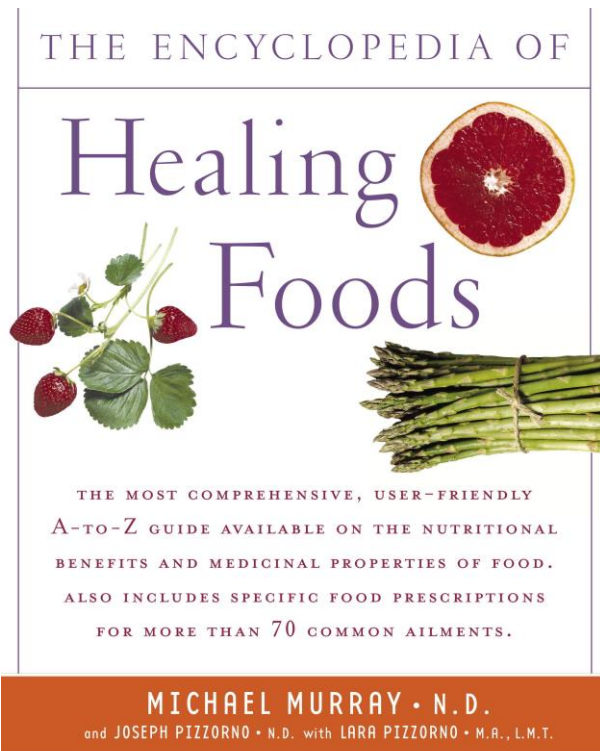




# *Provocative Concepts in Nutrition and Fertility*

**Michael T. Murray, N.D.**

[www.doctormurray.com](http://www.doctormurray.com)



**WHAT THE  
DRUG COMPANIES  
WON'T TELL YOU  
AND YOUR DOCTOR  
DOESN'T KNOW**

THE TRUTH ABOUT THE BENEFITS AND DANGERS OF  
PRESCRIPTION MEDICINES AND THEIR ALTERNATIVES



**MICHAEL T. MURRAY, N.D.**



# Agenda

- Today's goal
- Emerging concepts:
  - Epigenetics, biochemical individuality, and metabolic imprinting
- What is a nutrient?
- “Conditionally essential” nutrients
- Nutritional factors in fertility
  - Targeting mitochondrial dysfunction
- Improving insulin sensitivity



# Human Genome Project

## Goals:

- Identify all the approximate 30,000 genes in human DNA,
- Determine the sequences of the 3 billion chemical base pairs of DNA

## Milestones:

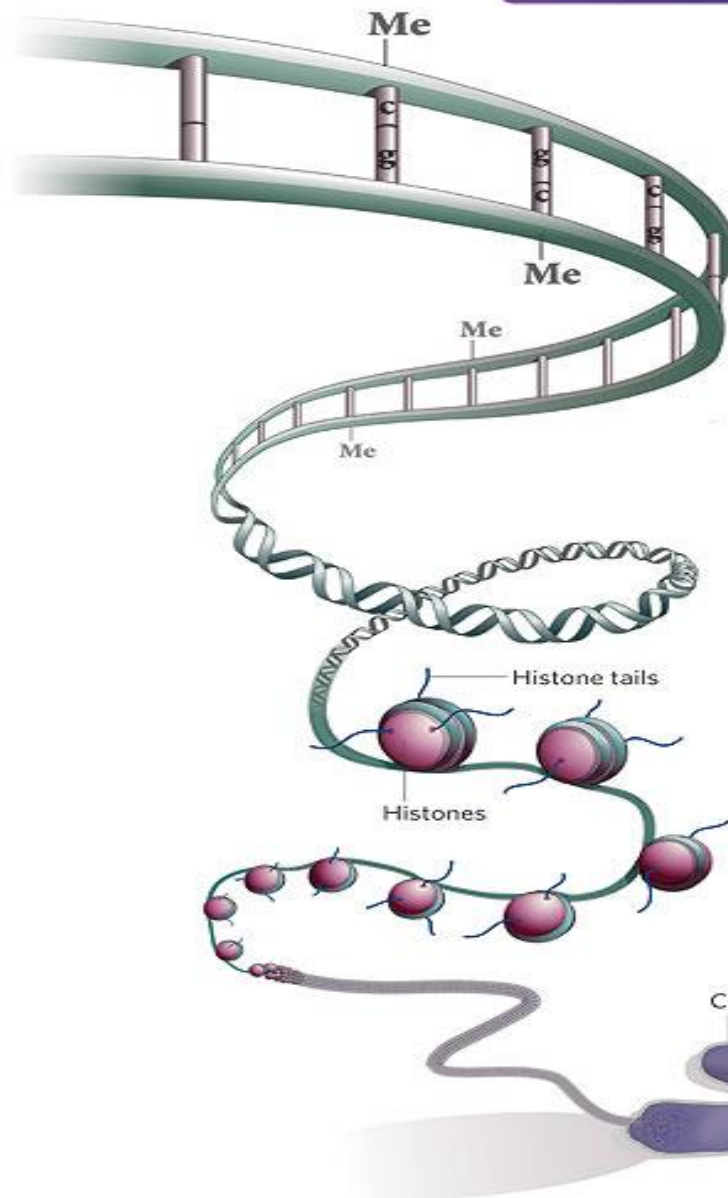
- 1990: Project initiated as joint effort of U.S. Department of Energy and the National Institutes of Health
- June 2000: Completion of a working draft of the entire human genome
- February 2001: Analyses of the working draft are published
- April 2003: Sequencing is completed and Project is declared finished two years ahead of schedule



# Epigenetics and Nutrigenomics

- Epigenetics:
  - The expression of genetic programming is influenced by non-genetic factors
- Nutrigenomics:
  - The influence of nutrition on genetic expression that is primarily related to its epigenetic factors





## The two main components of the epigenetic code

### DNA methylation

Methyl marks added to certain DNA bases repress gene activity.

### Histone modification

A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.



# Methylation, silencing, and cancer

- Epigenetic hypermethylation can lead to silencing of tumor suppressor genes.
- Conversely, epigenetic hypomethylation is associated with the over-expression of oncogenes (cancer causing genes).



# ***Metabolic Imprinting***

Refers to the effects of diet

- During pregnancy, infant feeding, and early childhood on the development of chronic diseases in later life.

Increasing evidence of role especially in the development of:


- Diabetes or metabolic syndrome, atherosclerosis, hypertension, cancer, and mental function
- Food allergy and intolerance, asthma



# A Tale of Two Mice







# What Determines Litter Outcome?

## Maternal Diet



**Yellow Mouse**

- High risk cancer, diabetes, obesity
- Reduced lifespan



**Agouti Mouse**

- Lower risk of cancer, diabetes, obesity
- Prolonged life



# ***7 Key Dietary Principles of the Optimal Health Diet***

- Eat to support blood sugar control
- Eat a rainbow assortment of fruits and vegetables
- Reduce exposure to pesticides
- Do not over consume animal foods
- Eat the right types of fats
- Keep salt intake low, potassium intake high
- Drink sufficient amounts of water each day



# ***What is a Nutrient?***

## Classic categories:

- Proteins
- Carbohydrates
- Fats
- Vitamins
- Minerals
- Water



# ***What is an “Essential” Nutrient?***

Classic definition:

“An essential nutrient is a nutrient required for normal body functioning that either cannot be synthesized by the body or cannot be made in amounts adequate for good health”





# ***A Call for a New Order***

- Expand the definition of a “**nutrient**”
  - Include all food compounds as well as physiological substances
- Utilize the definition of “**essential**”
- Establish new nutrient categories



# What are **“Essential”** Fatty Acids?

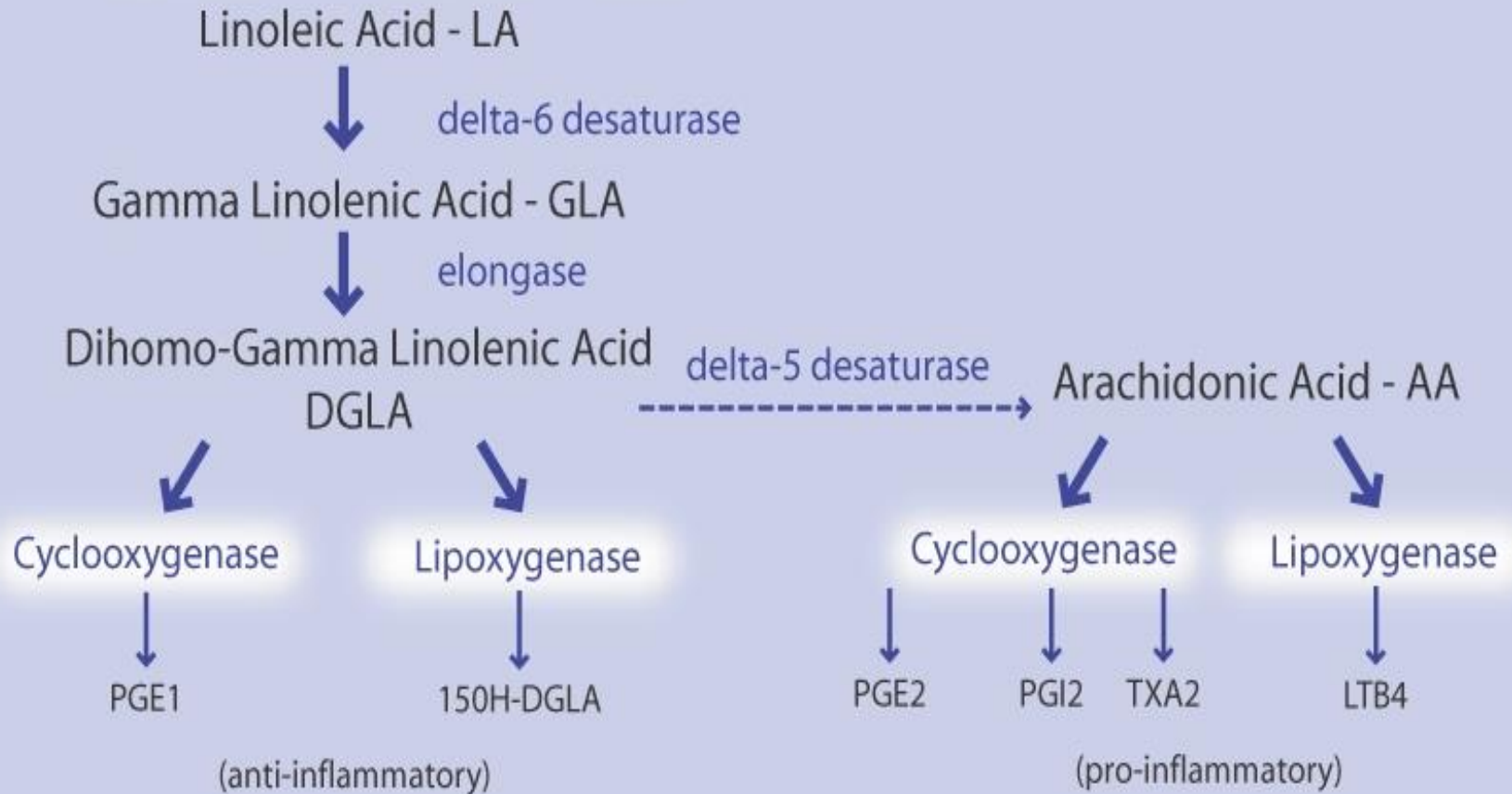
- Using the strict definition, there are only two fatty acids are truly “essential” fatty acids:
  - Linoleic Acid (LA) – an omega-6 fatty acid
  - Alpha-Linolenic Acid (ALA) – an omega-3 fatty acid



# **“Conditionally” or “Semi-” Essential Fatty Acids**

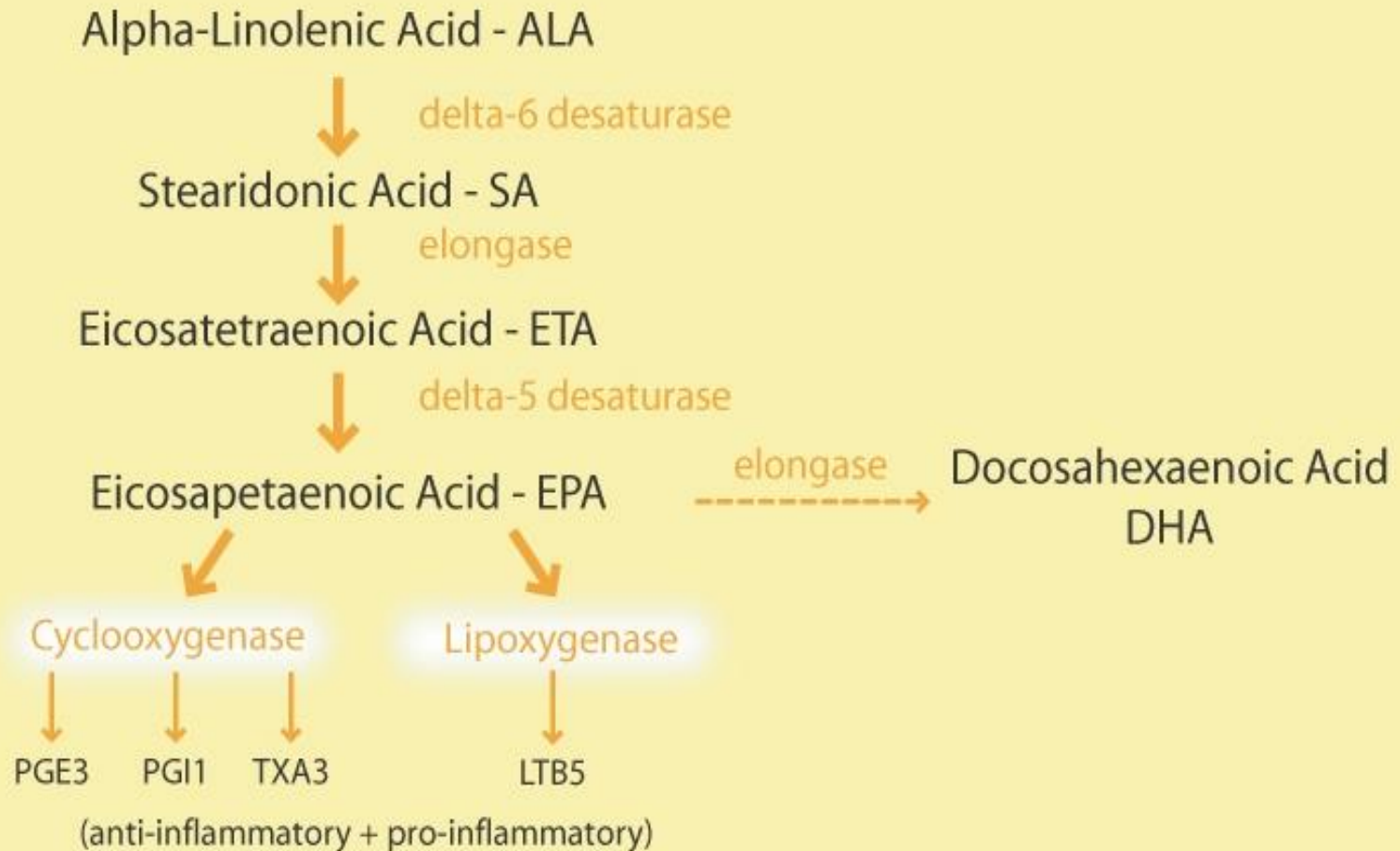
- Examples:
  - Omega-6 fatty acids
    - Gamma-Linolenic Acid (GLA)
    - Arachidonic Acid (AA)
  - Omega-3 fatty acids
    - Stearidonic Acid (SDA)
    - Eicosapentaenoic Acid (EPA)
    - Docosahexaenoic Acid (DHA)

# Omega-6 Fatty Acids





# Omega-3 Fatty Acids





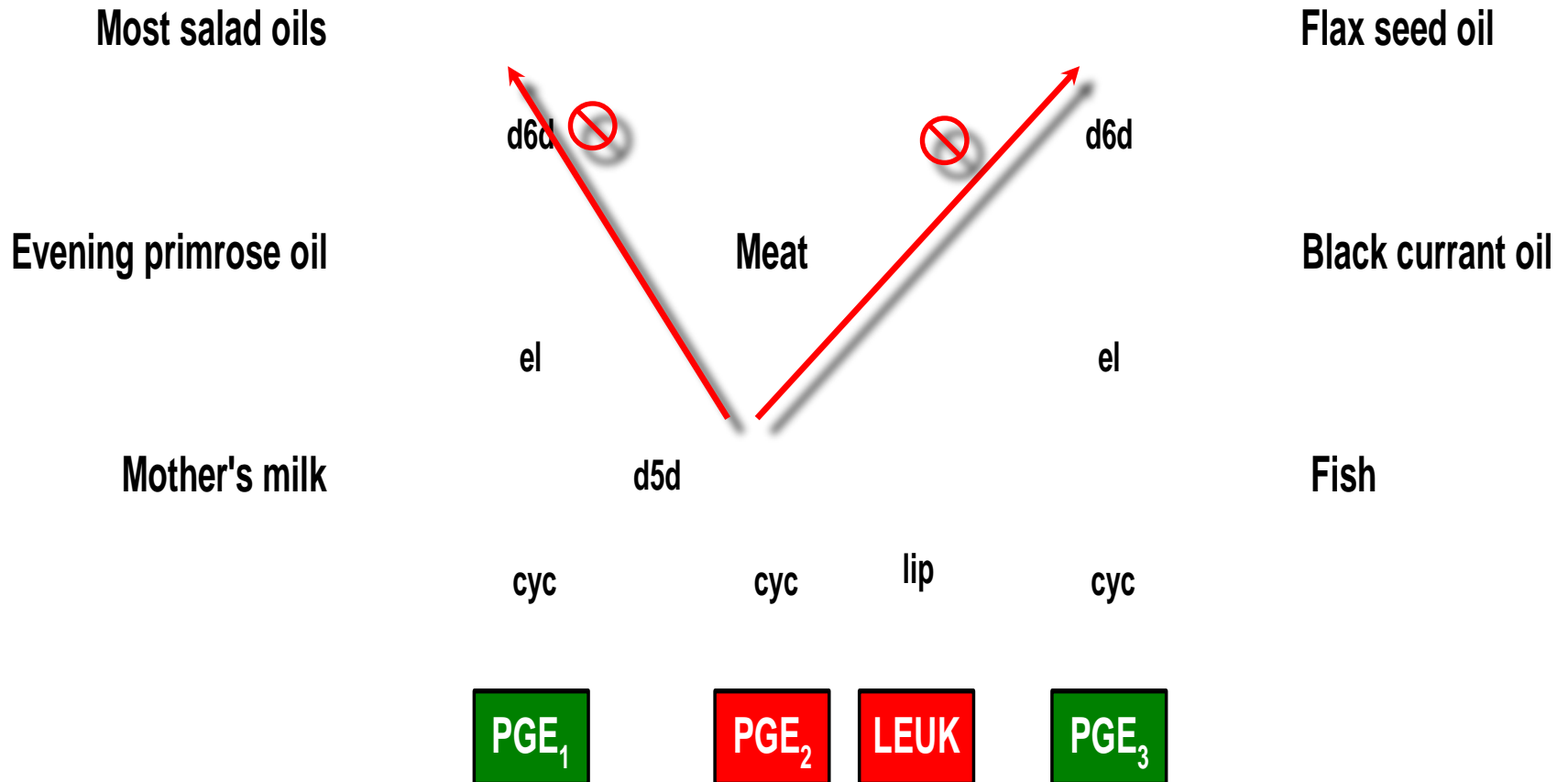
# **Inhibitors of Delta 6 Desaturase**

- Insulin resistance
- Viral infection
- Atopic disease
- Cholesterol
- Stress hormones
  - Corticosteroids
  - Catecholamines
- Aging
- Alcohol
- Smoking
- Arachidonic acid
- Saturated fat
- Trans fatty acids
- Nutrient deficiency
  - Zinc, B6, vitamin C



# Fatty Acid Metabolism

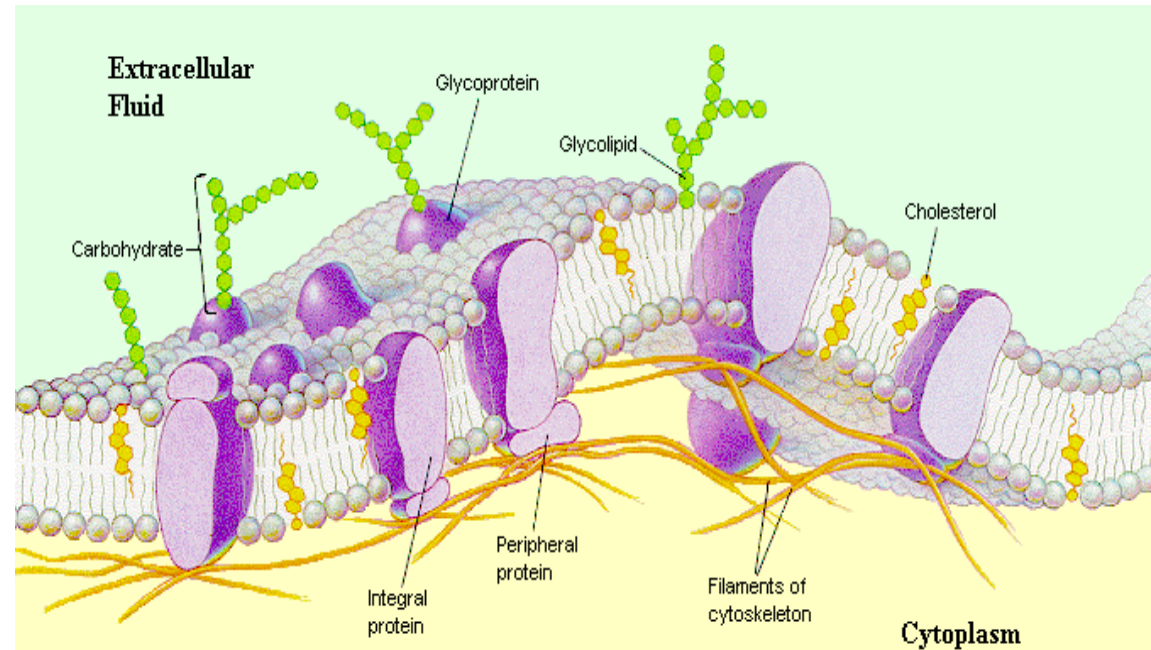
Omega 6 Fatty Acids    Omega 3 Fatty Acids





# Functions of EFAs

- Membrane Functions and Integrity
- Regulation of Cell Processes
- Biosynthesis of Eicosanoids







# Cell membrane consequences of fatty acid structure

- Saturated and trans fatty acid chains pack tightly and form more rigid membranes.
- Unsaturated chains bend and pack in a less ordered way, with greater potential for motion, elasticity, and function especially long chain omega-3 fatty acids.
- Determines receptor site affinity and post-receptor action.



# Are Omega-3 FAs “Conditionally Essential” in Cases of Infertility?

- Absolutely
  - Effects in Females
    - Improves pregnancy outcome, reduces miscarriage risk
    - Increases uterine perfusion
    - Improves endometrial and prostaglandin production
  - Effects in males
    - Associated with more favorable sperm levels, morphology, and motility (Hum Reprod. 2012 May;27(5):1466-74)
    - Also, reduce omega-6 & saturated fats, increase omega-9



# What is An Effective Dosage?

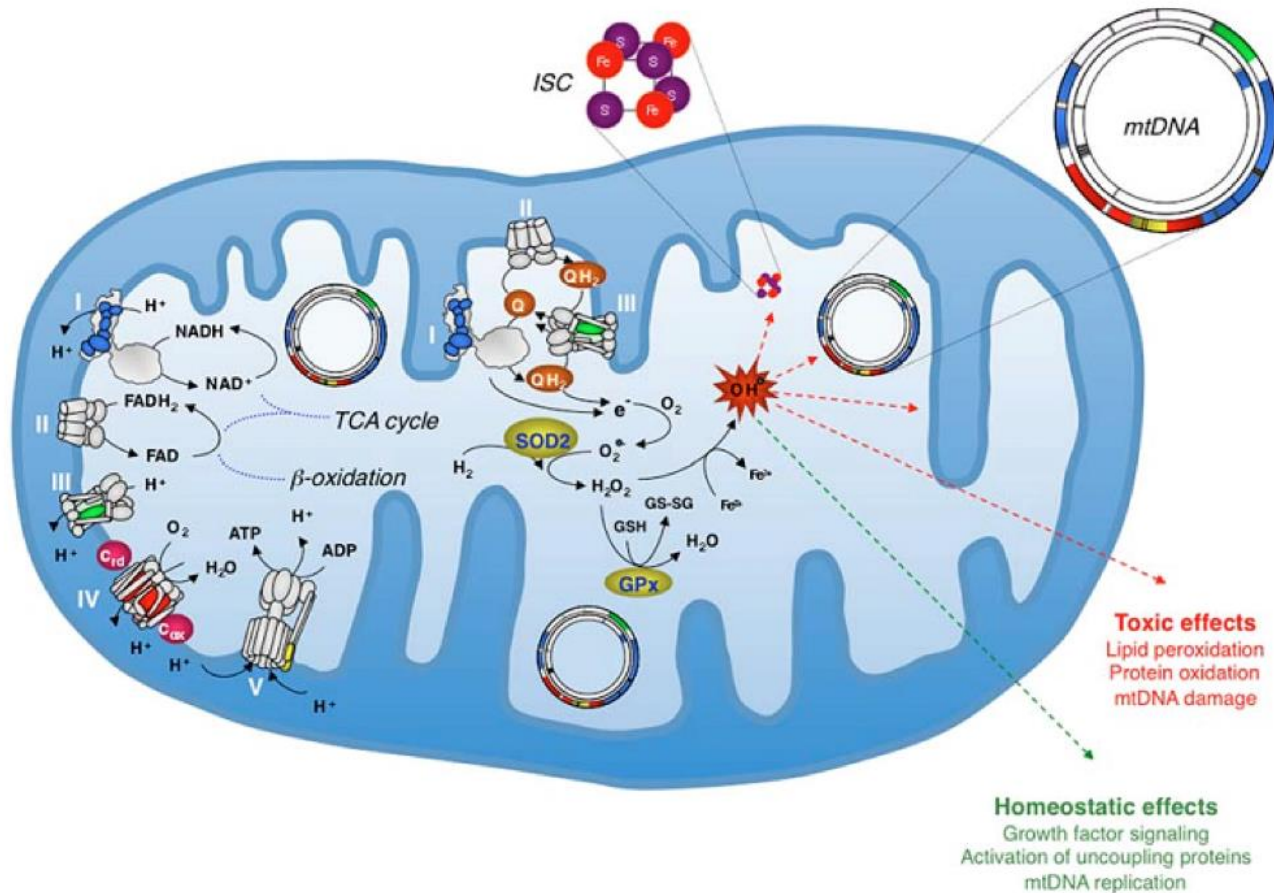
- Ideally, measure RBC or whole blood EFAs
  - Goals: Omega-3 index of >8%; WB omega-3 60-70%
- Recommended dosage
  - Females: 1,000-2,000 mg EPA+DHA daily
  - Males with oligo-, astheno-, and/or teratozoospermia: 2,000-3,000 mg EPA+DHA daily



# Other Examples of Conditionally Essential Nutrients

<b>Glucosamine</b>	<b><i>Coenzyme Q10</i></b>	<b><i>Carnitine</i></b>	<b><i>Alpha-lipoic acid</i></b>
<b>SAMe</b>	<b>Glutamine</b>	<b>Melatonin</b>	<b>Phosphatidylserine</b>
<b>Glutathione</b>	<b>5-HTP</b>	<b>Arginine</b>	<b>Hyaluronic acid</b>
<b>Ribose</b>	<b>Beta-alanine</b>	<b>GABA</b>	<b>Glycerophosphocholine</b>
<b>Choline</b>	<b>Inositol</b>	<b>Betaine</b>	<b>Nucleotides</b>
<b>Tocotrienols</b>	<b>Carnosine</b>	<b>Lutein</b>	<b>Lycopene</b>

# Is Mitochondrial Dysfunction a Factor in Infertility?







# Conditions Associated with Mitochondrial Dysfunction

- Aging
- Alzheimer's disease & dementia
- Autism
- Chronic fatigue syndrome
- Fibromyalgia
- Heart disease
- Diabetes
- Migraine headache
- Parkinson's disease



# How do you improve mitochondrial function?

- A four-part strategy is required:
  - Provide essential nutrients
  - Provide protection from oxidative damage
  - Reduce exposure to damaging factors
  - Boost glutathione levels to enhance detoxification processes



# BioFoundation-G

## Benefits:

- Provides rate limiting nutrients for glutathione production, necessary for xenobiotic detoxification
- Full spectrum multiple vitamin and mineral, with 2000 IU vitamin D3 per serving
- Contains clinical doses of resveratrol, lipoic acid, CoQ10, milk thistle and green tea extract
- Broad spectrum antioxidant support, including bilberry and citrus extracts, lipoic acid, lycopene and lutein
- Highly bioactive and bioavailable nutrients, such as pyridoxal-5-phosphate and vitamin K2 (Menaquinone 7)



# Selected Nutrients in Female Infertility

Nutrient	Benefit
L-Carnitine (3-4g/d)	Improves peritoneal fluid and mitochondrial role in DNA arrangement and oxygen utilisation of oocyte
Alpha-Lipoic Acid (300-600mg/d)	Protection against oxidative stress to reduce time for conception; increase fertilisation; improve oocyte penetration, function and viability; improve implantation rates and reduce loss of implantation <sup>4</sup>
CoEnzyme Q10 (dosage discussed later)	Mitochondrial ATP synthesis; supports mitochondrial function; protects maturing oocytes from oxidative damage; improves zona pellucida integrity and receptivity to sperm and ART (especially ICSI procedures)



# Selected Nutrients in Male Infertility

Nutrient	Benefit
L-Carnitine (3-4g/d)	When carnitine levels are low, sperm development, function, and motility are drastically impaired. Carnitine supplementation improves all aspects sperm.
Antioxidants	A Cochrane review concluded there is sufficient evidence to prove that antioxidant supplementation in subfertile males improves the outcome of live births and pregnancy rates for subfertile couples undergoing ART cycles.
CoEnzyme Q10 (dosage discussed later)	Considered to be the most crucial and powerful antioxidant in sperm structure owing to its role in mitochondria. Believed to promote motility and foster sperm survival





# Coenzyme Q10

## Function:

- Required for the production of ATP (chemical energy) by mitochondria and important cellular antioxidant

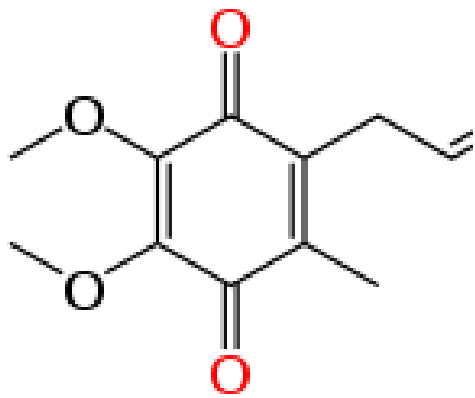
## Primary Clinical Applications:

- ★ Heart disease (angina, cardiomyopathy, congestive heart failure, high blood pressure, etc.)
- ★ Neurodegenerative disease (e.g., Alzheimer's & Parkinson's)
- ★ Prevents statin-induced depletion and cardiotoxicity of chemotherapy drugs
- ★ Boost immune function, anti-aging, periodontal disease, macular degeneration, etc.

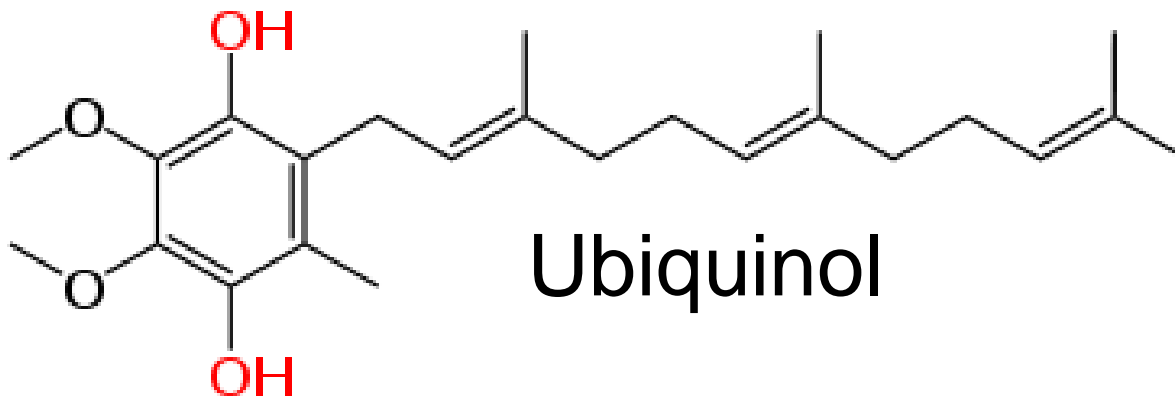
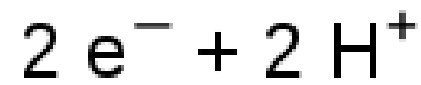


# CoQ10 Levels in Humans

- **Normal blood ranges:**
  - 0.7 to 1.0 mcg.ml
  - Approximately 95% is ubiquinol
- **Deficiency can be caused by:**
  - Decreased dietary intake
    - Normal intake about 5 mg/day
  - Impaired biosynthesis
  - Increased need
    - Aging, CV disease, cancer, diabetes, periodontal disease



Ubiquinone



Ubiquinol



## What do we know?

- When CoQ10 is given with food it is absorbed twice as fast and at least two-fold greater than on an empty stomach.
- The absorption of CoQ10 may be limited in some individuals.
- When dosages of CoQ10 begin to exceed 300 mg the percentage of CoQ10 absorbed declines rapidly.
- Divided dosages (e.g., b.i.d. or t.i.d.) result in higher plasma levels compared to single dosages, especially at higher dosage levels.
- Eventually a steady-state is produced (usually after 3-4 weeks of constant dosing)



# Ubiquinol Absorption Study

- Active soft gelatin capsule contained 30 mg of ubiquinol emulsified with diglycerol monooleate, canola oil, soy lecithin, and beeswax. Placebo was without ubiquinol.
- In the 4-week study, subjects received 10 capsules daily, 5 capsules each after breakfast and dinner with 180 ml of water for 28 days. The intakes were 0 + 5 and 0 + 5 for the placebo group, 2 + 3 and 1 + 4 for the ubiquinol 90 mg group, 3 + 2 and 2 + 3 for the ubiquinol 150 mg group, and 5 + 0 and 5 + 0 for the ubiquinol 300 mg group.





# Coenzyme Q10 in CHF

## Analysis of a “negative” study

Summary: 55 patients with CHF NY class III and IV, ejection fraction less than 40%, and peak oxygen consumption less than <50% during standard therapy were randomly assigned to receive CoQ10 (200 mg) or placebo. There were no changes in ejection fraction, peak oxygen consumption, and exercise duration in either group. The mean serum concentration of coenzyme Q10 increased from 0.95 mcg/ml to 2.2 mcg/ml, but 19 of 22 pts. on CoQ10 had levels below 2.5 mcg/ml and 18/22 were on beta-blockers.



# Coenzyme Q10 in CHF

## Effect of Ubiquinol in unresponsive patients

**Summary:** Seven patients with plasma CoQ10 levels of 1.6 microg/ml on an average dose of 450 mg of ubiquinone daily (150-600 mg/day) were changed to an average of 580 mg/day of ubiquinol (450-900 mg/day). Mean plasma CoQ10 levels increased from 1.6 mcg/ml up to 6.5 mcg/ml. Mean ejection improved from 22% (10-35%) up to 39% (10-60%) and NYHA class improving from a mean of IV to a mean of II (I to III).



# Comparative Absorption

100 mg Estimated plasma levels in mcg/ml

Ubiquinone powder in hard gelatin capsule 1.25

Ubiquinone in soft gelatin capsule w/rice bran oil 1.8

Ubiquinone solubilized in soft gelatin capsule (Q-Gel) 2.25

Ubiquinone powder nanonized and dispersed in water 2.25

Ubiquinone (BioQ10 SA) in soft or hard gelatin capsule 2.50

Ubiquinol in soft gel capsule 2.50



# Comparative Absorption

300 mg Estimated plasma levels in mcg/ml

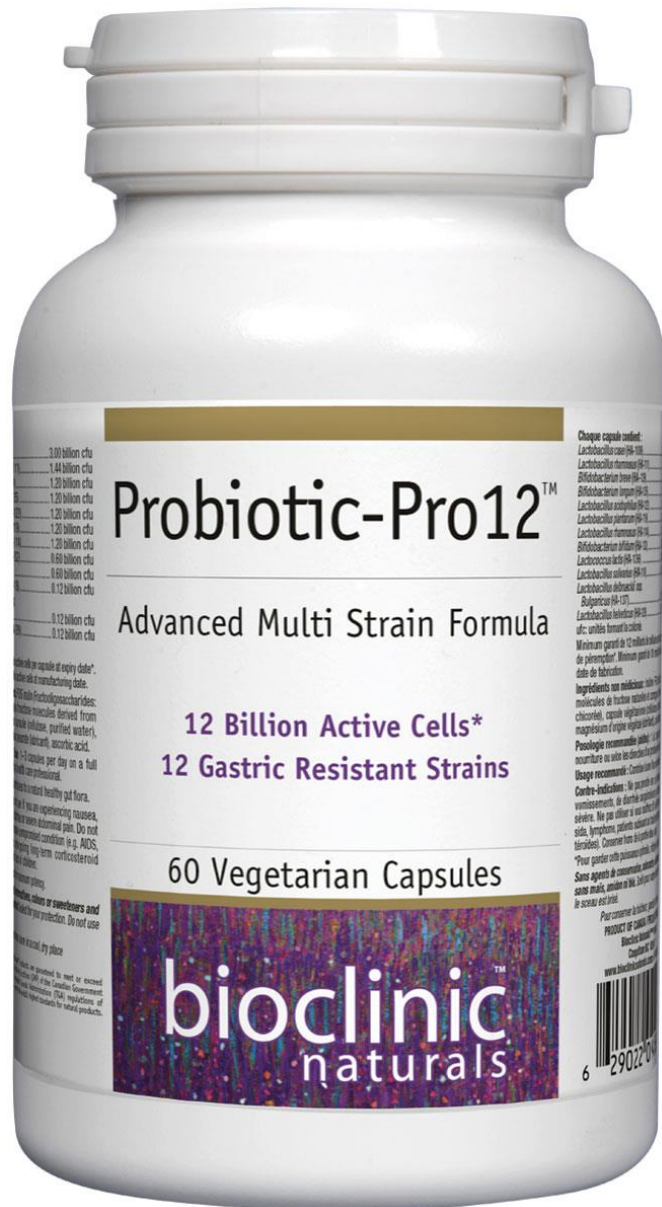
Ubiquinone powder in hard gelatin capsule	2.5
Ubiquinone in soft gelatin capsule w/rice bran oil	3.5
Ubiquinone solubilized in soft gelatin capsule	5.0
Ubiquinone powder nanonized and dispersed in water	5.5
Ubiquinone (BioQ10 SA) in soft or hard gelatin capsule	7.0
Ubiquinol in soft gel capsule	7.0



# Probiotics in Infertility

- Dysbiosis is linked to reproductive failure and adverse pregnancy outcomes such as preterm labor, miscarriage, and spontaneous preterm birth.
- Women with dysbiosis were four times more likely to have a spontaneous preterm birth compared to the overall preterm birth rate.





- **Key Benefits:**

- Human or Dairy Origin
- Highly resistant to gastric acid and bile
- Multiple, highly efficacious strains
- Verified compatibility
- Guaranteed potency at expiration date



# Estrogen Detoxification

Estrogen

Conjugated with glucuronate in liver



General circulation

Excreted into the intestines with bile



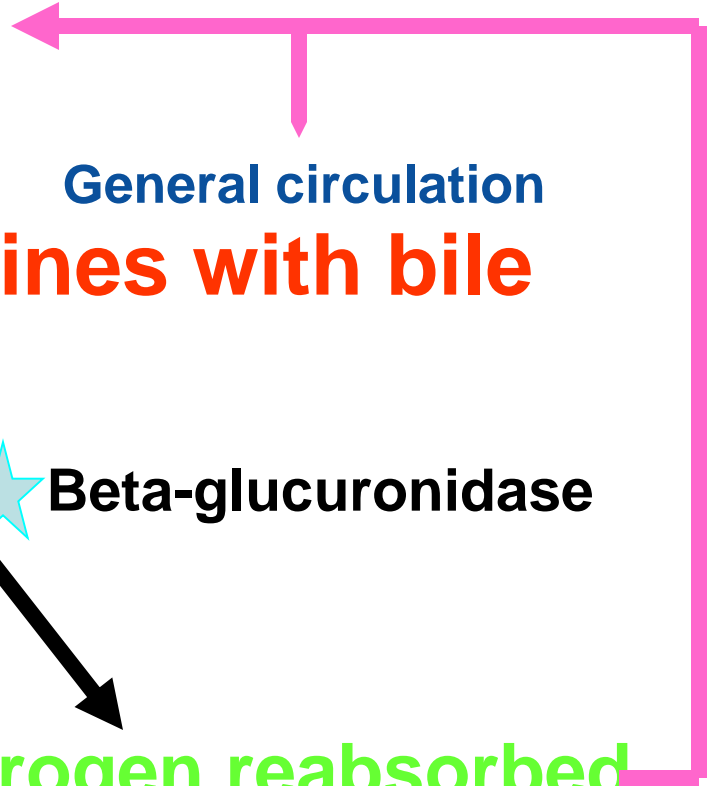
Beta-glucuronidase

Eliminated in feces

Free estrogen reabsorbed



Enzyme inhibited by certain probiotics, D-glucarate





# Obesity in Infertility

## *Results from recent studies*

### ***In Women:***

*Fertil Steril. 2012 May 12. The effect of body mass index on the outcomes of first assisted reproductive technology cycles.*

### **CONCLUSION:**

Obesity has a significant negative effect on ART outcomes. Patients with BMI >30 kg/m<sup>2</sup> have up to 68% lower odds of having a live birth following their first ART cycle compared with women with BMI <30.

### ***In Men:***

*BJU Int. 2012 Feb 2. Association between obesity and alteration of sperm DNA integrity and mitochondrial activity.*

### **CONCLUSION:**

Increased BMI values are associated with decreased mitochondrial activity and progressive motility and increased DNA fragmentation in sperm.

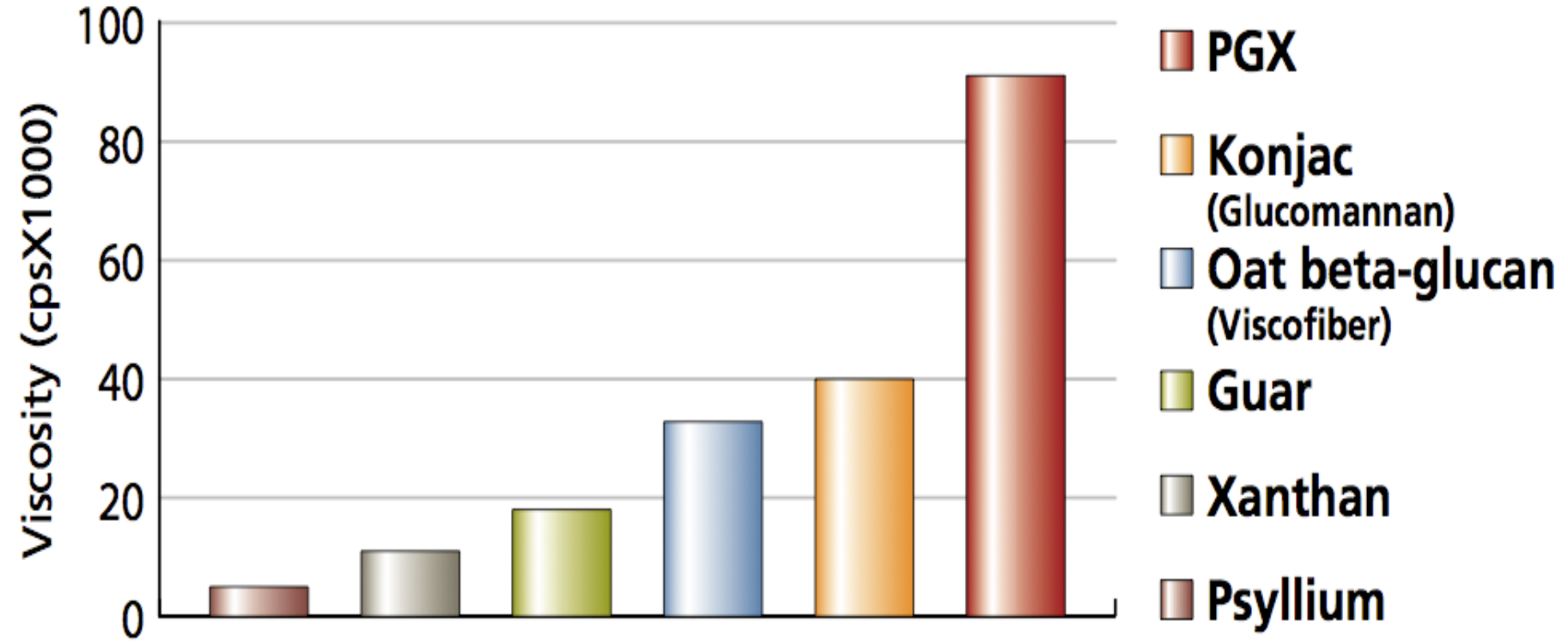


# PGX<sup>®</sup> (PolyGlycopleX<sup>®</sup>)

- Patented soluble fibre matrix with exceptional viscosity
- PGX is NOT a blend
  - IUPAC (International Union of Pure and Applied Chemistry) name: ( $\alpha$ -D-glucurono- $\alpha$ -D-manno- $\beta$ -D-manno- $\beta$ -D-gluco), ( $\alpha$ -L-gulurono- $\beta$ -D mannurono),  $\beta$ -D-gluco- $\beta$ -D-mannan
- PGX possesses unique physical qualities and physiological benefits
- Binds more than 600 times its weight in water
- Produces clinical results at practical dosages



# PGX compared to other plant fibres







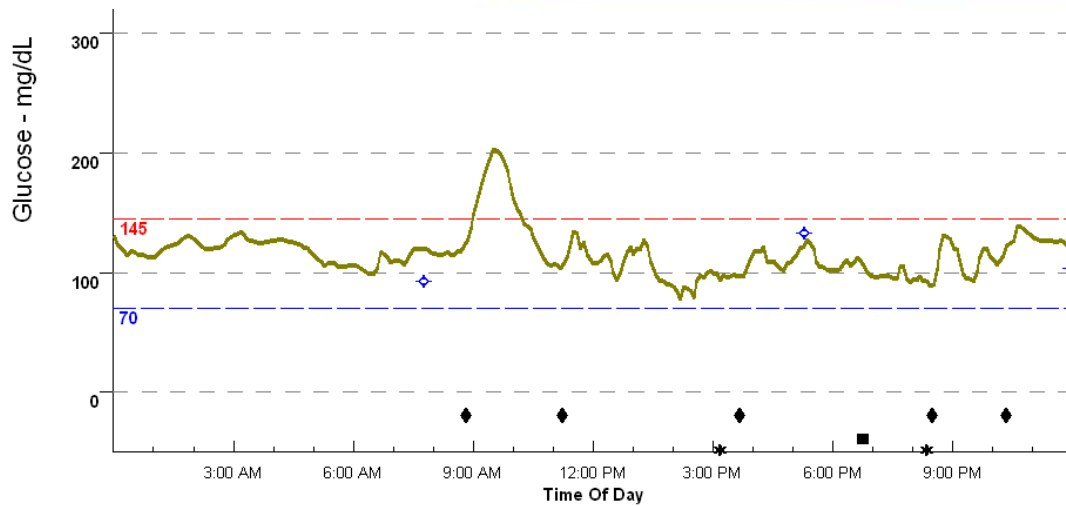
# PGX Provides Unique Benefits

- Reduces appetite and promotes effective weight loss
- Increases the level of compounds that promote satiety
- Decreases level of compounds that stimulate overeating
- Reduces the glycemic index of any food or beverage
- Increases insulin sensitivity
- Stabilizes blood sugar levels
- Lowers blood cholesterol and triglycerides

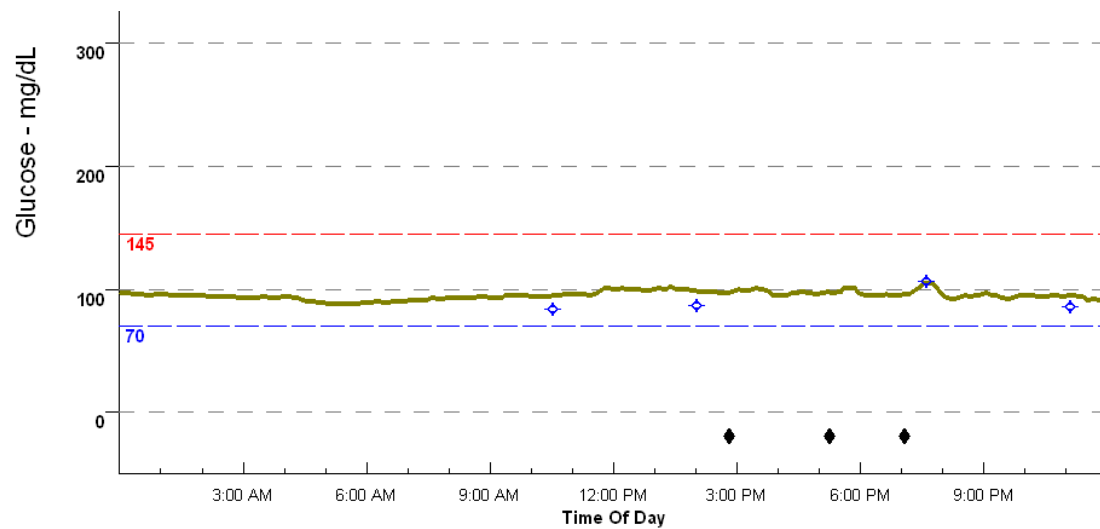


# Continuous Glucose Monitoring System (CGMS)





**Figure 1 - Overweight adult before weight loss demonstrating elevated blood sugar (glycemic) volatility.**



**Figure 2 - 24 hour continuous blood sugar in an overweight adult 4 weeks into the PGX Program**



# Practical Matters with PGX

- **Dosage**
- Side Effects
- **Drug Interactions**
- Nutrient Interactions



# Questions and Answers

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**[www.doctormurray.com](http://www.doctormurray.com)**

