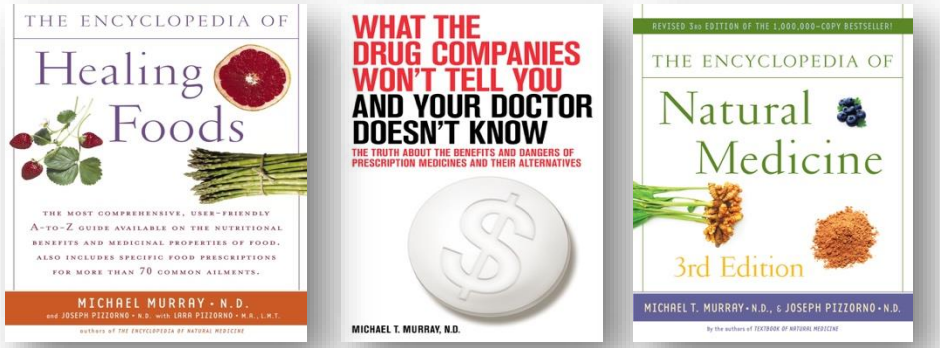
DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE



Advances in Managing Stress with Natural Products

- What determines our state?
- Nutritional considerations
- Botanical adaptogens

Michael T. Murray, N.D.

So, what determines how we feel?

Our mental and emotional state is determined by an interplay between two factors.

(1) Internal focus:

- Images held up before the mind's eye
- Self-talk, habitual questions, and explanatory style

(2) Physiology:

- Breathing pattern, kinesiology, and physical factors
- Hormonal, nutritional, and chemical factors

Is Stress GOOD? YES!

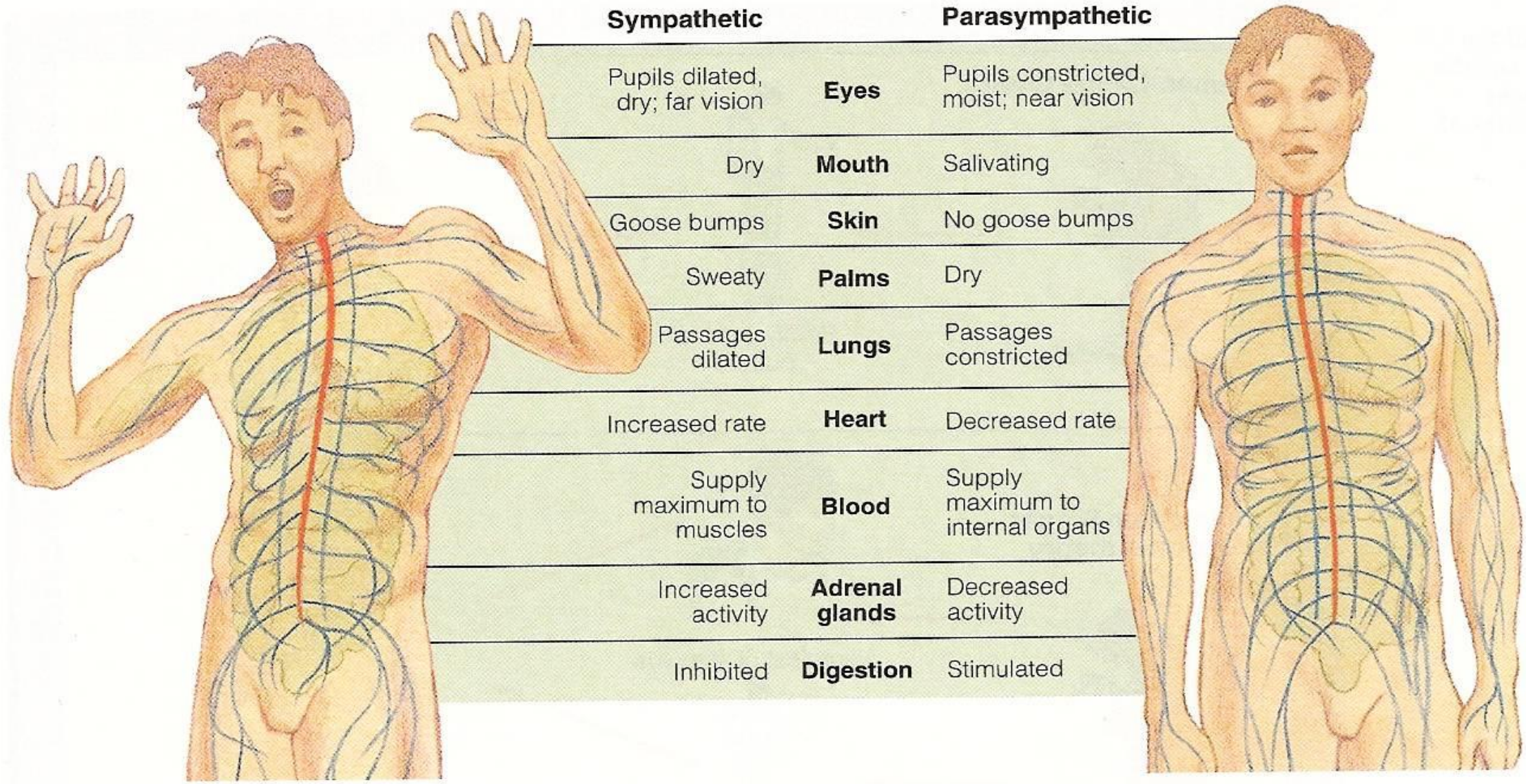
"No one can live without experiencing some degree of stress all the time. . . . . Stress is not even necessarily bad for you; it is also the spice of life, for any emotion, any activity causes stress. But, of course, your system must be prepared to take it."

Dr. Hans Selye

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

BIOLOGY OF THE STRESS RESPONSE

1. Activation of the sympathetic nervous system

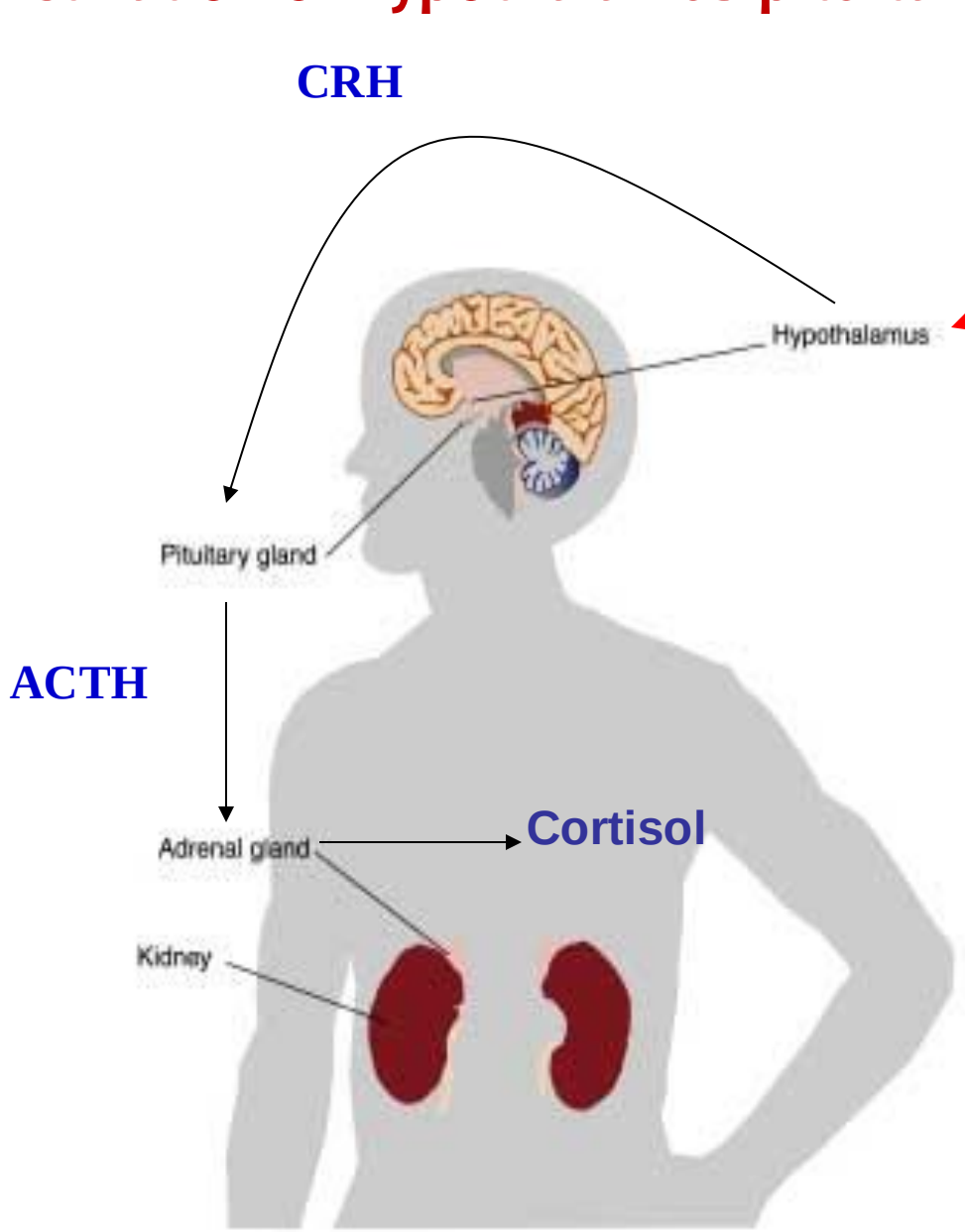


Sympathetic		Parasympathetic
Pupils dilated, dry; far vision	**Eyes**	Pupils constricted, moist; near vision
Dry	**Mouth**	Salivating
Goose bumps	**Skin**	No goose bumps
Sweaty	**Palms**	Dry
Passages dilated	**Lungs**	Passages constricted
Increased rate	**Heart**	Decreased rate
Supply maximum to muscles	**Blood**	Supply maximum to internal organs
Increased activity	**Adrenal glands**	Decreased activity
Inhibited	**Digestion**	Stimulated

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

BIOLOGY OF THE STRESS RESPONSE (continued)

2. Activation of hypothalamus-pituitary adrenal cortex axis (HPA)



Stress

Short-term effect of cortisol

Glucose release from liver and muscles

Long-term effects

Immune dysfunction
Loss of muscle and bone mass
Loss of insulin sensitivity
Hippocampus neuronal death

Comprehensive Stress Management

- Develop positive coping strategies.
- Stabilize blood sugar levels.
- Nourish your body and brain.
- Get a good night's sleep.
- Manage your life.
  - Time, relationships, exercise, lifestyle, etc.

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

Activation of the Parasympathetic Nervous System

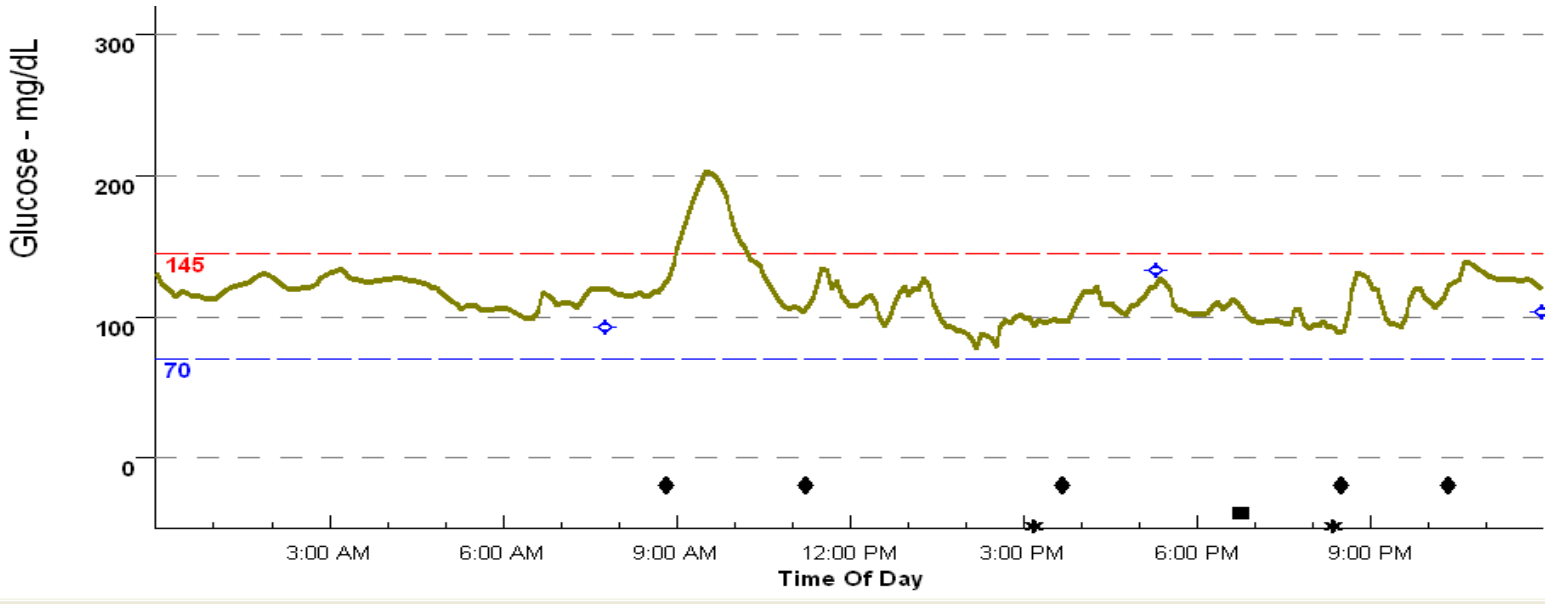
A key factor in stress management

- **Promote the "Relaxation Response"**
  - Popular techniques:
    - Deep breathing exercises
    - Meditation
    - Prayer
    - Progressive relaxation
    - Self-hypnosis
    - Biofeedback

Blood Sugar Roller Coaster: Signs and Symptoms

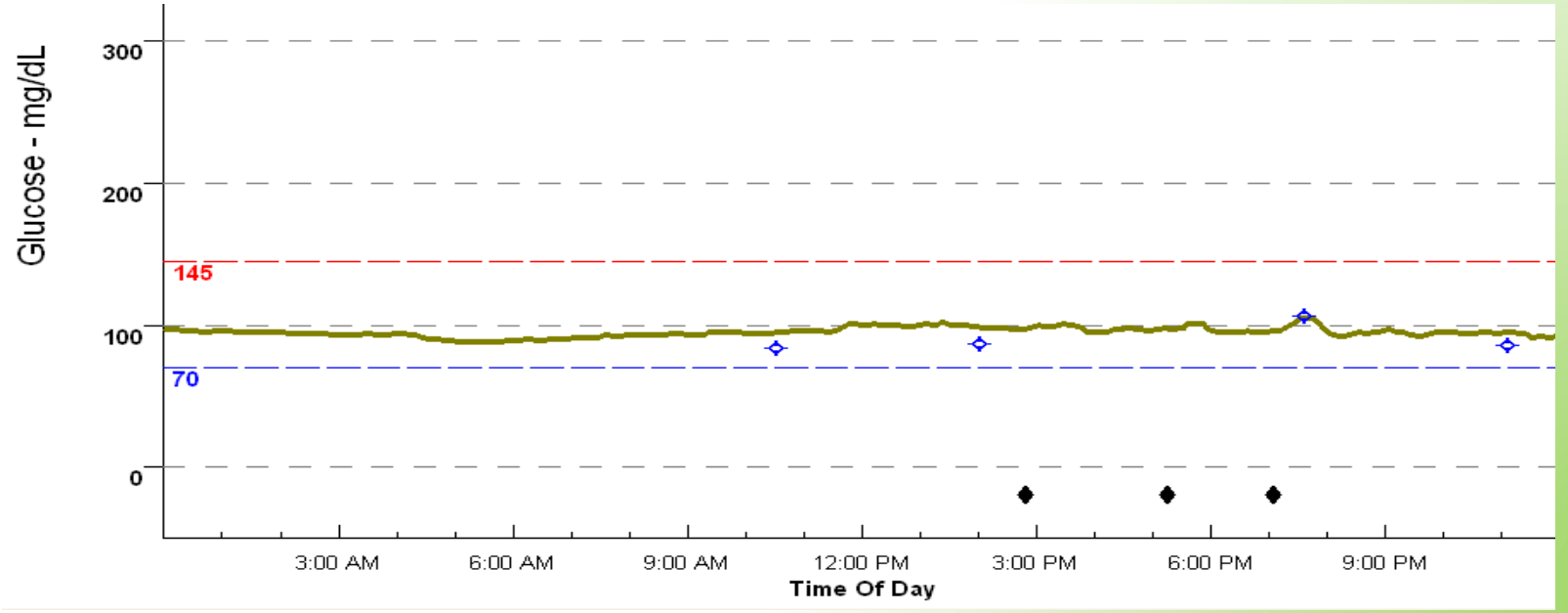
- Waist circumference is larger than hips.
- Overweight and a struggle to lose weight.
- Brain fog, spacey, and disconnected.
- **Easily stressed.**
- Elevated blood sugar or triglyceride levels.
- Afternoon fatigue.
- Crave sweets.
- Feels much better after eating.
- Irritable if a meal is missed (Hangry).
- Wakes up often during the night.
- Feels hungry most of the time.

Continuous Blood Sugar Measurement Graphs

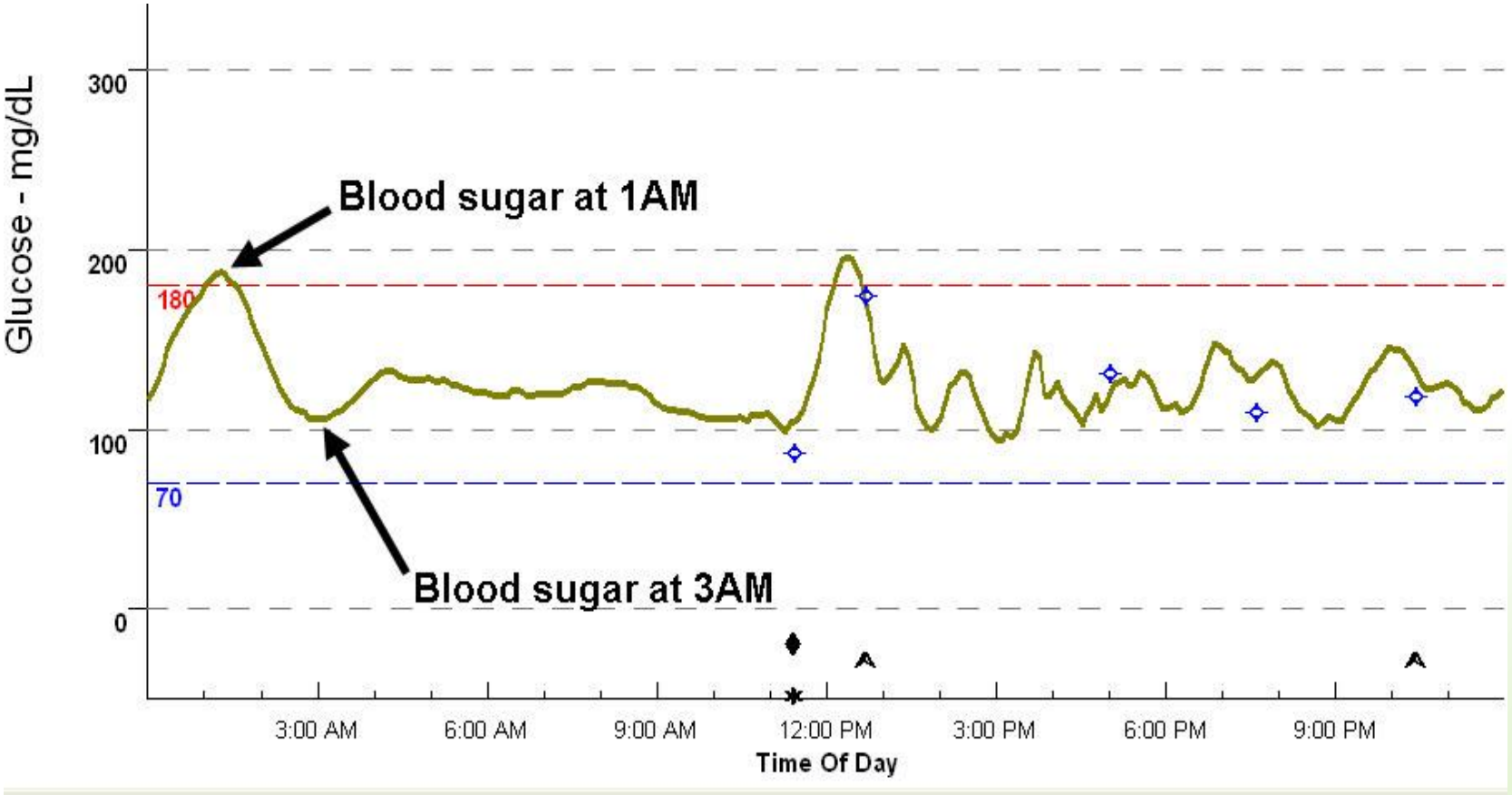


Before

After 4 Weeks with Low Glycemic Load Diet and PGX® Before Meals

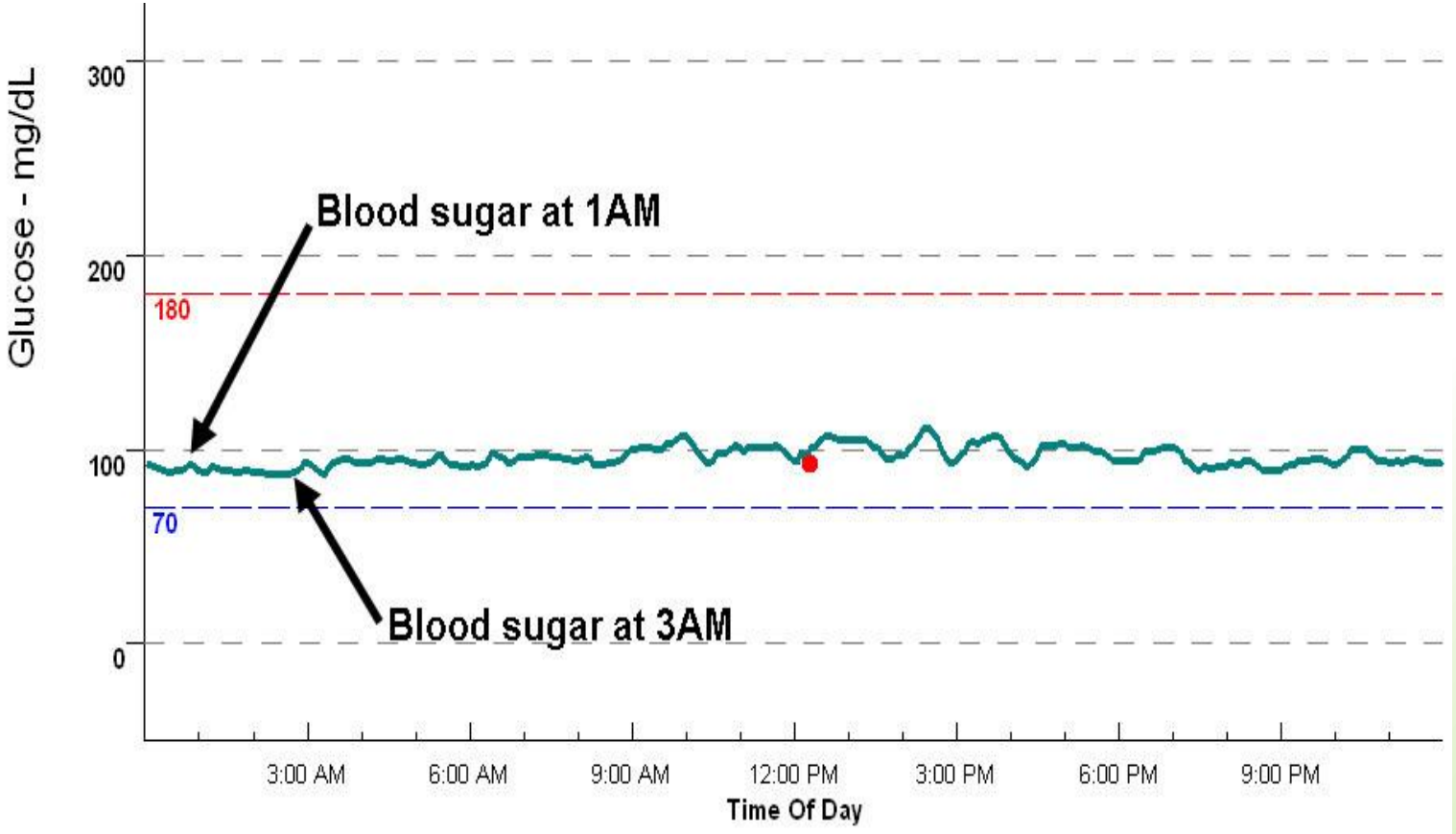


Case history – 40-year-old woman, significant stress event 7 years prior, more than doubled body weight, significant food cravings including nocturnal hyperphagia.



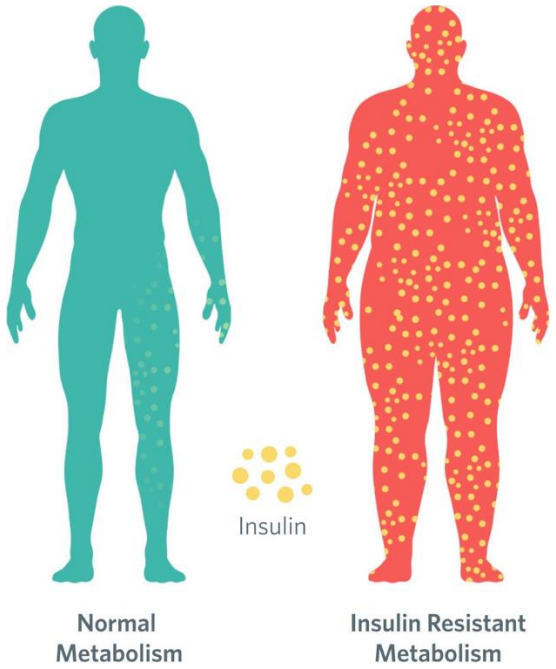
Before

At four week check up: "I am so happy to report that within 3 days of your program, I slept through the night for the first time in years and I have done so every night ever since. . . . I am losing so much weight that some people's jaw's drop when they see me now. "



After 4 Weeks Low Glycemic Load Diet and PGX® Before Meals

Keys to Improving Insulin Sensitivity and Getting Off the Blood Sugar Rollercoaster



- **Diet**
  - Low glycemic load (no more than a GL of 20 in a 2.5 hour period)
  - Optimal fatty acid intake profile (focus on mono-unsaturated fats and omega-3 fatty acids)
  - Rich in phytochemical antioxidants, particularly flavonoids
- **Lifestyle**
  - Exercise, efficient sleep, and promotion of health
- **Supplementation**
  - Supply key nutrients involved in insulin action
  - Highly viscous soluble fiber (e.g., PGX®)
  - Berberine, alpha-lipoic acid, and other activators of AMPK

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

Foundational Supplements for Stress

- High Potency Multiple
  - with methyl forms of B12 and Folate
- Vitamin D3
  - 2,000 to 5,000 IU daily
- Plant-based antioxidant
  - e.g., Grape Seed Extract 150-300 mg daily
- EPA+DHA 1,000-2,000 mg daily

MTHFR Polymorphism

Nearly 50% of people may be MTHFR compromised:

- 5-35% of the general population are homozygous for C677T
  - (70% reduced MTHFR activity)
- 20-45% of the general population are heterozygous for C677T
  - (35% reduced MTHFR activity)
- 15-20% of the general population of compound heterozygous for C677T and S1298C
  - (40-50% reduced MTHFR activity)
- Studies show 75-98% of children with autism

Cyano B_{12} versus Methyl B_{12}

Feature	Cyano B_{12}	Methyl B_{12}
Active form	No	Yes
Absorption	Good	Fair
Tissues	Less retained	More retained
Urinary Excretion	More	Less
Methyl donor	Inactive	Active
Effect on Homocysteine	Good	Very Good
Clinical advantage	No	Yes
In breast milk	Low	High concentration

Critical Roles of Omega-3 Fatty Acids in Brain Cells

EPA, DPA, and DHA influence:

- The fluidity of brain cell membranes.
- Neurotransmitter synthesis.
- Neurotransmitter binding.
- Signal transmission.
- The activity of key enzymes that break down neurotransmitters like serotonin, epinephrine, dopamine, and norepinephrine.

Omega-3 Fatty Acids Exert an Adaptogenic Effect on Stress Response

EPA, DPA, and DHA:

- Reduces cortisol levels.
- Reduces stress-induced aggression and hostility.
- Reduces the increase in heart rate and sympathetic nerve activity produced by mental stress.
- Reduces stress-related inflammation and oxidative damage.
- Prevents telomer shortening.
- Increases the resilience to stress and the production of protective compounds.

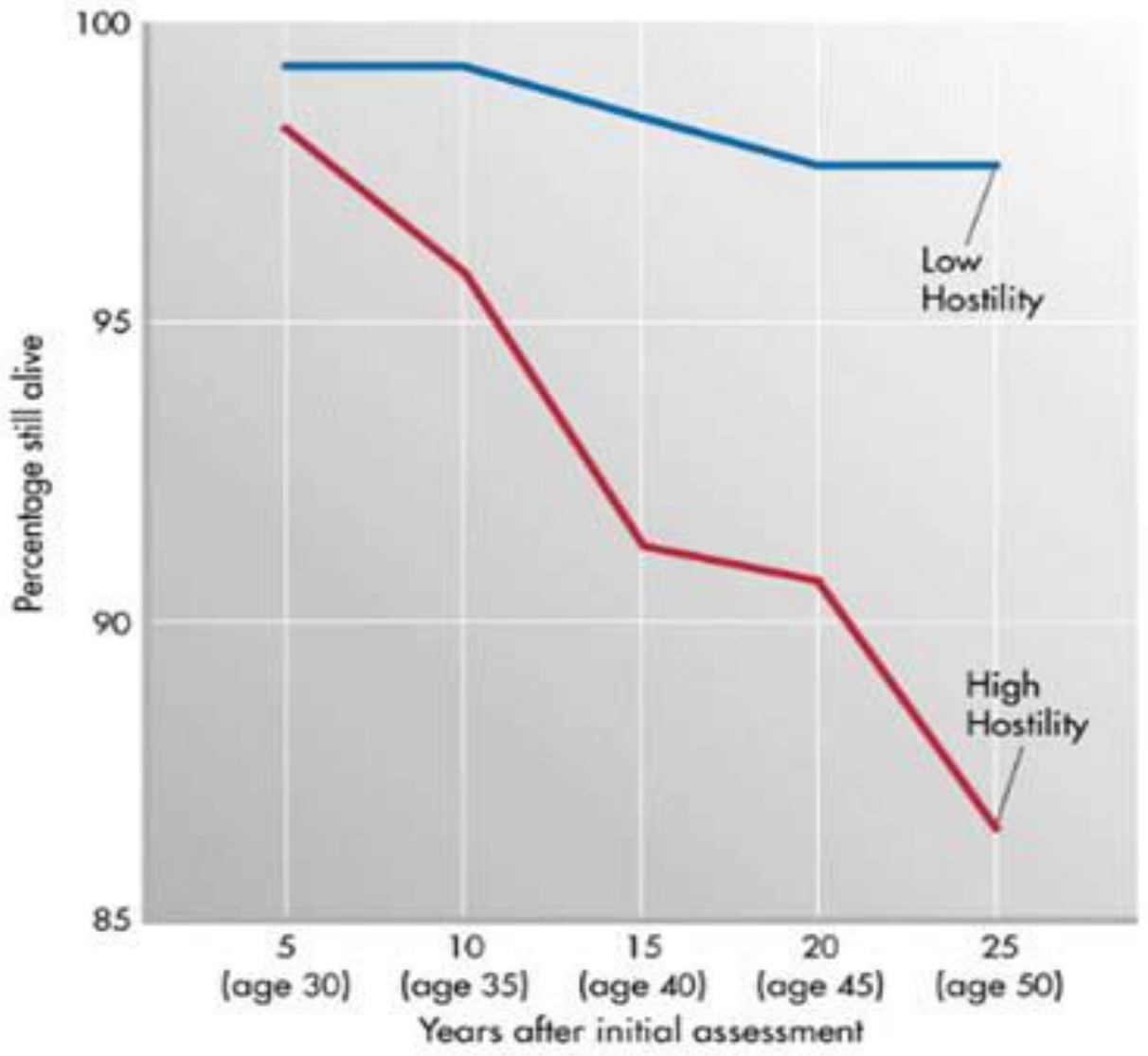
See: Madison AA, Belury MA, Andridge R, et al. Omega-3 supplementation and stress reactivity of cellular aging biomarkers: an ancillary substudy of a randomized, controlled trial in midlife adults. Mol Psychiatry. 2021 Jul;26(7):3034-3042.

Type A vs. type B personality

- Type A
  - time urgency
  - general hostility
  - intense ambition and competitiveness
  - associated with heart disease
- Type B
  - more easygoing
  - not associated with heart disease

Research on Type A Personality & Mortality

- Time urgency & competitiveness not associated with poor health outcomes
- Negative emotions, anger, aggressive reactivity are associated with poor health outcomes
- High levels of hostility increase chance of all disease (e.g., cancer)



Omega-3 Fatty Acids:

Practical Recommendations

- Use the highest quality fish oils providing at least a 60% concentration of EPA and DHA.
- For general health, take 1,000 to 1,500 mg of DHA/EPA/DPA daily.
- For inflammatory and other therapeutic indications increase dosage to 2,000 to 3,000 mg of DHA/EPA/DPA daily.
- For stress, depression, and CNS benefits, dosage based upon EPA content: 1,000-3,000 mg daily.
- Consider using Omega-3 Index to monitor dosage/need.

What does all the marketing claims on different forms of fish oil mean?

- Absorption is only a part of the equation.
- The bigger question is "Which form of fish oil can produce clinically relevant results?"
- Dosage of EPA+DHA+DPA biggest factor in clinical outcome.

Form of fish oil	Positive clinical results
Fish	YES
Triglycerides	YES
Re-esterified triglycerides	YES
Phospholipid	YES
Ethyl esters	YES

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

Magnesium Supplementation:

Clinical Applications

- **ADHD**
- **Anxiety**
- **Asthma and COPD**
- **Cardiovascular disease**
  - Angina
  - Cardiac arrhythmias
  - Cardiomyopathy
  - Congestive heart failure
  - High blood pressure
  - Intermittent claudication
  - Low HDL levels
  - Mitral valve prolapse
  - Raynaud's disease
  - Stroke
- **Depression**
- **Diabetes**
- **Fatigue**
- **Fibromyalgia**
- **Glaucoma**
- **Hearing loss**
- **Hypoglycemia**
- **Insomnia**
- **Kidney stones**
- **Migraine**
- **Osteoporosis**
- **Pregnancy (also toxemia, premature delivery, and other complications)**
- **Premenstrual syndrome and dysmenorrhea**

Meta-analysis of Magnesium in Insomnia and Anxiety

Study: *Rawji A, Peltier MR, Mourtzanakis K, et al. Examining the Effects of Supplemental Magnesium on Self-Reported Anxiety and Sleep Quality: A Systematic Review. Cureus. 2024 Apr 29;16(4):e59317.*

Design: Meta-analysis of 15 double-blind studies, eight measured sleep-related outcomes, seven measured anxiety-related outcomes, and one examined both.

Results: Five out of eight sleep-related studies reported improvements in sleep parameters, while two studies reported no improvements, and one reported mixed results. Five out of seven studies measuring anxiety-related outcomes reported improvements in self-reported anxiety. Dosages, formulations, and durations of the magnesium interventions differed across studies.

Conclusion: "Supplemental magnesium is likely useful in the treatment of mild anxiety and insomnia, particularly in those with low magnesium status."

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

Magnesium Relieves Depression and Anxiety

Study: *Tarleton EK, Littenberg B, MacLean CD, et al. Role of magnesium supplementation in the treatment of depression: A randomized clinical trial. PLoS One. 2017 Jun 27;12(6):e0180067.*

Design: 126 adults (mean age 52; 38% male) diagnosed with and currently experiencing mild-to-moderate depression were given 6 weeks of active treatment (248 mg of magnesium per day) compared to 6 weeks of control (no treatment).

Results: Mg supplementation resulted in a clinically significant net improvement in PHQ-9 scores of -6.0 points ($P<0.001$) and net improvement in Generalized Anxiety Disorders-7 scores of -4.5 points ($P<0.001$). Effects were observed within two weeks. Magnesium is effective for mild-to-moderate depression in adults. It works quickly and is well tolerated without the need for close monitoring for toxicity.

Conclusion: Magnesium is a safe and effective treatment in mild to moderate depression and anxiety.

Magnesium Improves Sleep

Study: *Abbasi B, Kimiagar M, Sadeghniiat K, et al. The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. J Res Med Sci. 2012 Dec;17(12):1161-9.*

Design: 46 elderly subjects received 500 mg magnesium or placebo daily for 8 weeks.

Results: Magnesium supplementation brought about statistically significant increases in sleep time ($P = 0.002$), sleep efficiency ($P = 0.03$), concentration of serum renin ($P < 0.001$), and melatonin ($P = 0.007$), and also resulted in significant decrease of ISI score ($P = 0.006$), sleep onset latency ($P = 0.02$) and serum cortisol concentration ($P = 0.008$).

Conclusion: Supplementation of magnesium improves subjective measures of insomnia such as ISI score, sleep efficiency, sleep time and sleep onset latency, early morning awakening, and likewise, insomnia objective measures such as concentration of serum renin, melatonin, and serum cortisol, in elderly people.

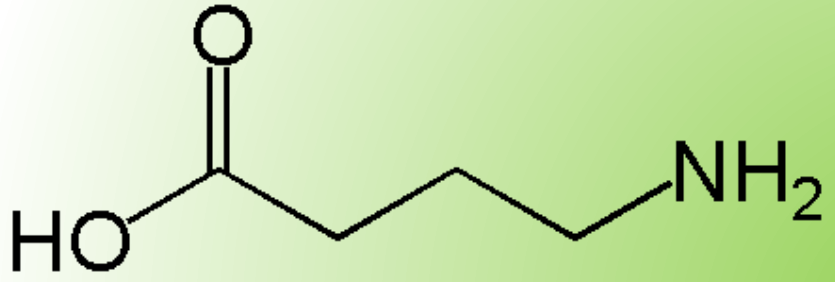
Natural Forms of GABA

GABA (Gamma-aminobutyric acid) is:

- One of the most important neurotransmitters in the human brain.
- Intricately involved in the feelings of relaxation and is associated with producing greater focus and concentration.
- One of the most successful natural food ingredients in Japan. #1 FOSHU ingredient.
- Synthetic forms of GABA are not approved in Japan and may contain toxic compounds.
- Safe and effective with excellent scientific documentation.

Natural, clinically proven forms of GABA® include:

- PharmaGABA® - produced via fermentation with *Lactobacillus hilgardii*.
- Sanwa GABA – produced from fermented barley.



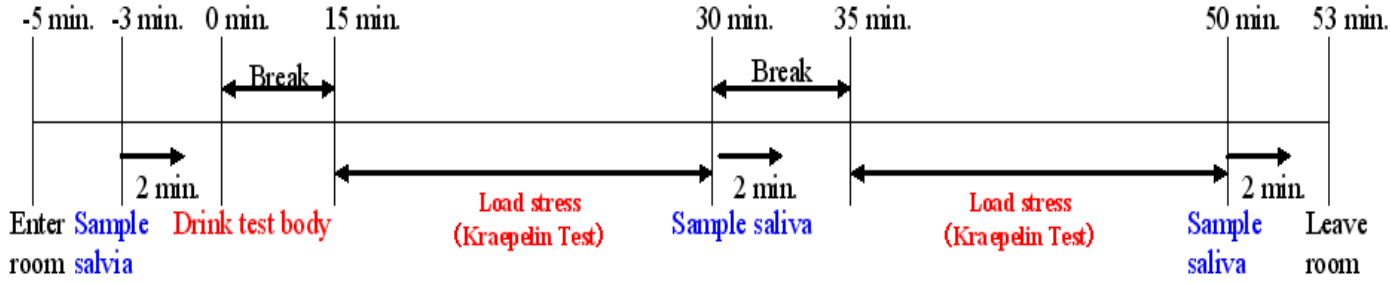
Natural vs. Synthetic GABA

内田クレペリン検査®
標準型　検査用紙

著者：内田勇三郎　© 著作権登録番号5530号の1
本検査用紙の一部または全部を無断で転載、複製することを禁じます。

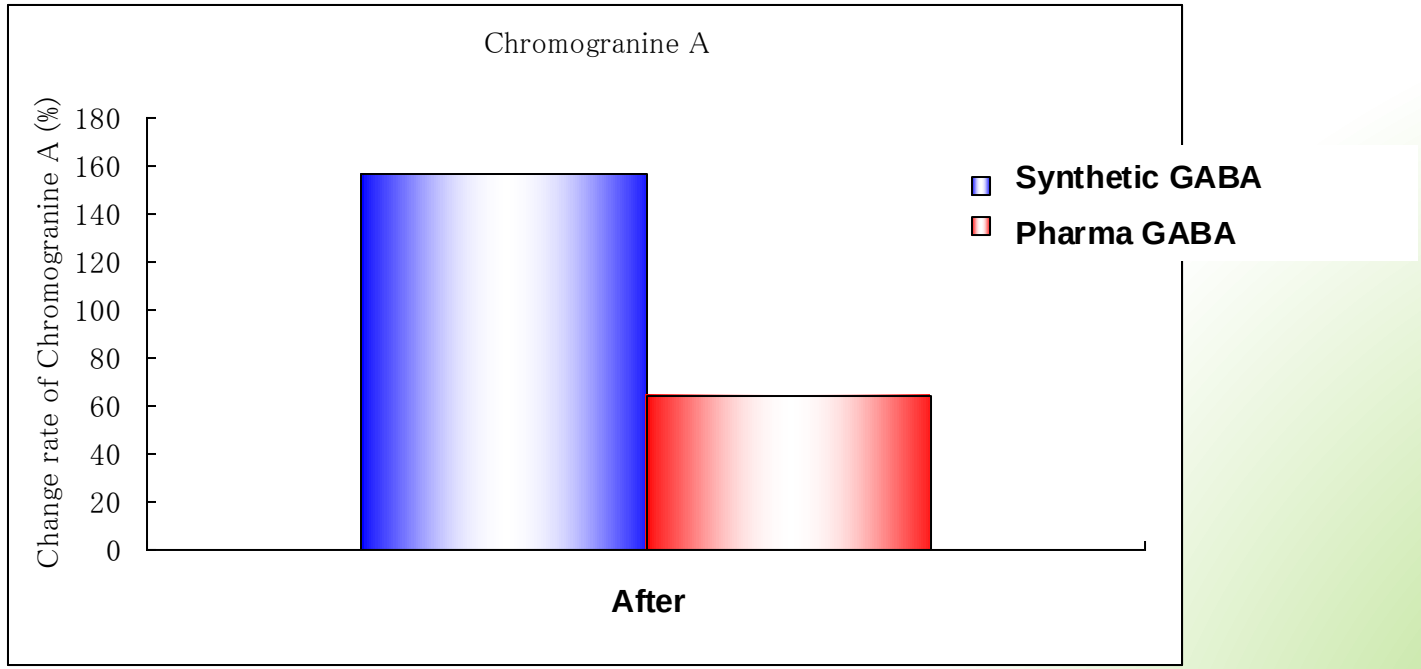
7 9 4 6 3 8 6 7 5 9 8 5 6 3 9 7 4 8 9
3 8 5 9 8 7 6 5 4 9 6 8 3 7 9 8 4 5 8
8 7 4 9 8 4 7 3 8 5 9 8 5 6 7 3 6 9 4
4 7 8 6 5 3 9 5 8 4 5 6 7 9 8 4 6 5 7
8 3 5 9 4 8 7 5 3 8 4 5 8 7 6 8 9 7 5

Test protocol



Test result: CgA (Chromogranine A)

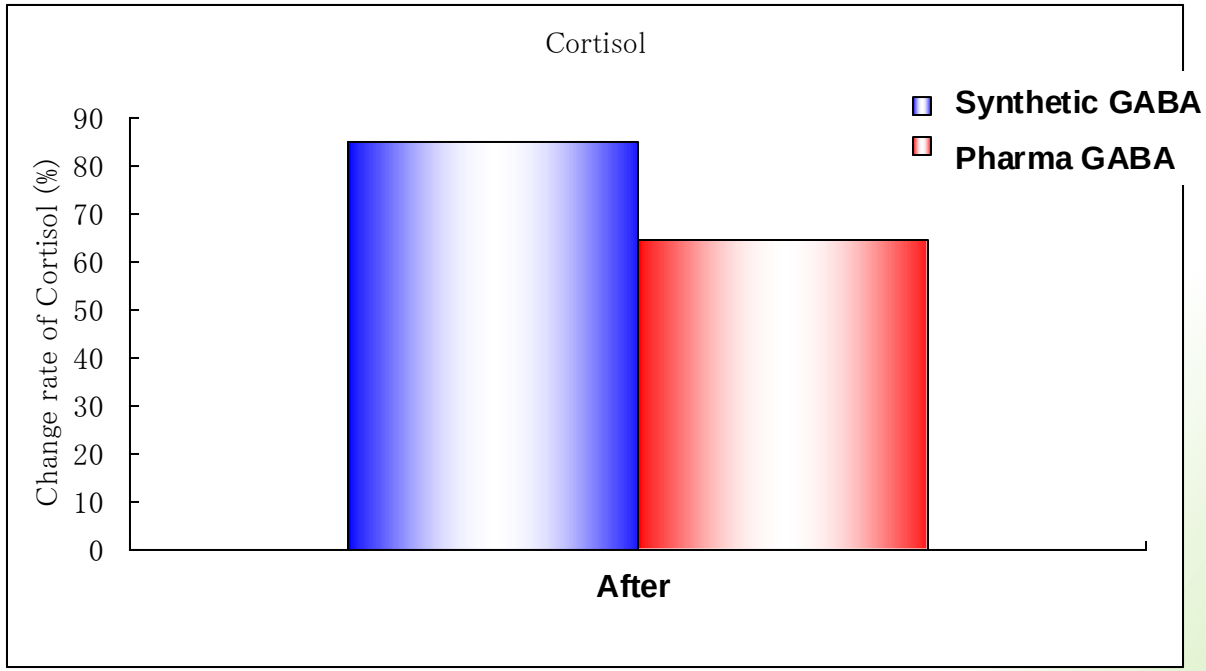
Pharma GABA group significantly reduced the CgA amount compared with synthetic GABA group.



***CgA – A protein that is a stress marker in saliva as it rapidly goes up when people get stressed.**

Test result: Cortisol

Pharma GABA group shows less cortisol appearance than synthetic GABA group.

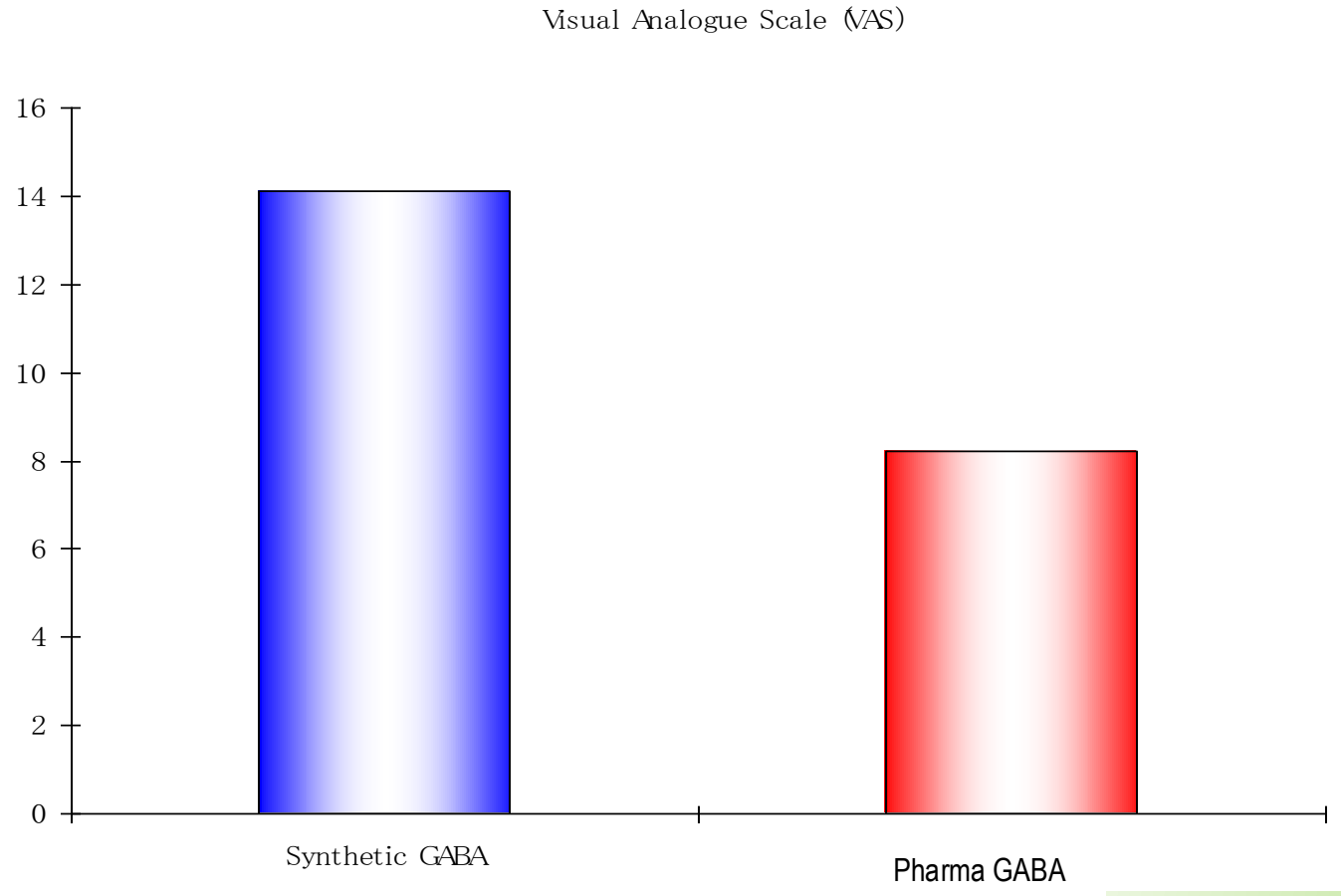


***Cortisol - One of the stress markers and it appears when people feel certain level of stress. Compared with CgA, the value of cortisol normally is not changed under the low level of stress.**

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

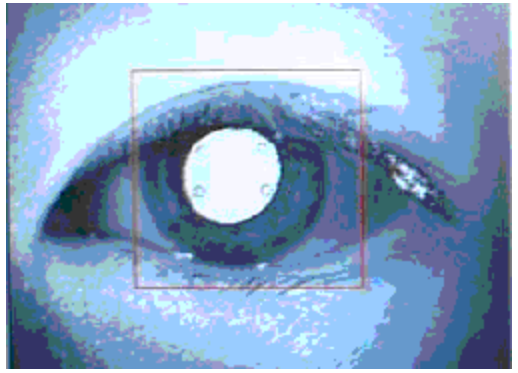
Test result: VAS (Visual Analogue Scale)

VAS: Intuitive feeling/mood that he/she actually feel at a certain moment. We measured how those volunteers felt differently, what kind of mood they are in and sum up in both synthetic GABA group and Pharma GABA group.



DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE

Effect of GABA on autonomic nervous system



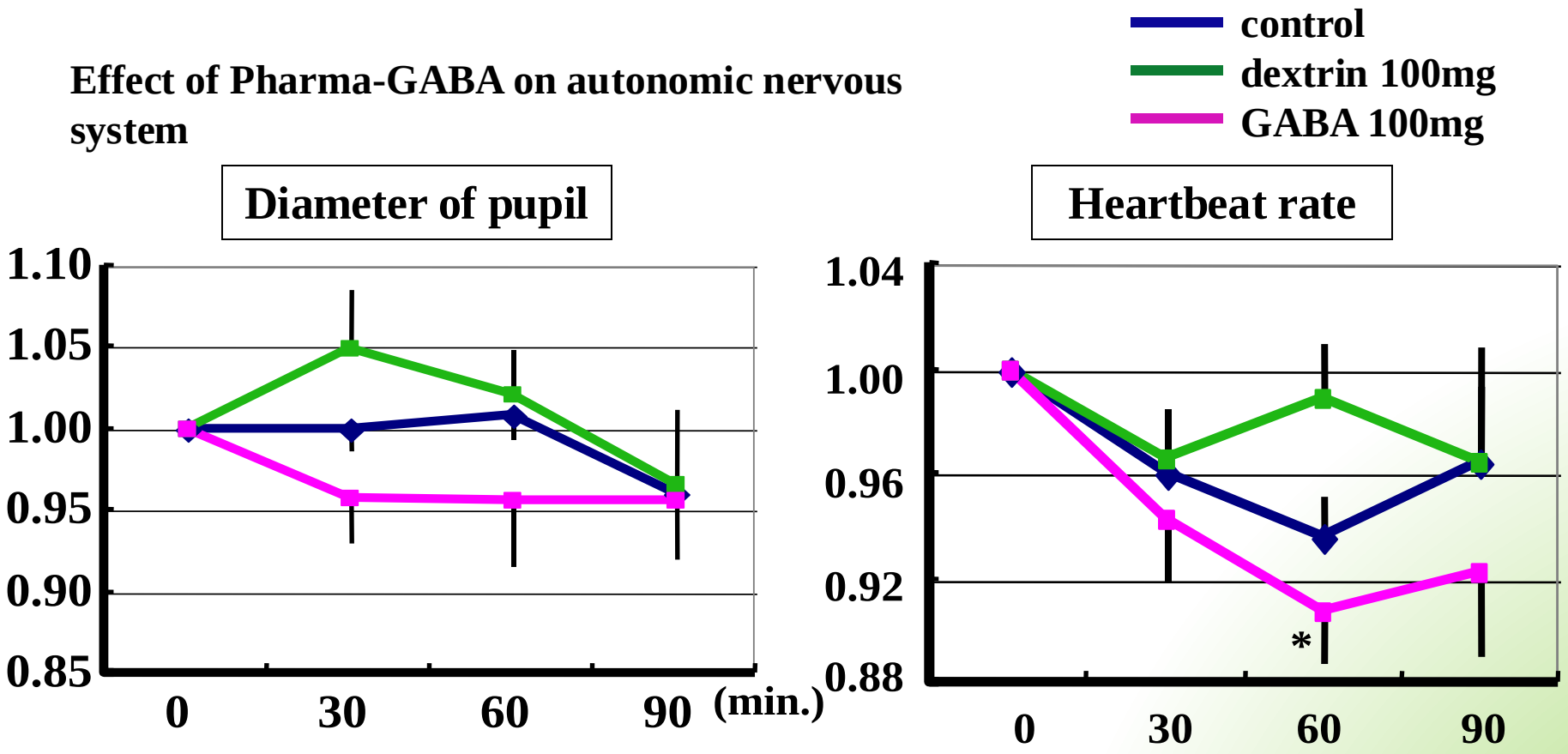
diameter of **pupil**

large → **sympathetic nerve**

small → **parasympathetic nerve**

Diameter of pupils and heart beat rate were measured before intake and 30 min., 60min., and 90 min. after intake of GABA (100mg), to identify the effect of GABA on autonomic nervous system.

Effect of Pharma-GABA on autonomic nervous system



Diameter of pupils and heart beat rate were measured before intake and 30 min., 60min., and 90 min. after intake of GABA (100mg), to identify the effect of GABA on autonomic nervous system.

Natural GABA:
Clinical Summary

- Promotes relaxation, activates parasympathetic nervous system
- Exerts anti-stress effects
- Improves sleep quality
- Exerts anti-caffeine effects
- Enhances both mental performance

Dosage: 50 to 200 mg up to 6 times daily

GABA-Producing Probiotics

- *Levilactobacillus brevis P30021, Lactiplantibacillus plantarum P30025, and L. plantarum* Lp815 are probiotic strains that can promote the synthesis of clinically relevant amounts of GABA.
- 1 billion CFU dosage may produce up to 100 mg of GABA.

See: Fogliano V, Ercolini D. Gaba-producing lactobacilli boost cognitive reactivity to negative mood without improving cognitive performance: A human Double-Blind Placebo-Controlled Cross-Over study. Brain Behav Immun. 2024 Nov;122:256-265.

What is An Adaptogen?

By definition:

- Prevents the negative effects of stress and increases the ability to deal with stress.
- Produces a broad range of beneficial effects without causing any major side effects.
- Exerts a balancing effect regardless of the direction of disturbance.
- Restores vitality and increase feelings of energy.
- Improves mental and physical performance.

The Most Popular Adaptogens

- Chinese or Korean ginseng (*Panax ginseng*)
- Rhodiola (*Rhodiola rosacea*)
- Ashwagandha (*Withania somnifera*).

The Most Popular Adaptogens

- Chinese or Korean ginseng (*Panax ginseng*)
- Rhodiola (*Rhodiola rosacea*)
- Ashwagandha (*Withania somnifera*).

The Most Popular Adaptogens

- Chinese or Korean ginseng (*Panax ginseng*)
- Rhodiola (*Rhodiola rosacea*)
- Ashwagandha (*Withania somnifera*)

Chinese or Korean ginseng (Panax ginseng)

- Best choice for those with metabolic syndrome or recovering from a significant stress, illness, or who have used corticosteroids such as prednisone for more than six months.
- Dosage is based upon ginsenosides content, 10-20 mg one to three times daily. For example, for a 4% ginsenoside content the dosage is 250-500 mg one to three times daily. For a 10% ginsenoside content, 100-200 mg one to three times daily.

Rhodiola (Rhodiola rosacea)

- Best choice to help relieve acute stress. Produces a greater immediate feeling of relaxation and anti-anxiety effects.
- A single dose of Rhodiola extract prior to acute stressful events is beneficial.
- Dosage is a target of 3.6 to 7.2 mg of rosavin per day. For a 1% rosavin content extract, the daily dose would be 360 to 720; for 2% rosavin 180 to 360 mg; and for 3% rosavin 120 to 240 mg.

Ashwagandha (Withania somnifera)

- Number one adaptogen in the marketplace by a large margin.
    - Ashwaganda ~10X sales of Ginseng or Rhodiola (~$150 million vs. ~$12 million each)
- Best choice for generally healthy people, those with poor sleep quality, and low DHEA levels.
- Dosage is based upon withanolide content. For an extract standardized at 10% withanolides the dosage is 125 to 250 mg twice daily. For the extract standardized to contain 1.5% withanolides the dosage is 300 mg twice daily.

Summary of Key Points

Summary:

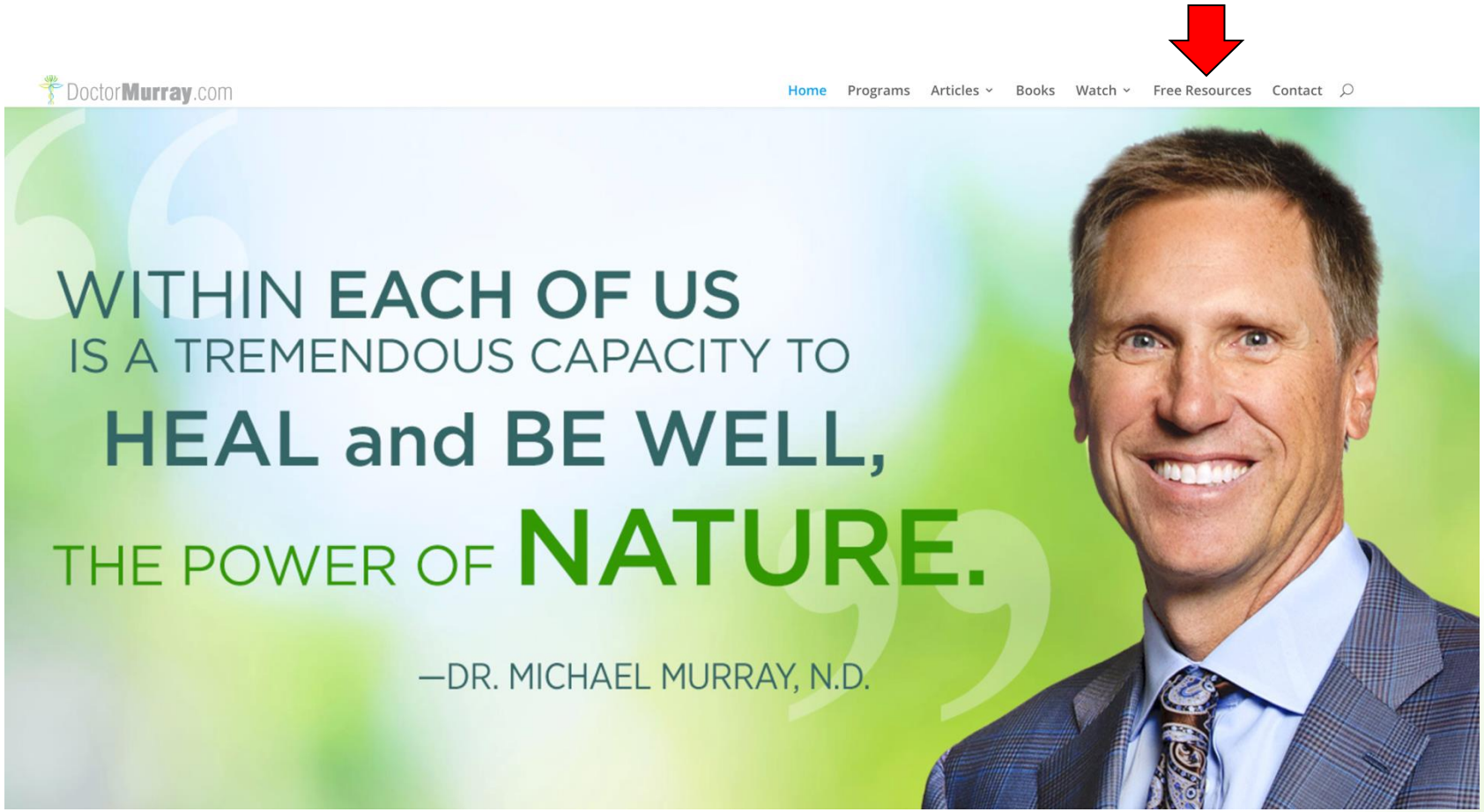
- Our ability to handle stress is based on an interaction of many factors.
- Nutritional status plays a big role in stress management.
- Omega-3 fatty acids, magnesium, and GABA are key consideration for improving stress management.
- Botanical adaptogens can improve the ability to handle stress.

An Important Consideration

A large body of scientific work has shown that people who are more grateful have higher levels of well-being, are happier, less depressed, less stressed, and more satisfied with their lives and social relationships.

Wood AM, Froh JJ, Geraghty AW. Gratitude and well-being: a review and theoretical integration. Clin Psychol Rev. 2010 Nov;30(7):890-905.

DoctorMurray.com
YOUR NATURAL MEDICINE RESOURCE



Thank You!