

PARTIAL REVERSAL OF PARAMETERS OF AGING AND INFLAMMATION IN A NORMAL AGING POPULATION SUPPLEMENTED WITH A PATENT PENDING ORAL GLUTATHIONE OPTIMIZER; IMPLICATIONS FOR DISEASES OF AGING

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The following are potential conflicts of interest

Speakers Bureau: Glaxo Smith Kline

Grant Research Support: Max International

Consultant: Biosource Therapeutics

GLUTATHIONE BACKGROUND

One of only four Endogenous Antioxidants:

Glutathione*

Superoxide Dismutase

Catalase

Co Enzyme Q10

*Most Concentrated Intracellular Antioxidant. Levels of up to 5mmols/gm active tissue

GLUTATHIONE BACKGROUND

- Discovered by Dr. Pailhead in 1888
- Correct structure determined by Haring and Mead in 1935
 - 82,778 peer reviewed articles in Pub Med
- Under studied and under utilized in Clinical Medicine
- Anecdotes abound especially use of IV Glutathione in Autism, Parkinson's and others
- Paucity of double blind placebo controlled cause and effects studies

Diseases Associated with Decreased Glutathione

GENERAL

- Obesity •Immune Signaling •Endothelial dysfunction •Alcoholism
- Inflammation •Heavy metal poisoning

CARDIOVASCULAR

- Angina and spastic angina •Unstable angina •Heart attacks •Positive stress tests
- Reperfusion after cardiac bypass surgery

PULMONARY

- Emphysema (COPD) •Pulmonary Fibrosis (IPF) •Asthma •Muscle wasting in COPD
- Chronic bronchitis •Tobacco abuse

NEURO/PSYCH

- Migraine headaches •Alzheimer's •Parkinson's •Multi infarct dementia
- Autism •ADHD (Attention Deficit Hyperactivity Disorder) •Bipolar disease
- Schizophrenia •Lou Gehrig's disease •Huntington's chorea •Multiple Sclerosis (MS)
- Depression

OPHTHAMOLOGY

- Cataracts •Macular Degeneration

Diseases Associated with Decreased Glutathione

INFECTIOUS DISEASES/IMMUNOLOGY

- Hepatitis A, B, and C
- Herpes Simplex
- Herpes zoster/shingles
- Influenza and Bird Flu
- HIV
- MRSA
- Common viral infections (upper respiratory, gastroenteritis)
- Others

RHEUMATOLOGY

- Systemic Lupus Erythematosus (SLE)
- Rheumatoid arthritis (RA)
- Multiple Sclerosis (MS)
- Systemic Sclerosis (Scleroderma) Syndrome
- Behcet's Syndrome
- ME/CFS
- Fibromyalgia
- Others

DERMATOLOGY

- Wrinkles, sagging
- Acne
- Psoriasis
- Atopic dermatitis
- Eczema
- Others

ONCOLOGY Every cancer studied including:

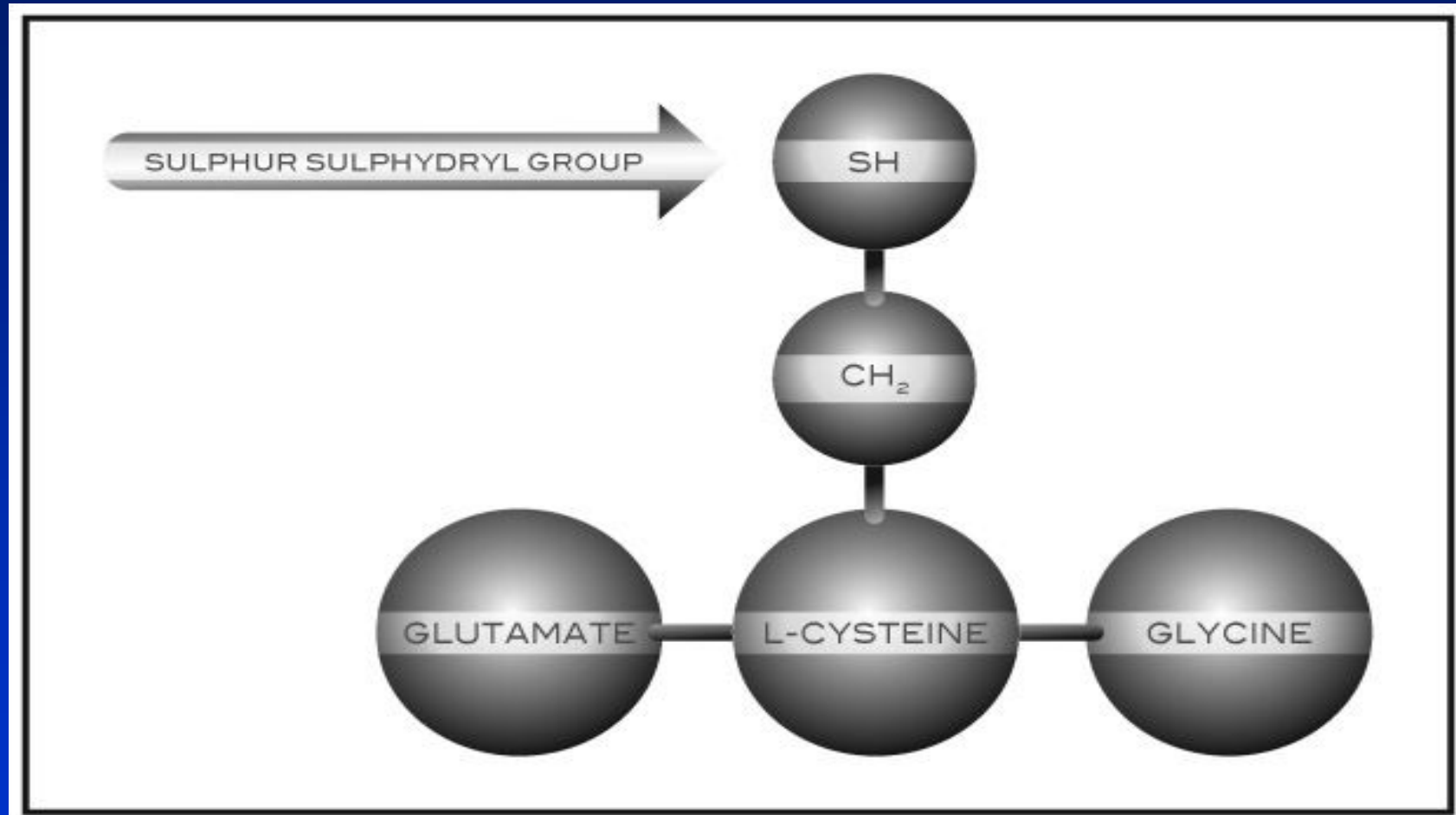
- Brain
- Head and neck
- Thyroid
- Lung
- Esophagus
- Stomach
- Intestine
- Liver
- Pancreas
- Kidney
- Uterine
- Ovarian
- Prostate
- Leukemia (acute and chronic)
- Lymphoma
- Multiple myeloma
- Others

OB/GYN

- Infertility
- Spontaneous abortions
- Pre Menstrual Syndrome

GLUTATHIONE BACKGROUND

IMPORTANCE I



SCHEMATIC DEPICTION OF GSH
(adapted from Guttman, J.)

GLUTATHIONE BACKGROUND

IMPORTANCE II

- GSH, alone in the antioxidant world, regenerates (recycles) directly and indirectly a variety of other antioxidants including vitamin C, alpha lipoic acid and vitamin E.
 - More than six (6) percent of the total energy (ATP) production of the whole body may be used to synthesize and regulate intracellular Glutathione levels.
- GSH is the only non enzyme antioxidant that does not itself become a free radical after it has quenched a free radical. In fact oxidized Glutathione (GS-SG) induces Delta Wave sleep.

GLUTATHIONE BACKGROUND

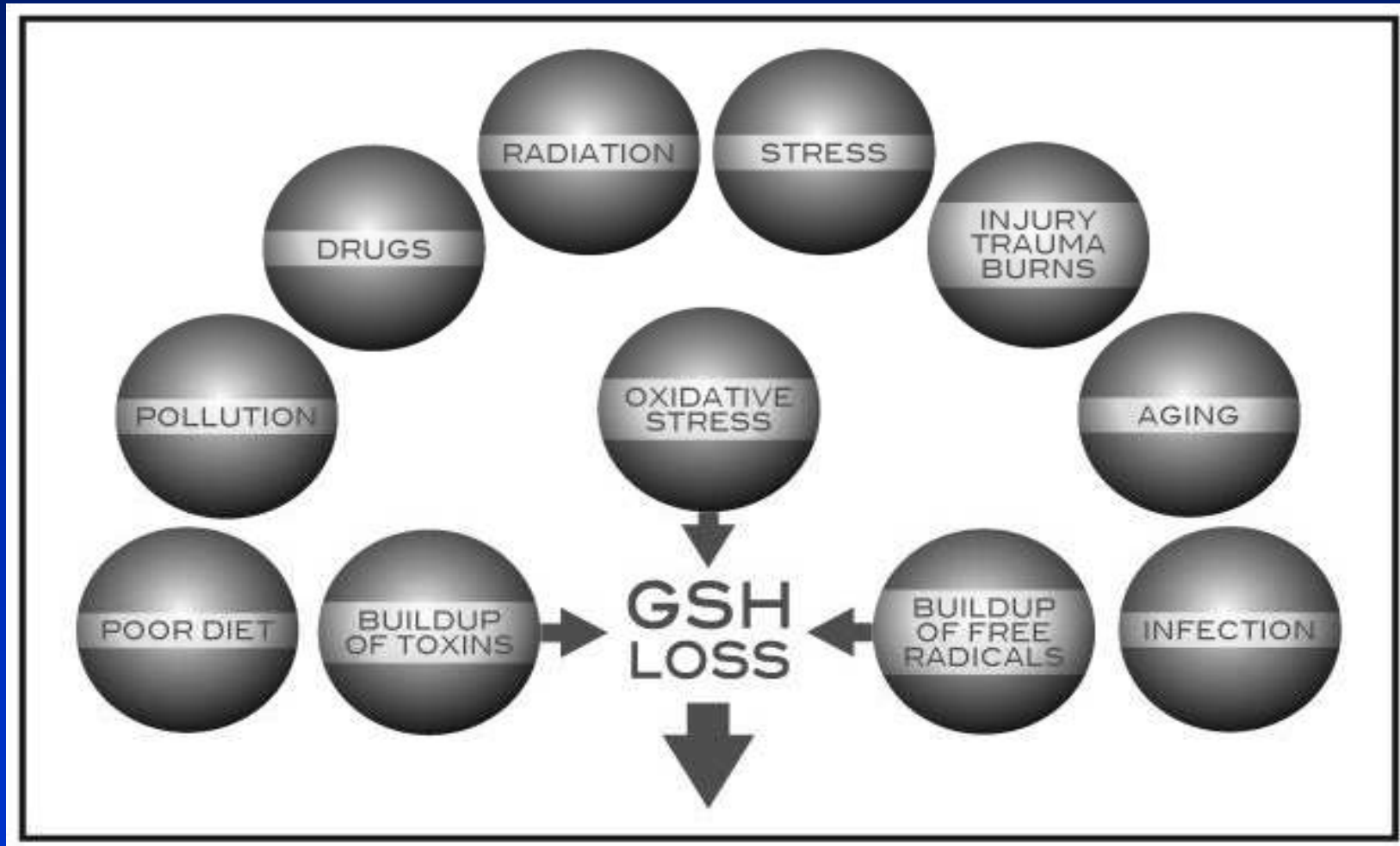
IMPORTANCE III

- GSH not only functions as a multifunctional antioxidant itself but as an essential component of antioxidant enzymes including Glutathione peroxidases and genetically determined family of Glutathione transferases
- Major chelator of heavy metals (50% as effective as free radical chelator) in removing mercury.
- Detoxifies organic pollutants via Phase II Hepatic Detoxification.

GSH BACKGROUND- IMPORTANCE IV

- GSH levels decrease with age (1% per year)
- Age matched normals reveal those with any defined disease have decreased GSH levels compared to aged matched normals.
 - GSH is major protector of Mitochondrial DNA (MtDNA). Compared to 5 year olds, only 5% of MtDNA is normal in 90 year olds.
 - Maintenance of normal MtDNA directly correlates with maximum life span
- Centenarians demonstrate GSH levels similar to 30-50 year old well normals.
 - Caloric restriction (animals) increases GSH and SIRT1.

ENVIRONMENTAL CAUSES OF GLUTATHIONE DEPLETION



SCHEMATIC DEPICTION OF GSH
(adapted from Guttman, J.)

GSH BACKGROUND- MOA OF MtDNA PROTECTION

Food (Krebs cycle, PPP) + O₂ → mitochondrial activity → ATP production



Free radical production (intense)



SOD → Superoxide Free Radicals



Hydroxyl & Peroxide Free Radicals



GSH Neutralizer Hydroxyl
GSH px Neutralizer Peroxide



MtDNA Production

GSH BACKGROUND

COMPONENT/PRECURSORS

AMINO ACID

Glutamine

PHYSIOLOGIC USES

- Conditionally essential (must be ingested) in illness or injury
- GSH production
- GI health; Strengthens GI barrier to entry of abnormal substances
- Promotes intestinal cell production
- Accelerated wound healing
- Major role in protein synthesis
- A substrate (necessary building block) for DNA synthesis
- Aids in Immune function
- Alternate source of fuel for brain cells.

AMINO ACID

Glutamic Acid

Cysteine

PHYSIOLOGIC USES

- Form of glutamine used in GSH Synthesis
- Complexed to nitrogen waste products for safe elimination (UREA)
- Excitatory neurotransmitter (NMDA)
- Precursor to inhibitory neurotransmitter (GABA)
- Antioxidant by itself
- Can become oxidant in states of inflammation (homocysteine)
- GSH production

AMINO ACID

PHYSIOLOGIC USES

Cysteine (continued)

- Binds to heavy metals
- Involved in apoptosis (programmed cell death or cell suicide)

Glycine

- Inhibitory neurotransmitter in the brain
- Major component of collagen (35%)
- Component of blood (hemoglobin) and muscle (myoglobin) proteins

GSH BACKGROUND

GSH PROMOTING DRUGS, SUPPLEMENTS AND CO FACTORS

DRUGS

Glutathione

N Acetyl Cysteine

Drug Candidates

OTC

OTZ

Procysteine

GSH monoesters

GSH Diesters

SUPPLEMENTS

Glutamine

N Acetyl Cysteine

Sam-E

Melatonin

Alpha Lipoic Acid

Silymarin

Cordyceps

Quercitin

Whey Protein (bioactive)

Transdermal Glutathione

Oral Glutathione

Max GXL

CO FACTORS

Selenium

Vitamin B1

Vitamin B2

Vitamin B3

Vitamin B5

Vitamin B6

Vitamin B12

Folic Acid

Vitamin E

Vitamin D3

Beta Carotene (Vitamin A)

PATENT PENDING ORAL GSH OPTIMIZER STUDY

Demographics

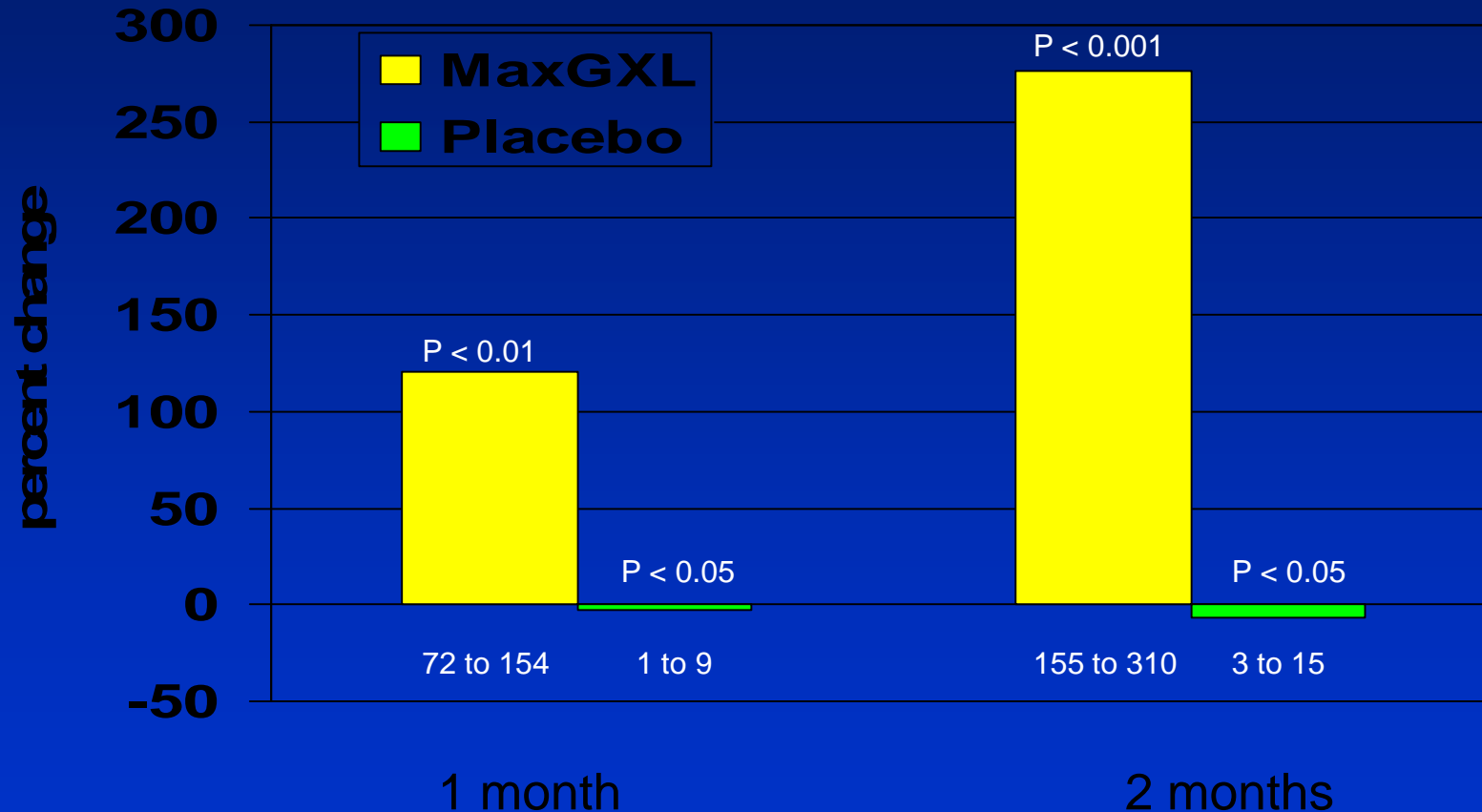
- 25 subjects evaluated
- Age range – 30-75 years old
 - 14 females and 11 males
- No immunosuppressive drugs, active Cancer, IDDM, Auto immune diseases
 - No blood thinners

PATENT PENDING ORAL GSH OPTIMIZER STUDY

Study Schematic

- IRB approved placebo controlled double blind crossover design
 - 2 months on each arm
 - 2 week washout between crossover
 - Lab evaluation, screening, baseline, monthly and post crossover
 - SF 32 QOL survey on same schedule as lab evaluation

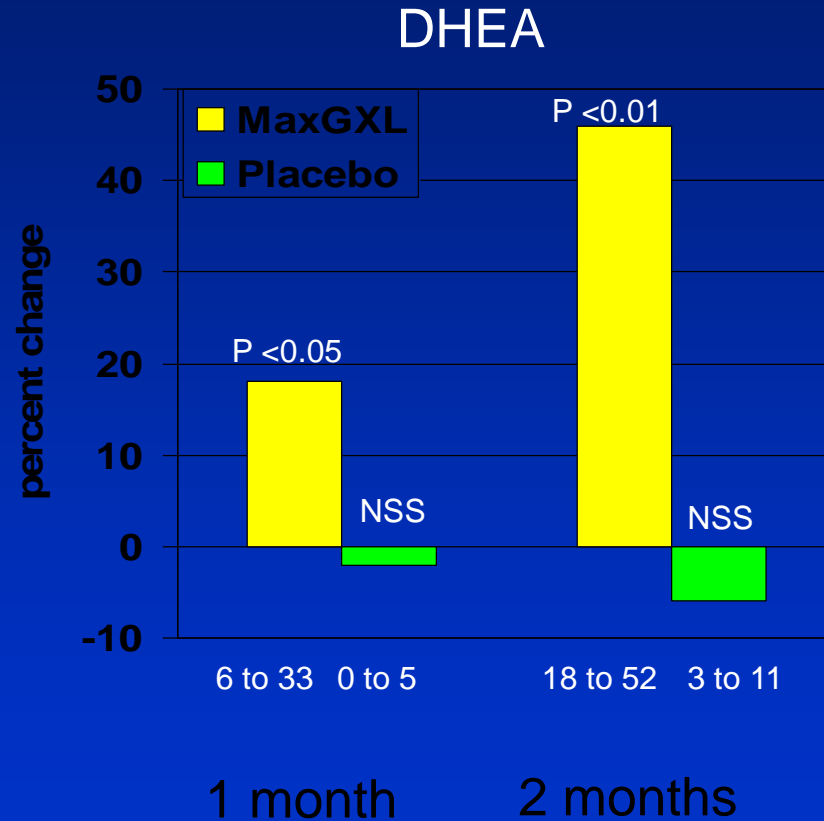
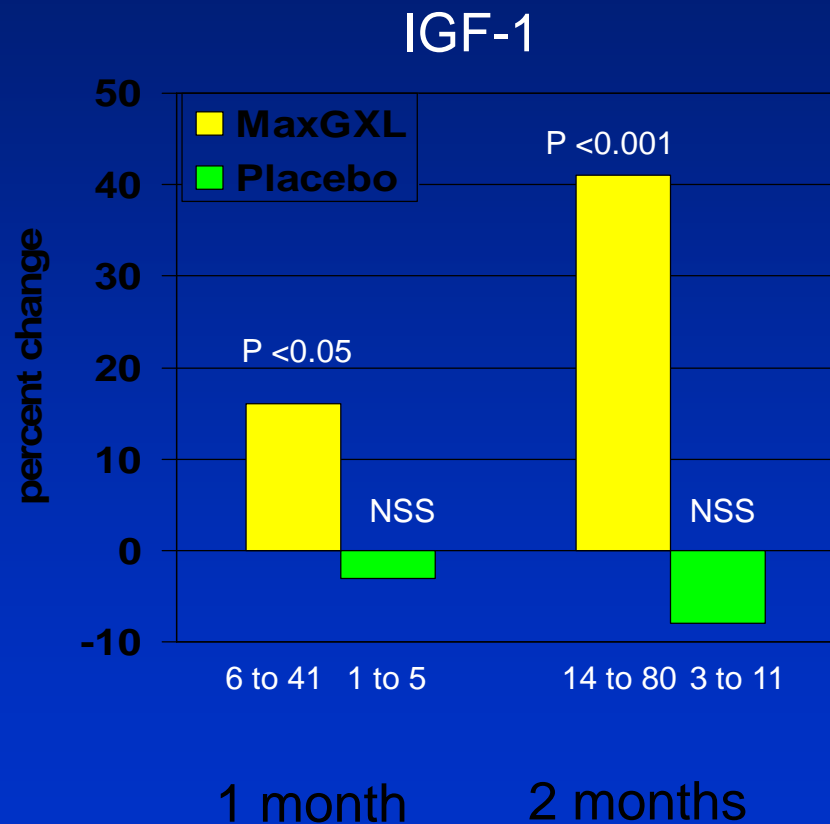
Improvement in Lymphocyte Glutathione* Levels using a Patent Pending Oral Glutathione Optimizer



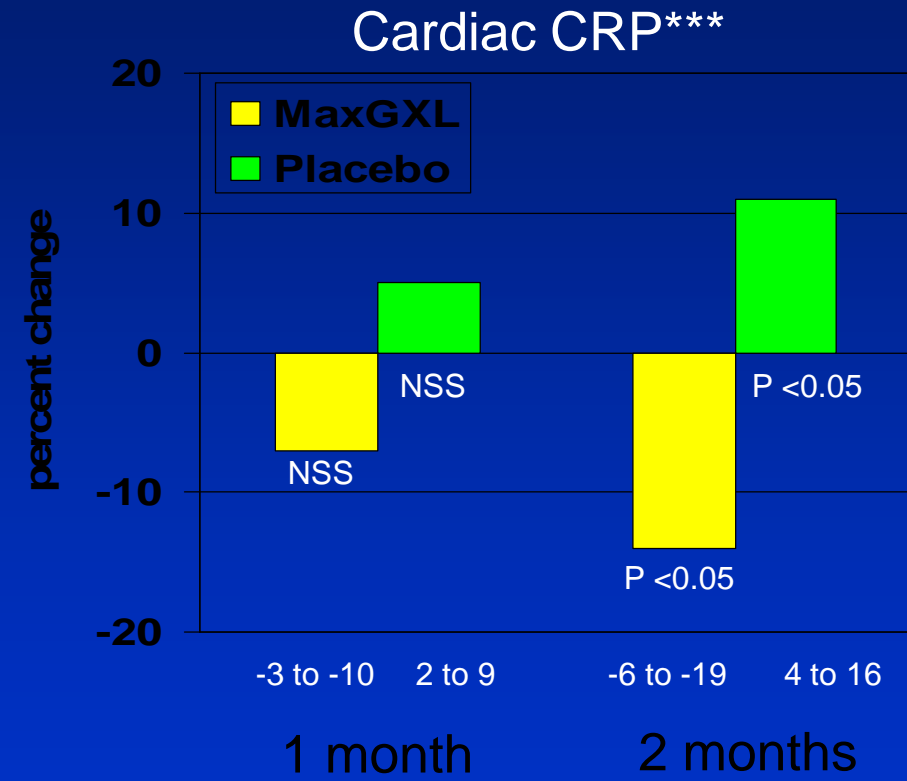
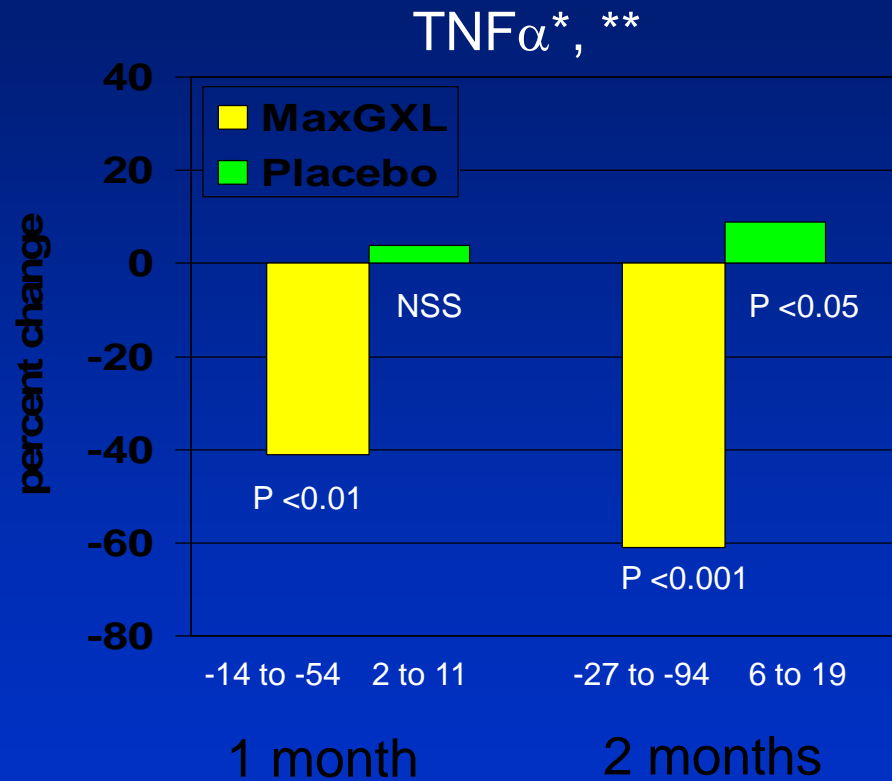
*Improvements in nanomolar range

3 Subjects with Chronic Insomnia showed least improvement

Improvement in Age-Associated Hormone Levels using a Patent Pending Oral Glutathione Optimizer



Improvement in Markers of Inflammation using a Patent Pending Oral Glutathione Optimizer



*19/25 Subjects demonstrated improved TNF α

**TNF α Assay sensitive to 6 ng/mL

***6/25 Subjects demonstrated improved CRP levels

IMPROVEMENT IN QOL (SF32) WITH PATENT PENDING ORAL GSH OPTMIZER

- IMPROVED ENERGY
- INCREASE IN QUALITY OF SLEEP
 - IMPROVED MOOD
 - IMPROVED MENTAL FOCUS
- DECREASED ACHES & PAINS

SUMMARY

- Patent pending oral GSH optimizer significantly raises lymphocyte GSH levels
- Increasing lymphocyte Glutathione* is associated with improved levels of age related hormones and markers of inflammation
 - Similar although nonstatistical improvements observed in fasting glucose, insulin and lipid profiles
- Increased GSH associated with improvements in Quality of Life parameters
- All improvements increase sequentially over duration of study (mo. 2 > mo.1)

* Proprietary testing modality

STUDY LIMITATIONS

- Small number of patients
 - Duration of study

Questions

Would expanded longer term studies slow sequential improvements in levels of age related hormones and decreases in markers of inflammation?

CONCLUSIONS

These data, despite the limitations suggest double blind placebo controlled cause and effect studies are warranted in the many diseases associated with age matched decreases in Glutathione.