues, increased sensitivity to pain, low libido, low mood, memory issues, sleep disturbances, and weight control issues.

**THERAPEUTIC CONSIDERATIONS:** Supplementation with precursors (tyrosine or L-DOPA) and/or cofactors (iron, vitamin B6, tetrahydrofolate) to promote biosynthesis may be beneficial.

**DOPAC**

DOPAC is low-normal (<20th percentile). DOPAC is the primary metabolite of dopamine formed via the actions of monoamine oxidase. Research shows that DOPAC is reduced in the urine of patients with Alzheimer's disease (Liu et al., 2011). Lower than optimal levels suggest that dopamine and its upstream precursors L-Dopa or tyrosine may be insufficient. DOPAC may also be lower due to MAO genetic SNPs which can slow down this enzyme or insufficient vitamin B2 or copper levels. Evaluate this level in combination with dopamine, but also 5HIAA (the serotonin metabolite) since it also uses the MAO enzyme.

**THERAPEUTIC CONSIDERATIONS:** Consider supplementing with the building blocks of dopamine (tyrosine and/or l-dopa). L-dopa is found naturally in the herb mucuna as well as supporting nutritional co-factors used with MAO enzymes.

**HVA**

Homovanillic acid (HVA) is within reference range. HVA is a dopamine metabolite.

**NOREPINEPHRINE**

Norepinephrine is within reference range. Norepinephrine functions both as a neurotransmitter and a hormone, participating in the body's "fight or flight" response. Norepinephrine increases alertness, focuses attention, fine-tunes vigilance, increases blood pressure, heart rate, and blood sugar, reduces digestive activity, pain, and sleep, prevents bladder emptying, and regulates body temperature. Norepinephrine is very similar in structure and physiological effects to epinephrine. The adrenal gland produces approximately 20% of the total output with 80% produced by the sympathetic nerve fibers.

**NORMETANEPHRINE**

Normetanephrine is within reference range. Normetanephrine is a norepinephrine metabolite formed via the actions of catechol-O-methyl (COMT) transferase enzyme in response to stress.

**EPINEPHRINE**

Epinephrine is within reference range. Epinephrine, also called adrenaline, functions both as a neurotransmitter and a hormone, participating in the body's fight or flight response. Epinephrine increases alertness, focuses attention, fine-tunes vigilance, increases blood pressure, heart rate, and blood glucose, reduces digestive activity, pain and sleep, prevents bladder emptying, and regulates body temperature.

**VMA**

Vanillylmandelic acid (VMA) is within reference range. VMA is a norepinephrine and epinephrine metabolite formed via the actions of monoamine oxidase, catechol-O-methyl transferase (COMT), and aldehyde dehydrogenase.

**INFLAMMATORY MARKERS****KYNURENINE**

Kynurenine is high-normal (>80th percentile). Kynurenine is a central metabolite of the amino acid tryptophan with vasodilatory properties. Kynurenine is utilized by the body in the production of niacin (vitamin B3), eventually leading to the formation of NAD+, which plays a pivotal role



in energy metabolism, gene expression, cell death and regulation of calcium homeostasis. More than 90% of the body's tryptophan is metabolized to the kynurenine pathway.

Kynurenine is synthesized by the enzyme tryptophan dioxygenase, which is expressed primarily but not exclusively in the liver, and indoleamine 2,3-dioxygenase, which is made in many tissues in response to immune activation by interferons and cytokines, or free radicals. In the brain, approximately ~40% of kynurenine is produced locally, whereas the rest is absorbed from the blood.

Kynurenine degradation generates a series of neuroprotective and neurotoxic compounds that can activate or inhibit N-methyl-d-aspartate (NMDA) glutamate receptors (see kynurenic acid and 3-OH kynurenine). Upregulation of this pathway may be a hallmark of neuroinflammation and is associated with certain disorders.

Research shows that kynurenine is high in high with tryptophan administration (Michael, Drummond et al. 1964), hydrocortisone treatment (Rose and Braidman 1971), metabolic syndrome (Oh, Seo et al. 2017), with major coronary events (Pedersen, Svingen et al. 9/2013), and in women in pregnancy (Rose and Braidman 1971). High kynurenine levels have been implicated in disorders like Irritable Bowel Syndrome (Fitzgerald, Cassidy Eugene et al. 2008), lupus (Akesson, Pettersson et al. 2018), Crohn's disease (Gupta, Thaker et al. 2012), and Alzheimer's Disease (Chatterjee, Goozee et al. 2018). Additionally, caffeine (Orlikov and Ryzov 1991) and regular black tea (Gostner, Becker et al. 2015) consumption can elevate kynurenine levels as well.

**TREATMENT CONSIDERATIONS:** reduction of inflammation through diet and supplementation may be beneficial. Glutathione support and modulation of the NMDA receptor (e.g. magnesium) may help reduce symptoms.

#### KYNURENIC ACID

Kynurenic acid is within range. Kynurenic acid is a neuroactive metabolite produced from kynurenine. Kynurenine is formed from tryptophan via the enzyme tryptophan dioxygenase and indoleamine 2,3-dioxygenase; and metabolized along two independent pathways to produce kynurenic acid via aminotransferases and 3-OH kynurenine.

Kynurenic acid (unless in excess amounts) is regarded to have a neuroprotective role because it inhibits the N-methyl-d-aspartate (NMDA) glutamate receptor, reduces the neurotransmitter glutamate release and thereby prevents excitotoxicity.

#### 3-HYDROXYKYNURENINE

3-Hydroxykynurenine is high. 3-Hydroxy Kynurenine (3-OH Kynurenine) is a metabolic intermediate of the kynurenine pathway, one of the major metabolites of tryptophan degradation. Kynurenine is transformed into 3-OH Kynurenine, which acts as a N-methyl-d-aspartate (NMDA) glutamate receptor agonist and has been demonstrated to exert neurotoxic effects.

Neurotoxicity elicited by 3-OH Kynurenine appears to be also related to generation of oxidative stress produced by reactive radical species, formed as a result of auto-oxidation. Additionally, 3-OH Kynurenine gives rise to neurotoxic metabolites, such as quinolinic acid, which activate the NMDA receptor, induce lipid peroxidation and promote oxidative stress.

Research shows that urinary levels of 3-OH Kynurenine are high with hydrocortisone treatment (Rose and Braidman 1971) and in women in pregnancy (Rose and Braidman 1971). High 3-OH Kynurenine is implicated in vitamin B6 deficiency (Theofylaktopoulou, Ulvik et al. 2014) and Alzheimer's disease (Schwarz, Guillemin et al. 2013).

**TREATMENT CONSIDERATIONS:** consider glutathione support and antioxidant support to prevent the oxidative stress produced by 3-hydroxykynurenine. Consider B6 supplementation (under 200 mg/day for safety).

#### XANTHURENIC ACID

Xanthurenic acid is within range. Xanthurenic acid is a metabolite of the kynurenine pathway, formed directly from 3-OH Kynurenine, and serves as an indirect marker of vitamin B6 status.

#### URINARY FREE CORTISOL (F) AND CORTISONE (E)

Urinary free cortisol (F) and cortisone (E) are NOT following a normal circadian rhythm and levels are outside the expected reference ranges, particularly in the first two morning voids. F and E are very high in the first morning void, but drop precipitously in the second void but begin to recover to normal reference ranges in the evening and at night before bed. This individual has reported use of a synthetic glucocorticoid, commonly used topically for treating skin conditions associated with inflammation. Synthetic glucocorticoids that enter the systemic circulation suppress endogenous cortisol synthesis by negative feedback to the hypothalamic-pituitary-adrenal axis and lower ACTH/cortisol synthesis. The negative feedback is transient and may result in a rebound with higher synthesis of cortisol several hours afterward. Low second morning cortisol likely results from use of the synthetic glucocorticoid after collecting the first morning void. As seen in these results cortisol recovers to expected levels in the evening and at night before bed. A high F and E in the first morning void suggests that levels are high during sleep at night or rise rapidly just before waking (possible rebound from evening use of the synthetic glucocorticoid).

Overall, these results indicate that endogenous cortisol synthesis is high and is somewhat amplified by use of the topical synthetic glucocorticoid. Self-reported symptoms (e.g. excessive stress, fatigue, depression, irritability, decreased mental sharpness, weight gain most in the waist (belly fat), are consistent with overall high cortisol exposure.

While a normal daily adrenal output of cortisol is essential to maintain normal metabolic activity, help regulate steady state glucose levels (important for brain function and energy production), and optimize immune function, excessive levels of glucocorticoids (natural and synthetic) can have the opposite effect over time. For information about strategies to support adrenal health and reduce stress(ors) that can lead to excess or deficient cortisol synthesis, the following books are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "The Role of Stress and the HPA Axis in Chronic

Disease Management" by Thomas Guilliams, PhD.

#### MELATONIN METABOLITE 6-SULFATOXYMELATONIN (MT6s)

The melatonin metabolite 6-sulfatoxymelatonin (MT6s) is not following a normal circadian rhythm. MT6s should be at its highest level in the first morning void, which is reflective of the dark period (night), but instead is low. Lower MT6s in the first morning void may reflect work during a night shift or staying up at night with excessive lighting (e.g. watching television). Some sleep (benzodiazepines, barbituates), pain (ibuprofen, opiates) and blood pressure medications (beta blockers like propranolol) are known to interfere with melatonin production and secretion and lower the circulating and excreted (MT6s) urinary levels of melatonin. Use of any of these medications at night before bed would result in a lower melatonin in the first morning void. The second morning void in this individual is also lower than the reference range. MT6s begins to rise thereafter in the evening and is within normal reference range at night before bed.

In a healthy individual the circadian rhythm of melatonin is inversely related to circulating levels of adrenal cortisol levels, i.e. melatonin rises with darkness and peaks about 2-3 am, while cortisol falls to its lowest level at this time of day. With morning and onset of light exposure, melatonin drops rapidly and cortisol rises, peaking to its highest level about 30 min to 1 hr after waking (referred to as a Cortisol Awakening Response-CAR). By mid-afternoon (evening void) with maximal light exposure melatonin reaches a nadir. It then gradually begins to rise again with nightfall and less light exposure, while cortisol continues to rise. Cortisol and melatonin reach their nadir and peak, respectively, about 2-3 am. Melatonin synthesis by the pineal gland is controlled by light exposure, while cortisol synthesis is controlled by the hypothalamic-pituitary axis in response to stressors. While melatonin and cortisol have opposing circadian rhythms neither hormone directly and acutely controls the synthesis of the other.

Melatonin is known to have many different beneficial effects in the body. For an excellent review of melatonin's many benefits please read: Pandi-Perumal et.al. Melatonin, Nature's most versatile biological signal. FEBS 273: 2813-2838, 2006. Melatonin has multiple roles in maintaining health. It helps slow the aging process, is a potent anti-oxidant, regulates the immune system, inhibits formation and growth of tumors such as breast and prostate cancers, and helps regulate the synthesis of the sex-hormones estradiol and progesterone (melatonin increases progesterone, decreases estrogens by inhibiting aromatase, and down-regulates cellular estrogen receptors, which diminishes response of estrogen-sensitive tissues to estrogens). Low melatonin is also thought to contribute to obesity in people with insomnia or those who do night shift work.

Because of its established role in the regulation of the circadian rhythm, treatment with exogenous melatonin has been found useful in people with circadian rhythm sleep disorders, such as delayed sleep phase disorder, jet lag, shift worker disorder, and the non-24-hour sleep-wake disorder most commonly found in totally blind individuals; however, its utility for the treatment of insomnia is not established and remains controversial.

If melatonin is taken as a supplement (available OTC) to correct low levels or treat a condition, the timing and dosage are important to its effectiveness, especially as a sleep aid. Response to supplemental melatonin can be very individual. For optimal benefit it is best to work with a health care provider familiar with melatonin dosage and timing. Excessive dosing can result in spillover of melatonin into daylight hours, excessive sleepiness during the day, and disruption of the normal melatonin-cortisol circadian rhythms.

For more general information about melatonin please see: <http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html>

#### DIURNAL EPINEPHRINE

Epinephrine is elevated during the night (1st morning), but returns to normal range in the morning (2nd sample), and remains within normal ranges throughout the day (evening collection) and at night (evening/night sample) before bed. The pooled sample is within range, but the diurnal results are more accurate for true epinephrine status. Epinephrine, also called adrenaline, functions both as a neurotransmitter and a hormone, participating in the body's "fight or flight" response. Epinephrine increases alertness, focuses attention, fine-tunes vigilance, increases blood pressure, heart rate, and blood glucose, reduces digestive activity, pain and sleep, prevents bladder emptying, and regulates body temperature. It is commonly triggered by stress, fear, blood sugar irregularities or anxiety.

Research shows that urinary epinephrine levels are increased in patients with attention deficit disorder (Faraone et al., 2014), anxiety and depression (Hughes et al., 2004), bipolar disorder (Koslow et al., 1983), hyperglycemia (Troisi et al., 1991), hyperinsulinemia (Troisi et al., 1991), obstructive sleep apnea (Kheirandish-Gozal et al., 2013), post-traumatic stress disorder (Yehuda et al., 1992), and stress (Holzman et al., 2009; Fujiwara et al., 2004). Fluctuating levels throughout the day have been commonly associated with an inverse relationship with cortisol (e.g. high epi when cortisol is low).

**THERAPEUTIC CONSIDERATIONS:** Because epinephrine is almost exclusively from the adrenal glands, treatments geared to support normal adrenal function and calm the sympathetic nervous system may be beneficial. Supplements such as adrenal adaptogens, B vitamins, essential fatty acids, vitamin C, as well as stress management, blood sugar balance and sleep support may be helpful.

Creatinine is within range throughout the day reflecting normal concentration of urine.

Creatinine levels reflect urine concentration.

Low values suggest overly dilute urine; High values suggest overly concentrated urine.

Extreme low or high values may be induced by kidney or other metabolic disorders, but most values will be due to inadequate hydration (high creatinine) or excessive water intake in the several hours prior to testing (low creatinine). Creatinine is used to adjust the lab results for kidney function. No samples were refused due to quality issues.