

Pathology Testing for Mood Disorders

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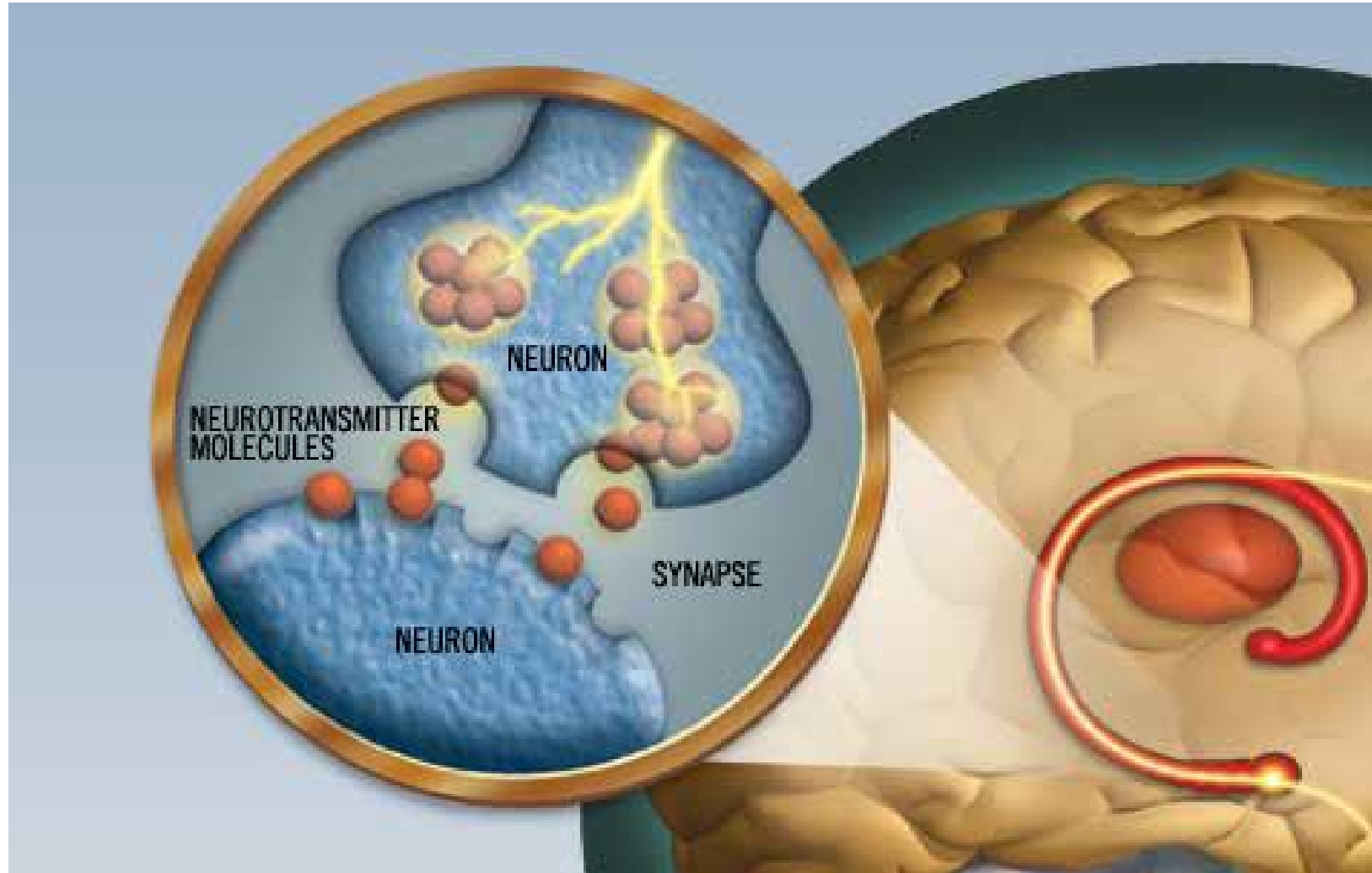
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Pathology Testing for Mood Disorders

- Neurotransmitters:
 - Metabolism
 - Imbalances
 - Testing – Neuroendocrine markers
- Kryptopyrroles:
 - Relevance for mood disorders
 - Testing
- Other useful tests:
 - Histamine
 - Amino acid profiles
 - Thyroid function profile
 - Digest function profile
 - IgG food allergy panel
 - Adrenal hormones
 - Vitamin analysis
 - Melatonin levels
 - Liver detoxification

Mood disorders and Neurotransmitters



Neurotransmitters

- They affect many processes of the body including mood, pain, hormone regulation, digestion, and metabolism.
- The signals that the brain sends to the body and feedbacks it receives need to be strong, or the processes that affect health will be impaired.
- Therefore, the balance of NTs can facilitate or hamper well being and impact the efficacy of treatments.

Neurotransmitter Imbalances

- Neurotransmitter imbalances & resulting symptoms are extremely common.
- Years of research confirm that 8 / 10 people have some level of NT imbalance.
- Once imbalances are identified, an Amino Acid Replenishment (AAR) program re-establishes NT levels and effectively resolve many of the symptoms.

Common Neurotransmitter-related Conditions

- Depression • 10-12%
- Migraine • 5%
- Anxiety • 10-30%
- Obesity/Overweight • 50-60%
- Insomnia • 10%
- PMS • 15%
- Irritable Bowel Syndrome • 15%
- ADD/ADHD • 20-22%
- Hypertension • 10%
- Fibromyalgia • 5%

Neurotransmitter Imbalances

- They occur when the current levels of neurotransmitters are unable to properly relay the electrical signal from one neuron to the next.
- These situations include:
 - Low NT levels
 - Low postsynaptic receptor levels
 - High NT levels

1. Low NT levels

- Unable to simultaneously engage enough postsynaptic receptor sites & cause membrane depolarization.
- This disrupts signal transduction.
- Occurs from:
 - Prolonged Stress
 - Genetic predisposition
 - Diets low in Amino Acid precursors
 - Excessive breakdown
 - Medication
 - Nutritional precursor and/or co-factor deficiency

2. Low Postsynaptic Receptor Levels

- Postsynaptic neuron fires when enough of its receptors are engaged by the NTs.
- If number of receptors are low, increased levels of NTs are required for the neuron to fire and relay a signal.
- Causes – Neurotoxics:
 - Heavy Metals, pesticides, illicit amphetamines, some prescriptive drugs can cause permanent damage reducing the number of active receptors
 - Excessive NT release

3. High NT levels

- High NT levels are also seen
- Occurs from:
 - Biogenic amines, peptides, neurosteroids, which can potentiate the effects of NTs.
 - Over-methylation
 - Imbalances of other neurotransmitters

“Excitatory” Neurotransmitters

- The *accelerator* is equivalent to the “**excitatory NT system**”.
- The only true **excitatory** neurotransmitter is glutamate.
- Other neurotransmitters that are primarily excitatory include aspartate, histamine, PEA, epinephrine and norepinephrine.
- When these chemicals are released, the hypothetical *accelerator* is pushed, and the nervous system revs up.
- The excitatory NT system is responsible for sending a signal.

“Inhibitory” Neurotransmitters

- The brake is equivalent to the **inhibitory neurotransmitter system**.
- The only true inhibitory neurotransmitter is GABA.
- Other neurotransmitters, which are primarily inhibitory include serotonin and glycine.
- When these chemicals are released, the hypothetical **brake** is pushed, and the system slows down.
- The inhibitory NT system is responsible for preventing a signal from continuing.

Maintenance

- Just like in a car, the brakes must be maintained or the car will not be able to stop.
- If the inhibitory system isn't maintained or replenished, then the excitatory system will be allowed to go out of control, and eventually, it will become exhausted.
- In order to tell how far along the wear on the systems is, which parts are wearing, and how the parameters that make them more effective are factoring in, it is important to perform NT testing.

Major Neurotransmitters

Glutamate

- Major excitatory NT in the brain.
 - 70% of the fast excitatory CNS synapses use glutamate as a NT.
 - Synthesised from glutamine
 - Dramatic increase in function of glutamate often induces death of neurons (e.g. ischemia, trauma, hypoxia, hypoglycaemia, hepatic encephalopathy). – excitotoxicity
- ↑ ***glutamate associated with Huntingdon's, Parkinson's, Alzheimer's, vascular dementia, amyotrophic lateral sclerosis, Tourette's, and Korsakoff syndrome.***

GABA

- Major brain inhibitory NT occurring in 30-40% of all synapses.
- GABA concentration in the brain is 200-1000 times greater than that of the monoamines or acetylcholine.
- Synthesized from the amino acid glutamine and glutamate.
- Benzodiazepines (e.g. valium) potentiate the effects of GABA
- Alcohol & barbituates have similar effects on the GABA receptor.

↓ ***GABA associated with anxiety symptoms and sleep problems***

Serotonin

- An amine NT synthesised from the amino acid tryptophan (5-HTP being an intermediate)
 - Like GABA works to inhibit glutamate activity & NT firing.
- ↓ ***serotonin associated with depression, compulsive disorders, anxiety, insomnia, migraines***

Epinephrine (adrenaline)

- NT & hormone essential to the body's metabolism.
 - Regulates attentiveness & mental focus.
 - Synthesized from norepinephrine.
 - Secreted by the adrenal medulla.
 - Medically used as a stimulant in cardiac arrest, as a vasoconstrictor in shock, bronchodilator & antispasmodic in bronchial asthma, & anaphylaxis.
 - Modulates neurons to favour glutamate activity & NT firing.
 - Inhibits insulin secretion
- ↑ ***epinephrine associated with fear & anger, flight or fight response, resulting in increased heart rate and hydrolysis of glycogen to glucose.***

Norepinephrine

- Synthesized from dopamine by dopamine beta-hydroxylase
- Cells using norepinephrine to make epinephrine use SAMe as a methyl group donor.
- Epinephrine levels in CNS are only 10% of the levels of norepinephrine.
- Benzodiazepines, (the primary antianxiety drug), decrease firing of norepinephrine neurons

↑ ***norepinephrine associated with stress and anxiety***

Dopamine

- An amine NT derived from tyrosine.
 - Precursor to norepinephrine & epinephrine.
 - Dopamine, norepinephrine & epinephrine is stored in vesicles in the axon terminal.
 - Role in cardiovascular, renal, hormonal, and CNS.
 - Thought to control diverse processes from movement to drug addiction.
 - Modulates neurons to favour glutamate activity & NT firing.
- ↓ ***dopamine associated with fatigue, Parkinson's disease, exhaustion, stress, poor memory***

Histamine

- Found to have a pacemaker function within the brain.
 - Firing rates of these neurons correlate positively with brain activity levels and displays distinct day-night rhythms. (Relevant to control of sleep and wakefulness)
 - Like the other biogenic amines (serotonin, dopamine, norepinephrine, epinephrine & PEA) is stored in presynaptic vesicles & released into the synapse.
- ↓ ***histamine associated with schizophrenia, memory loss, anxiety, nausea***

PEA (Beta-phenylethylamine)

- An amine NT derived from phenylalanine.
- Promotes energy & improves mood.
- As a neuromodulator inhibiting the reuptake of dopamine or norepinephrine.
- Lipid soluble & crosses blood-brain barrier.
- It has been implicated in migraines and the antidepressant effects of exercise.

↓ ***PEA associated with depression***

↑ ***PEA associated with schizophrenia***

Identifying Neurotransmitter Imbalances through Testing

Neurotransmitter Testing

- NT testing should be a component of any primary care screening & workup.
- Efforts to address NT levels should be front-line strategies for healthcare practitioners, as essential for well-being as interventions based on blood chemistry results, blood pressure readings, and physical examination.
- The process of NT influences many aspects that contribute to health and disease in the human body.

Why Test?

- Testing objectively documents the need for intervention.
- Objective evidence helps boost patient compliance with the treatment program.
- Retesting allows practitioners to adjust dosing and monitor patient progress.
- Regular retesting during maintenance ensures that the patient's course is charted toward maintaining optimum health.

Basic Testing Procedure

STEP 1

- Patient rings lab and purchases box of collection materials, instructions & return postal kit.
- Patient collects specimen & mails back to lab. Specimens are stable at room temp up to 1 month.

STEP 2

- Lab receives specimen and performs analysis.
- Patient's results are reviewed along with symptoms analysis scored by patient.
- NT recommendations are included in the report.
- Turn-around time 10-14 days.

Basic Testing Procedure

STEP 3

- Reports are forwarded to health care provider via fax, mail, email, medical director or equivalent.

STEP 4

- Healthcare provider to review report & recommendations.
- Consider symptoms & therapy recommendations.
- Proceed with Phase 1 & Phase 2 of therapy (3-6 months).

Basic Testing Procedure

STEP 5

- Retest. If patient proceeds as expected, a retest is recommended after 6 – 8 weeks of therapy.
- This test will verify appropriate levels of NTs have been achieved.
- Earlier testing is recommended if patient fails to achieve desired outcome.

STEP 6

- After NT levels have been restored & clinical complaints are reduced, Phase 3 is recommended.
- During this phase, therapies are reduced to the minimum effective dose of current Amino Acid Replenishment products. Doses are slowly titrated down.

Testing available

1. Current tests available

- Neuroendocrine (monoamine) metabolites
 - Serotonin, dopamine, epinephrine, norepinephrine
- Histamine
- Kryptopyrroles
- Other useful tests – organic acid profile, adrenal hormones, Amino acid profiles, Thyroid function profile, Digest function profile, IgG food allergy panel, Adrenal hormones, Vitamin analysis, Melatonin levels, Liver detoxification.

- Tests:

1. Neuroendocrine (monoamine) Metabolites
[Currently available]

- Dopamine – Homovanillate, Dihydroxyphenylacetate
- Noradrenalin – Methoxyphenylglycol, Dihydroxyphenylglycol
- Adrenalin – Vanylmandelate, Dihydroxymandelate
- Serotonin – 5-OH-Indolacetate (5HIA)
- Catechol-O-methyltransferase & MAO enzymes

2. NT (9) – Actual Neurotransmitters
[Available SOON!]

Dopamine, Noradrenaline, Adrenaline, Serotonin, GABA, glutamate, phenylethylamine, histamine, glutamine.

Testing Details

- **Testing: Baseline**
- Baseline Testing establishes levels of up to 9 neurotransmitters & precursors & steroid hormones.
- ***Current test only tests the metabolites of 4 NTs and 2 enzymes.***
- This serves as a reference point for therapy.

- **Receive Test Results**
- All NT lab reports include suggestions for health care providers for Amino Acid Replenishment products based on the results & any additional patient information available.
- Health Care Practitioners are responsible for final decisions regarding treatment.

Specimen Types – Neuroendocrine and Neurotransmitter testing

- **Urine, 24 hour**
 - Gold standard
 - Evens out diurnal variations in NTs
 - Record the volume or weight on request slip
 - Only send 10-20ml of the urine
- **Urine, 1st Morn. Void**
 - Convenient and adequate for most therapies & diagnosis.
 - Avoids the fluctuations that occur later in the day due to stress, meals or therapies.
 - Can do spot urine at different time intervals.
 - Only send 10-20ml of the urine.

Instructions For Reliable Test Results

- 12 hours prior to collecting your urine specimen:
- Do not eat. (No late night snacks)
- You may drink plain water until bedtime, but not in the morning until after the specimen is collected.
- The morning of collection, prior to collecting your specimen:
 - Do not eat (No breakfast)
 - Do not drink (No juice, water, milk, especially avoid coffee, tea, soda/soft drinks, alcohol)
 - Avoid tobacco (smoking and chewing)
 - Avoid exercise
 - Do not take any supplements or medications, unless required or instructed by your doctor, until after specimen collection.
- You may continue your normal routine after collecting your specimen.

Results Ranges

- **Observed or Ref Range**
 - Represents physiological levels with SD above & below the mean value.
- **Optimal Range**
 - Represents a benchmark for determining the need for therapy as well as the goal for the therapeutic outcome.
- **Therapeutic Range**
 - This range serves as a goal for patients using amino acid replacement therapy. Supraphysiological NT levels in order to replenish NT stores & resolve symptoms. A target to reach for.

Testing: Therapeutic Monitoring every 4-6 weeks or as needed.

- Therapeutic monitoring tests NT restoration during Phase 2.
- Due to individual differences, NT levels during therapy can vary.
- Monitoring will avoid over or under dosing and improve therapy.

Interpreting Results

- Many NT work together to ensure proper neuron signaling & function & have regulatory feedbacks.
- High or Low levels of one NT will affect levels of other NTs.
- e.g. serotonin is an important modulator of catecholamine activity.
- * *Important to consider all neurotransmitter levels in relation to each other.*

Implementing Nutritional prescriptions based on test results

- **Phase 1**
 - Weeks 1 – 2
 - Address inhibitory neurotransmitter levels first
- **Phase 2**
 - Begin in week 3 lasting 3-6 months
 - Balance levels of excitatory and inhibitory neurotransmitters
- **Phase 3**
 - Continuation of therapy
 - Support with amino acids as required

Case Study:

Female 52y, with Anxiety & Insomnia, No medication

NT ug/gCr	Baseline results	Optimal ranges	Therapeutic ranges
Epinephrine	16.5	8-12	8-13
Norepinephrine	63.8	30-55	35-70
Dopamine	255.5	125-175	200-500
Serotonin	111.2	175-225	250-1200
GABA	15	2-4	15-30
PEA	942	175-350	400-1000
Histamine	23.7	10-22	NA
Glutamate	41.1	10-25	NA

Comments

- The patient's complaints of anxiety corresponds well with lab results. All of the "excitatory" NTs are elevated (epinephrine, norepinephrine, dopamine, histamine, glutamate, & PEA).
- GABA, the primary inhibitory NT is also elevated indicating that the regulatory feedback is still intact. However, the GABA response is insufficient to bring epinephrine, norepinephrine, dopamine and PEA under control. GABA may be low due to the low serotonin. Serotonin is the major potentiator of GABA function.
- PEA – an excitatory NT, elevated levels may cause insomnia as well as anxiety.

Conclusion

- The patient's nervous system is in an unbalanced excitatory state. This leads to a condition of anxiety and insomnia.
- The therapeutic approach will be to strengthen the inhibitory (GABA) system by first addressing serotonin levels and over-stimulation.
- This step is followed by therapies that support the GABA system. This will bring the excitatory system under control.

Therapy objectives

- To balance the excitatory and inhibitory NT system.

Phase 1 – weeks 1&2

Aim: To increase serotonin and decrease the high turnover seen in epinephrine, norepinephrine, dopamine, and reduce PEA.

Recommendations:

- 5-HTP to increase serotonin (Serotonin regulates catecholamine turnover, especially dopamine)
- L-Theanine (green tea) to reduce high PEA, histamine and glutamate levels and decrease catecholamines turnover.

Phase 2 – week 3 +

Aim: To replenish the releasable pool of NTs contained in presynaptic vesicles and increases GABA function.

Recommendations:

- L-Theanine and Taurine to enhance GABA function.
- Tyrosine, a precursor to dopamine, norepinephrine, epinephrine to provide low level support to the stimulatory NT system.

Results of 1st Retest

NT ug/gCr	Baseline results	1 st Retest of results	Optimal ranges	Therapeutic ranges
Epinephrine	16.5	9.8	8-12	8-13
Norepinephrine	63.8	50.2	30-55	35-70
Dopamine	255.5	157.9	125-175	200-500
Serotonin	111.2	1040.6	175-225	250-1200
GABA	15	8.8	2-4	15-30
PEA	942	423	175-350	400-1000
Histamine	23.7	19.4	10-22	NA
Glutamate	41.1	32-9	10-25	NA

Interpretation

- Retest results reveal significant improvement in NT values.
- GABA is still somewhat elevated but is much closer to the “*Optimal Range*”.
- Serotonin levels have increased dramatically and are in the “*Therapeutic Range*”.
- A value this high is desirable during the phase of therapy and will help replenish depleted presynaptic vesicles.
- PEA & glutamate, which can cause anxiety at high levels, has also decreased significantly.

Clinical Results

- Patient reports that anxiety improved and that sleep seems somewhat more restful.

Recommendations

- Current therapy should continue for another 1-2 months.

Nutritional Treatment

What amino acids are used in this therapy?

- The amino acids used depend on the unique situation and NT levels found in the urine test. The therapy will include any number of the following:
 - 5HTP, tyrosine, phenylalanine, cysteine, mucuna (herbal L-Dopa), theanine, glutamine, taurine, methionine, GABA, phosphorylated b vitamins, minerals, and anti-oxidants.

Medical Treatment

Rx target Neurotransmitters

- Neurological symptoms may be related to neurotransmitter imbalances.
- Drugs that affect NTs, like Prozac, work with existing NT stores to elicit a therapeutic response.
- Block re-uptake pumps that transport NTs from the synapse back into the neuron, increasing the amount of NT in the synapse.
- Some like Lexapro, only prevent reuptake of serotonin, others like Wellbutrin, only prevent reuptake of norepinephrine.

Antidepressants

Often prescribed for mood disorders, antidepressants can:

- Adversely affect NT signaling (in high doses)
- Act by temporarily increasing synaptic NT levels or imitating a NT function.
- *Chronically lead to a depletion of the vesicle pool available for secretion, or alter the number of post-synaptic receptors available for signaling.*

RATIOS & Balance

- Maintaining proper RATIOS & supporting NT in the correct sequence is critical to the success of amino acid therapies.
- Most patients have imbalances involving multiple NTs.
- This is why many patients who increase 5HTP fail to achieve a positive clinical response.

Test:

Kryptopyrroles

What are Kryptopyrroles?

- An abnormal production of a group of chemicals called 'pyrroles', this is called pyroluria, associated with depression and other mental health disorders.
- The pyrroles rob the body of B6 and Zinc causing them to be excreted in the urine. Results in a deficiency of B6 and zinc, which supplementation can correct.
- It is most often seen in females.
- It is thought that about 10% of a normal population has pyroluria, which may cause symptoms when the patient is stressed.

**What are the symptoms of
Pyroluria imbalance?**

Symptoms

- Frequent ear infections, colds, fevers and chills.
- Fatigue
- Nervous exhaustion
- Insomnia
- Poor memory or inability to think clearly
- Hyperactivity
- Seizures
- Mood swings
- Lack of regular periods in girls
- Stretch marks in the skin
- Impotence in males
- Unusual smelling breath and body odour
- Inability to tolerate drugs and alcohol
- Cold hands and feet
- Abdominal pain
- Intolerance to some protein foods, drugs or alcohol
- Morning nausea and constipation
- Difficulty remembering dreams
- Frequent head colds and infections

Pyrolurics can often be identified by their appearance:

- Pale skin. (A black pyroluric will have the lightest skin in the family).
- A lack of hair on the head, eye brows and eye lashes.
- Teeth in the upper jaw will often be overcrowded (unless orthodontic treatments has taken place) and poor appearance of tooth enamel.
- White marks on fingernails, opaque and tissue paper thin.
- Acne, eczema, and herpes may also be present.

Why does pyroluria occur?

- Pyroluria can occur at any age but appears to be brought on by stress.
- It is familial and may be a factor in the development of mental retardation, epilepsy, hyper activity and particularly depression.
- A family history of mental illness and all-girl families especially if there is also a history of miscarried boys.

Not all the symptoms are present for every pyroluric but any number of them should make you suspicious.

What does the test involve?

- Morning spot urine specimen – in special urine jar provided (with Ascorbate & Na Carbonate as a preservative).
- Wrap it in aluminium foil before shipping.
- **Note:** Even without preservative the results are accurate and reproducible for up to 7 days as long as the specimen is stored away from direct sunlight. It does not have to be shipped frozen to the lab. We recommend that you collect the urine, freeze it overnight and wrap it in foil and ship to us.
- We correct the kryptopyroles results to Creatinine. This gives an accurate concentration regardless of fluid consumption & enables accurate detection of lower levels.

Collection Details

- Patient Rings ADL or Distributor.
- Pre-purchases kryptopyroles test kit.
- Box with collection kit and instructions along with post pack is sent to patient.
- Specimen collected and sent to lab.
- Result turnaround time in 7 - 10 days.

Test:

Histamine Levels

Histadelia – High histamine

- Sneeze in bright sunshine
- Overly shy and sensitive as a teenager
- Cry, salivate and feel nauseous easily
- Hear pulse in own head on pillow @ night
- Referred itch when scratching leg
- Frequent stomach aches, muscle cramps, back pain
- Easy orgasm
- Regular headaches and seasonal allergies
- Inner tension and occasional depression
- Have abnormal fears, compulsions or rituals
- Light sleeper
- Burns up food rapidly
- Suicidal thoughts
- Tolerate large amounts of alcohol and other downers
- Long fingers and toes
- Little body hair and lean build

Histapenia – Low histamine

- Canker sores
- Difficult orgasm
- No headaches or allergies
- Heavy growth or body hair
- Excess fat in lower extremities
- Many dental fillings
- Ideas of grandeur
- Undue suspicion of people
- The feeling that someone controls their mind
- Seeing or hearing things abnormally
- Ability to stand pain well
- Ringing in the ears

What Does the test Involve?

- One blood sample in **Li Heparin** tube. Specimens collected in other tubes can give incorrect - low Histamine levels.

Example report:

Blood	Result	Units	Reference
Histamine	22 *L	Ug/l	28-51

Comments: Result is consistent with Histapenia (Low Histamine).

Other Considerations

- Other factors that may affect neurotransmitter function and production must be considered including:
 - Individuality
 - Sex hormones
 - Adrenal hormones

Patient Individuality

- While NT patterns are seen in some conditions/symptoms, NT imbalances may also result in symptoms unique to the patient.
- This is due to the unique genetic makeup and environmental factors that influence the patient.

For Example

- One patient with **LOW serotonin & HIGH norepinephrine** may suffer from HYPERTENSION while another may suffer from ANXIETY.
- In this case “low” GABA levels in the hypertensive patient & a “high” GABA level in the anxiety patient would provide an explanation for these differences, and thus suggest different therapies.

Sex/ Adrenal Hormones

- May influence the activity of multiple neurotransmitters.
- A low thyroid activity will impact on steroid hormones and cause imbalances.
- Low cortisol and or DHEA levels will also impact on all steroids and in turn to the NTs.
- Check: Cortisol, DHEAs, T3, Testo, Estrogens, Progesterone – FREE hormone levels (saliva or urine – if serum order SHBG & CBG & fT3).

Other relevant tests by ADL

- 96 Food Allergies IgG – delayed allergies
- 24hr Urine or fasting serum Amino Acids
- Essential Fatty Acids – fasting.
- Intestinal Permeability – Kit available.
- Liver Detox Profile – Kit available.
- Digestive Stool Analysis – Kit available.
- Organic Acids – Metabolic Profile – Kit available.
- Saliva or Urine Hormones.

ADL – Age Diagnostic Laboratories

- Contact **Mr. Warwick Greville**
in Chicago **1-773-528-8500** & fax **1-773-296-2314**
for Information on:

- Test kits
- Request Forms
- Electronic transmission of results from ADL
- Pricing
- Shipping Instructions
- Patient Collection Details