Autoimmune (AI) Diseases: A Women’s Health Epidemic?

Sylvie Wellhausenen DC, DABCI
“Horror Autotoxicus”

Definition: Immune reactivity against self

Coined by: Paul Ehrlich, German bacteriologist

• Winner of 1908 Nobel Prize in Medicine
• Known as the father of modern science of immunology

Coined by Paul Ehrlich, a German bacteriologist, the term “Horror Autotoxicus” refers to the phenomenon of the immune system reacting against self. Ehrlich was a winner of the 1908 Nobel Prize in Medicine and is known as the father of modern science of immunology.
AI Characteristics

- Systemic AI Diseases display autoantibodies against nuclear or cytoplasmic molecules involved in DNA replication / transcription and translation of messenger RNA
- Organ-specific AI diseases have autoantibodies against an organ, related organ or tissues type
- AutoAntibodies are used as markers and interpreted along with clinical presentation
Different ethnic groups are more susceptible to certain autoimmune diseases. In lupus, for example, African American, Hispanic, Asian and Native American women are two to three times more likely to develop the disease than Caucasian women. And 9 out of 10 people who have lupus are women.
...Autoimmune diseases strike **women 3 times more than men**. Some diseases have an even higher incidence in women. In fact, **of the 50 million Americans living with autoimmunity, 30 million people are women**, some estimates say. Autoimmune diseases have been cited in the **top ten leading causes of all deaths among U.S. women age 65 and younger**. Moreover, these diseases represent **the 4th largest cause of disability** among women in the United States.”

Current Theories Linking Autoimmunity to Women

1. Gender Differences in Immunity
2. Sex Hormones
3. Genetic Susceptibility
4. History of Pregnancy
1. Gender Differences in Immunity

Some researchers believe that women are at increased risk of developing AI diseases because their immune systems tend to be more sophisticated than men's. Women naturally have stronger inflammatory responses than men when their immune systems are triggered, and inflammation plays a key role in many autoimmune diseases.
Current Theories Linking Autoimmunity to Women

2. Sex Hormones

Many AI diseases tend to improve and flare along with female hormonal fluctuations (pregnancy, menstrual cycle, or with oral contraception), which indicates that sex hormones probably play a role in many autoimmune diseases.
3. Genetic Susceptibility

Some scientists have proposed that women, who have two X chromosomes are genetically predisposed to developing certain AI diseases. There is some evidence that defects in the X chromosome may be related to susceptibility to certain autoimmune diseases. The genetics of AI diseases are complex, and studies are ongoing.
4. History of Pregnancy

There is some evidence that fetal cells can remain in circulation in a woman's body for years after a pregnancy, and these fetal cells may be involved in the development or worsening of certain AI diseases.
Female: Male Ratios in AI Diseases

15:1 Hashimoto's thyroiditis
9:1 Systemic lupus erythematosus
9:1 Sjogren's syndrome
9:1 Antiphospholipid syndrome-secondary
9:1 Primary biliary cirrhosis
8:1 Autoimmune hepatitis
7:1 Graves' disease
4:1 Scleroderma
4:1 Rheumatoid arthritis
2:1 Antiphospholipid syndrome-primary
2:1 AI Thrombocytopenic purpura (ITP)
2:1 Multiple sclerosis
2:1 Myasthenia gravis
AI Environmental Triggers

- Diet
- Beauty products
- Sedentary lifestyle
- Stress
In a particularly graphic example, it’s been estimated that by the time the average woman grabs her morning coffee, she has applied **126 different chemicals in 12 different products** to her face, body, and hair. “
Timing of Exposure to Endocrine Disruptors

Early life exposures to EDCs may alter gene expression via non-genomic, epigenetic mechanisms, including DNA methylation and histone acetylation thus interfering with the germ-line.

Latini et al., Mini-Reviews in Medicinal Chemistry, 2010, 10, 846-855 Grun and Blumberg, Molecular Endocrinology 23: 1127-1134, 2009
AI Disease & Insecticides

“Compared to never use, personal use of insecticides was associated with increased RA/SLE risk, with significant trends for greater frequency and duration. Risk was also associated with long-term insecticide application by others and frequent application by others among women with a farm history.”

From 10,000 BC to 1945
All Agriculture was Organic
Endocrine Disruptors of Concern

Includes:

• Industrial Compounds
• Plastics & Plasticizers
• Fungicides
• Pesticides
• Pharmaceuticals
Endocrine Disruptors of Concern

Examples:

- Persistent halogenated pollutants, such as polychlorinated biphenyls (PCBs), polybrominated diphenylethers (PBDEs) and metabolites
- Industrial compounds, such as bisphenol A (BPA), alkylphenols and pthalate acid esters
- Pesticides, such as chlorpyrifos
- Fungicides including vinclozalin
Endocrine Disruptors of Concern

“Endocrine disruptors may be found in many everyday products— including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides.”

Historically the term was invented in 1991 and was defined by the US Environmental Protection Agency as 'an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.'

In particular, EDC may interfere with hormonal signaling systems and alter feedback loops in the brain, pituitary, gonads, thyroid, and other components of the endocrine system.
LET ME GET THIS STRAIGHT-
BOTTLED WATER IS BAD,
AND CHOCOLATE IS GOOD.

THE EVER-CHANGING RULES OF HEALTH.
AI Disease: Infection Triggers

- Viral
- Bacterial
- Fungal
Viral

Type 1 Diabetes: AI Disease or Viral Infection?

What does Coxsackie virus have to do with diabetes? Evidence is emerging that insulin-producing cells are highly susceptible to acute infection by Coxsackie virus if their production of interferon is inhibited, resulting in diabetes.
Viruses and AI Disease– Two Sides of the Same Coin?

Viral infections have long been associated with the exacerbation of AI disease, and it is possible that the type I interferons, via interleukin 12, provide the link between viruses and autoimmunity.

However, there is also evidence that viruses can actually protect against AI disease.
Epidemiological Associations of GI Microbes & AI

- Ankylosing Spondylitis & Klebsiella Enterocolitica
- Rheumatoid Arthritis, Citrobacter & Proteus
- Thyroiditis (Graves’ & Hashimoto’s) & Yersinia
- AI disorders (in general), E. coli & Proteus
- IBD & Klebsiella
Bacterial

GI Microbes & Systemic AI Pathology

When pathogens in the gut decrease and related antibodies in the blood improve so does the condition.

When remedies are given that bind bacterial endotoxins (e.g. psyllium and bentonite), these conditions usually improve.
Bacterial

Bacteria & RA

- Mucous Membrane Colonization in Healthy People
  - Bifidobacteria, lactobacilli, bateroides, escherichia, & enterococci
- Mucous Membrane Colonization in RA Subjects
  - Aerobic opportunistic conventionally pathogenic enterobacteria (enteropathogenic escherichia, Citrobacter, Enterobacter, Klebsiella etc), staphylococci, enterococci, & Anaerobic Bacteria (Bacteroides, peptococci, peptostreptococci, etc)
- Treatment for RA Patients
  - Taking into account significant changes of colonization resistance in remission period of RA, apply bacteriotherapy using bacterial drugs containing bifidobacteria & lactobacteria

Bacteria & Leaky Gut

• The Role of the Healthy Intestinal Barrier
  • Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self-antigens.

• Dysregulation of Macromolecules
  • When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune can occur.

• Treatment
  • This review is timely given the increased interest in the role of leaky gut in the pathogenesis of gastrointestinal diseases and the advent of novel treatment strategies, such as probiotics

Two groups of beneficial bacteria are dominant in the human gut, the Bacteroidetes and Firmicutes.
Fungal Dysbiosis-Milieu

- Toxins released by the microbial overpopulation cause chronic inflammation of the liver, gallbladder, pancreas, and intestines. This can have other health repercussions, including insulin-dependent diabetes.
- The tentacles of Candida penetrate the intestinal wall, causing not only inflammations but also 'leaky gut syndrome' in which only partly digested proteins enter the bloodstream and cause multiple allergies and autoimmune disease.
- Dysbiosis increases susceptibility to food poisoning, as with Salmonella bacteria. S aureus & other infections are greatly potentized when they occur together with Candida overgrowth. It explains why hospital infections are so deadly. Other factors that can cause dysbiosis are the contraceptive pill, steroids and other drugs, radiation treatment, and chemotherapy.
Fungal

Probiotics & Gliadin Toxicity

The production of NF-KB, TNF-α, and IL-1β was reduced (18.2-22.4%, 28.0-64.8%, and abolished, respectively) in cell cultures exposed to gliadin digestions inoculated with bifidobacteria. Bifidobacteria change the gliadin-derived peptide pattern, and thereby attenuate their pro-inflammatory effects on Caco-2 cells.
### Eubiosis v Dysbiosis

#### Eubiosis

- Good coexistence of host & microflora - Symbiosis
- **Protection** of the intestinal mucous membrane against invading microorganisms
- **Antagonistic effect** on undesired microorganisms
- Contribution to **maturation** & stimulation of host’s immune system
- **Nutrient** digestion
- **Vitamin** synthesis
- **Protein** synthesis

#### Dysbiosis

- Bad coexistence of host & microflora
- **Damage** to the intestinal epithelium. Gut wall thickening = reduced absorption of nutrients
- **Toxic metabolic substances** (NH$_3$, biogene amines, toxins)
- Decomposition & **increased gas production** (CH$_4$, H$_2$S, CO$_2$)
- **Weakening** of immune system
- **Immune reaction** = increased need of energy
- Acceleration of cell turnover = increased need of energy

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Dysbiosis

Products of Dysbiosis -
Intestinal Sources of Endogenous Toxins

- B-glucarondidase (causing enterhepatic recirculation of hormones and other toxins)
- Mycoestrogens and ETOH from yeast?
- Bacteria: putrescine, cadaverine, ammonia
- Yeasts: Arabinose, tartarate, citramalate, ketoglutarate
- Secondary bile acids (deconjugated)

Exposure Difference?

Why Do Women Crave Sugar?
Do Women’s Diets Promote Candida?
Causes of Sugar Craving

- Neurotransmitter & Hormonal Fluctuation
  - Serotonin, Cortisol, Progesterone, & DHEA
- Nutritional Deficiencies
  - Magnesium (chocolate craving), Chromium, Lipoic Acid, B Vitamins, Prebiotics, & Phytonutrients
- Candida-Dysbiosis
Candida

Candida disables our intestinal front line defense (IgA)!

At least three different Candida species are able to produce proteases which can degrade IgA1, IgA2 and SIgA. This protease activity can induce polyclonal B-cell response and inflammation.

Santelmann H, Eur J of Gasto and Hepat 2005
Fecal Calprotectin Elevated

Fecal Calprotectin Elevated in:

- Inflammatory Bowel Disease
- Post-Infectious Irritable Bowel Syndrome
- GI Cancer
- Certain GI infections
- NSAID enteropathy
- Food allergy
- Chronic Pancreatitis
Anti-Saccharomyces cerevisiae Antibodies (ASCA)

- IgA & IgG directed against yeast mannans (component of cell walls)
- Consistently higher frequency in Crohn’s disease
- ASCA+ predicts Crohn’s with high specificity (87%) & positive predictive value (78%)
Antineutrophil Cytoplasmic Antibodies (ANCA)

• Group of autoantibodies (IgG) against antigens in cytoplasm of neutrophils
• Found in wide range of autoimmune diseases, especially vasculitides
• May indicate defective apoptosis or exposure to microbial superantigens
• Perinuclear ANCA (pANCA)
“The multiple symptoms reported by women with both irritable bowel syndrome and premenstrual distress syndrome suggest that this group may be particularly challenging to treat and may require a multi component (e.g., education, diet, relaxation, cognitive restructuring) approach.”

“Compared with the controls, women with endometriosis were 3.5 times more likely to have received a diagnosis of IBS (OR 3.5 [95% CI:3.1-3.9]).”
IBS & Gynecology

IBS in Women Overlaps with Gynecological Symptoms

- Indigestion (nausea, belching, bloating)
- Abdominal distension
- Cramping & Spasms
- Altered Bowel Habits
- Frequently aggravated by spicy, fatty, or high fiber foods
- Excess caffeine
- Premenstrual Syndrome (PMS)
- Late Luteal Phase Dysphoric Disorder (LLPDD)
- Dysmenorrhea
- Endometriosis
- IC - Interstitial cystitis
- Urinary Frequency & Urgency
- Chronic Pelvic Pain
- Painful Intercourse

In synovial tissue of patients with RA, macrophage-like and fibroblast-like synoviocytes have been found to be positive for both ER-α and ER-β.

...increased aromatase activity induced by locally produced inflammatory cytokines (i.e., TNF, IL-1, IL-6) might explain the altered balance resulting in lower androgens and higher estrogens in all synovial-active RA fluids, as well as their effects on synovial cells.
Increased Estrogen Formation and Estrogen to Androgen Ratio in the Synovial Fluid of Patients with Rheumatoid Arthritis

LUIGI A. CASTAGNETTA, GIUSEPPE CARRUBA, ORAZIA M. GRANATA, ROSALBA STEFANO, MONICA MIELE, MARTIN SCHMIDT, MAURIZIO CUTOLO, and RAINER H. STRAUB

ABSTRACT. Objective. It has been proposed that physiologic levels of estrogens stimulate immune responses whereas androgens suppress inflammatory reactions. Thus, prevalence of synovial androgens relative to estrogens would be favorable in rheumatoid arthritis (RA). We investigated synovial fluid (SF) concentrations of several estrogens and androgens and conversion products of the sex steroid precursor dehydroepiandrosterone (DHEA) in supernatants of mixed synoviocytes.

Methods. SF steroid concentrations were measured by high performance liquid chromatography and mass spectrometry in 12 patients with RA and 8 subjects with traumatic knee injury (noninflammatory controls). Conversion of DHEA to downstream hormones was measured by thin-layer chromatography and phosphorimaging detection in 3 patients with RA and 3 patients with osteoarthritis (OA).

Results. Overall, SF concentration of free estrogens tended to be higher in RA patients versus controls (p < 0.06). Molar ratio of free SF estrogens/free SF androgens was elevated in RA compared to controls (1.17 ± 0.32 vs 0.29 ± 0.08, without unit; p = 0.017). The free SF concentration of the precursor androstenedione was significantly higher in RA patients than in controls (104.6 ± 32.6 vs 30.4 ± 0.4 ng/ml; p = 0.011), and SF estrone — the aromatase conversion product of androstenedione — was also elevated in RA compared to controls (13.6 ± 2.6 vs 6.6 ± 0.8 ng/ml; p = 0.035). The biologically active estrogen derivatives, 16α-hydroxyestrone and 4-hydroxyestradiol, were both higher in RA compared to controls (p = 0.085 and p = 0.044, respectively). In mixed RA synoviocytes, DHEA conversion yielded high local levels of 17β-estradiol (708 pmol/l = 0.193 ng/ml) compared to testosterone (88 pmol/l = 0.026 ng/ml).

Conclusion. SF levels of estrogens relative to androgens are significantly elevated, while those of androgens are markedly reduced, in patients with RA compared to controls. This imbalance is most probably due to increased aromatase activity. Thus, an available steroid precursor, such as DHEA, may be rapidly converted to proinflammatory estrogens in the synovial tissue, which may in turn stimulate the inflammatory process in patients with RA. (J Rheumatol 2003;30:2597–605)
Levels of 40HE & 16αOHE in RA

“On our studies SF (synovial fluid) levels of the powerful 4 hydroxyestradiol were significantly increased in RA patients compared to controls, while no significant differences of 2-hydroxyestrone SF levels could be detected between RA patients and controls… Concerning 16α-hydroxyestrone, this powerful estrogen tended to be elevated in RA patients with respect to control subjects.”
Epidemiologic evidence indicates that during the fertile period women are affected by rheumatic diseases, particularly autoimmune diseases, more often than men.

Several studies and reviews showed that there are reduced serum concentrations of DHEA-S, T, and progesterone in male and female patients who have RA or SLE. These data strongly support an accelerated peripheral metabolic conversion of androgen precursors to E2.
Autoimmune Disease and HRT

“As a matter of fact, an increase in 16-αOH-estrone relative to the sum of all 2- and 4-hydroxylated estrogens must be viewed as a proinflammatory signal, which is particularly evident in RA patients.

Since 17-estradiol administered during hormone replacement therapy will rapidly increase estrone sulfate after conversion in adipose tissue by aromatases, hormone replacement therapy can have proinflammatory effects by providing estrone sulfate to the inflamed synovial tissue.”

How Does Estrogen Relate to Inflammation?

- Adipose tissue secretes proinflammatory cytokines
- Obesity is a chronic inflammatory state
- Adipose tissue has aromatase and makes estrogen
- PGE2 (a proinflammatory cytokine) is a stimulator of aromatase
- Estrogen upregulates COX-2 production of PGE2
- Endometriosis and fibroids have high aromatase activity

Zhao et al, Endocrinology 1996, 137:5739-5742
The Total Estrogen Pool

- Ovarian production of free estradiol
- Conversion of testosterone and estrone to estradiol
- Estrogen bound to SHBG
- Sulfated estrogens
- Estrogen metabolites
- Exogenous estrogens - drugs and xenoestrogens
- Reabsorbed estrogens
Enterohepatic Circulation of Estrogens
Our results showed that TCDD increased the aromatase activity in a time-and-dose dependent manner. Further investigation indicated that TCDD slowed down the CYP19 mRNA degradation.

...The neuroendocrine systems do not exist in a vacuum: they communicate with one another and this cross-talk could exacerbate effects of exposures across multiple homeostatic systems.
Adipose Tissue as an Endocrine Organ

### Legend

- **ASP** = Acylation-stimulating protein
- **FFA** = Free fatty acid
- **FIAF** = Fasting-induced adipose factor
- **HGF** = Hepatocyte growth factor
- **IGF-1** = Insulin-like growth factor-1
- **IL** = Interleukin
- **MCP-1** = Monocyte chemotactic protein-1
- **MIF** = Macrophage migration inhibitory factor
- **NGF** = Nerve growth factor
- **PAI-1** = Plasminogen activator inhibitor-1
- **PGE$_2$** = Prostaglandin E$_2$
- **PGI$_2$** = Prostacyclin
- **PGF$_{2\alpha}$** = 8-iso-prostaglandin F$_{2\alpha}$
- **RAS** = Renin-angiotensin system
- **TF** = Tissue factor
- **TGF-β** = Transforming growth factor-β
- **TNF-α** = Tumor necrosis factor-α
- **VEGF** = Vascular endothelial growth factor

### Source

International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

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The Thyroid

“The Female Yellow Canary”

Tests to Use:
• TPO
• Thyroglobulin Antibodies
• Free T3 , free T4
• Reverse T3
• TSH

Results Can Indicate: (female / male)
• Goiters 9.5 / 1
• Hashimoto 15 / 1
• Graves 7 / 1
• Women need more Iodine
Environmental Neuroendocrine & Thyroid Disruption

Are they relevant to reproductive medicine?

“The thyroid hormone is well known to be essential for development of many tissues, including the brain and heart. Less is understood concerning the potential role of the thyroid hormone in the development of reproductive tissues that might impact fertility. However, important new information is appearing concerning the association between thyroid hormone levels and fertility in humans, as well as animal studies focused on its role in testis development.”
APECED
(Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dystrophy)

A genetic autoimmune disease with an extraordinary array of clinical features but characterized most often by at least 2 of the following 3 findings:

• Hypoparathyroidism
• Candidiasis
• Adrenal insufficiency
APECED

Introduction

• The first systemic autoimmune disease found due to a defect in a single gene.
• Caused by changes in the AIRE (AI regulator) gene
• Inherited as a recessive trait
• Generally rare, but more frequent in 3 genetically isolated populations: the Finnish, Iranian Jews, & Sardinians
Indications

- Abnormally low level of gammaglobulin in blood & an abnormally low T4/T8 white blood cell ratio (as in AIDS)
- Antibodies are directed against the adrenal glands, thyroid glands & cell nuclei (anti-adrenal, antithyroid and ANA)
APECED

Signs

In Children
- Hypoparathyroidism
- Hypogonadism
- Adrenal Insufficiency
- Type 1 Diabetes with Insufficient Insulin
- Childhood-onset Moniliasis (Yeast Infection)
- Juvenile-onset Pernicious Anemia

In Adults
- Total Baldness
- Inflammation of the Cornea & Keratoconjunctivitis
- Underdevelopment of Enamel of the Teeth
- IBS (Malabsorption, Diarrhea)
- Chronic Active Hepatitis.
APECED

Treatment

The medical treatment of APECED is directed at treating the specific problems: replacing the various hormones that are in short supply, giving insulin for the diabetes, treating the yeast infections, etc.
General Laboratory Assessment

- CBC
- Comp Chemistry + GGT
- TSH, Free T3, RT3
- 25 Hydroxy Vit D (50-90)
- Lipids
- HDL >50
- LDL <130
- VLDL <22
- Triglycerides < 90

- Sed Rate (ESR)
- Ferritin
- C Reactive Protein
- Protein C
- Fibrinogen - IL6
- Homocysteine
- Cortisol
- Uric acid
- Thyroglobulin Ab / TPO
- ANA
- Fasting Insulin / A1c

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Addison’s Disease

- Adrenal Antibody
- Primate Adrenal Cortex
  - An indirect immunofluorescence antibody test for the direction and semiquantitation of anto-adrenal cortex antibodies in human serum
- Cortisol-DHEA
Antiphospholipid Syndrome

- Cardiolipin IgA + IgG + IgM antibody
  - as an aid in assessing the risk of thrombosis in individuals with Systemic Lupus Erythematosus (SLE) or lupus like disorders

- β2-glycoprotein 1 (β2-GP1) IgG/IgM Antibody
  - as an aid in assessing the risk of thrombosis in patients with Systemic Lupus Erythematosus (SLE) or lupus like disorders
AI Hepatitis

- Anti-nuclear antibodies (ANA)
- Anti-mitochondrial antibodies (AMA)
- Anti-smooth muscle antibodies (ASMA)
- Anti-gastric parietal cell antibodies (AGPA) in human serum
- Enzyme linked immunosorbent assay (ELISA) for the detection and semi quantitation of anti-live/kidney/microsomal-1 antibodies (LKM-1)
AI Neuropathies

- Myelin Associated Glycoprotein Antibody
- Anti-Neuronal Granular Cell Nuclear Autoantibody
- Ganglioside GM1 IgG and IgM antibody
Chron’s & Ulcerative Colitis

• ANCA (Antineutrophil Cytoplasmic Antibodies) Perinuclear ANCA Cytoplasmic ANCA
  • ANCA are found in the sera of patients with necrotizing vasculitides.

• Saccharomyces Cerevisiae IgA Antibody (ASCA) ELISA
  • In human serum of patients with inflammatory bowel disorder (IBD) as an aid in the diagnosis of Chron's disease (CD)

• Myeloperoxidase (MPO) antibody ELISA

• Proteinase 3 (PR3) antibody ELISA

Anti-Saccharomyces cerevisiae antibodies (ASCA) tends to recognize Crohn's disease more frequently, whereas perinuclear antineutrophil cytoplasmic antibodies pANCA tend to recognize ulcerative colitis
Primary Sclerosing Cholangitis

- ANCA (Antineutrophil Cytoplasmic Antibodies) Perinuclear ANCA
  Cytoplasmic ANCA

- Myeloperoxidase (MPO) antibody ELISA

- Proteinase 3 (PR3) antibody ELISA
Pernicious Anemia
AL Gastritis

- Intrinsic Factor (IF) antibody
  - Enzyme linked immunosorbent assay (ELISA) for the qualitative and semi-quantitative detection of antibodies to intrinsic factor in human serum
- Gastric Parietal Cell (GPA) antibody
  - Enzyme linked immunosorbent assay (ELISA) for the qualitative and semi-quantitative detection of antibodies to the gastric parietal cell antigen H +K + ATPase (proton pump) in human serum
- ANA
- Anti-mitochondrial antibodies (AMA)
- Anti-smooth muscle antibodies (ASMA)
Glomerulonephritis - Goodpasture

Glomerular Basement Membrane Antibody

An enzyme linked immunosorbent assay (ELISA) for the detection and semiquantitation of anti-glomerular basement membrane (GBM) antibodies in human serum. The presence of GBM antibodies can be used as an adjunct to clinical and other laboratory findings.
Rheumatoid Arthritis

- Rheumatoid Factor (RF) IgA/IgM
- Cyclic citrullinated peptide antibody IgG
- Anti-nuclear antibodies (ANA)
- Anti-mitochondrial antibodies (AMA)
- Anti-smooth muscle antibodies (ASMA)
- Anti-gastric parietal cell antibodies (AGPA) in human serum
Scleroderma

• Scleroderma is characterized by the appearance of circumscribed or diffuse, hard, smooth, ivory-colored areas that are immobile, and which give the appearance of hidebound skin and vascular alteration

• 2 Types:
  • Localized scleroderma
  • Systemic scleroderma
    • CREST syndrome
    • Progressive systemic sclerosis
  • Diffuse systemic sclerosis/scleroderma is rapidly progressing and affects a large area of the skin and one or more internal organs, frequently the kidneys, esophagus, heart and lungs
Crest Syndrome

- Systemic Scleroderma is often referred to as CREST syndrome.

- "CREST" is an acronym for the five main features:
  - Calcinosis
  - Raynaud's syndrome
  - Esophageal dysmotility
  - Sclerodactyly
  - Telangiectasia
Crest Syndrome

Labs

• Anti-Centromere
  • Found in 22 to 36 percent of patients with scleroderma. Their presence is correlated with Raynaud's phenomenon. Anti-centromere antibodies are also present in some patients with primary biliary cirrhosis.

• Anti-Topoisomerase I (or anti-Scl-70)
  • Found in 22 to 40% of patients with scleroderma. It correlates with diffuse cutaneous disease, pulmonary fibrosis, cardiac involvement and longer disease duration

• Other autoantibodies can be seen, such as anti-U3 or anti-RNA polymerase
Sjögren's

Systemic autoimmune disease in which immune cells attack and destroy the exocrine glands that produce tears and saliva

- Anti-Ro(SS-A) and Anti-La(SS-B) presence is associated with extra-glandular manifestations of the disease
- Anti-Ro activity is also found in approximately 40% of patients with SLE and is associated with photosensitive skin rash, pulmonary disease and lymphopenia
- Anti-La activity is detected in 10-15% of patients with SLE and is associated with late-onset disease, secondary Sjögren's and neonatal lupus syndrome
Sjögren's

One of the most common AI diseases (after RA)

- 3 million affected in US
- 90% women typical onset age 40 & older
- Immune system attacks secretory glands & tissues
- Biopsy is definitive--antibody test negative in 40% of cases
- Associated with 44% increased risk of lymphoma
Sjögren's

Diverse Signs & Symptoms

- Dry, Irritated Eyes (Keratoconjunctivitis Sicca)
- Dry Mouth, Dysgeusia, Dysphagia,
- Thrush Periodontal Disease & Early Loss of Teeth
- Enlarged Parotids
- Dry Cough, Recurrent Sinusitis, Lung Infections
- Vaginal Dryness
- Dry Skin & Rashes
- Celiac Disease / Gluten Sensitivity
- Thyroiditis
- Memory Loss
- Paresthesias in Hands & Feet
Conditions Sensitivity with + ANA

- Drug-induced lupus: 100
- Systemic lupus erythematosus: 99
- Scleroderma: 97
- Sjögren's syndrome: 96
- Mixed connective tissue disease: 93
- Polymyositis and dermatomyositis: 78
- Rheumatoid arthritis: 40
- Systemic vasculitis: 15
Conditions Associated with a + Rheumatoid Factor

• Rheumatoid arthritis (50 to 90%)
• Systemic lupus erythematosus (15 to 35%)
• Sjögren's syndrome (75 to 95%)
• Systemic sclerosis (20 to 30%)
• Cryoglobulinemia (40 to 100%)
• Mixed connective tissue disease (50 to 60%)
Conditions Associated with a + Rheumatoid Factor

Nonrheumatic Conditions

- Infection: bacterial endocarditis, liver disease, tuberculosis, syphilis, viral infections (especially mumps, rubella and influenza), parasitic diseases
- Pulmonary disease: sarcoidosis, interstitial pulmonary fibrosis, silicosis, asbestosis
- Miscellaneous diseases: primary biliary cirrhosis, malignancy (especially leukemia and colon cancer)
Cryoglobulins

- A condition in which the blood contains large amounts of cryoglobulins (proteins) become insoluble at reduced temperatures (below 37 celsius) and will dissolve again if the blood is heated
- Infections such as Lyme disease, infectious mono, hep C and AIDS
- Kidney disease
- AI diseases such as SLE, rheumatoid arthritis, & Sjögren's syndrome
- Diseases characterized by an increase in lymphocytes such as multiple myeloma, lymphoma and lymphoid leukemia
- Vasculitis
- Raynaud
ESR

Polymyalgia Rheumatica & Temporal Arteritis

• An elevated ESR value has a sensitivity of approximately 80 percent for polymyalgia rheumatica & greater than 95 percent for temporal arteritis

• The ESR is a means for staging rheumatoid arthritis, rather than a major diagnostic criterion. However, the specificity of an elevated ESR is quite low, limiting its use as a diagnostic test
ESR

Other Factors that Increase the Sed Rate

• Pregnancy
• Anemia
• Macrocytosis
• Technical factors: dilutional problem, increased specimen temperature, tilted tube
• Elevated fibrinogen level: infection, inflammation, malignancy
Antineutrophil cytoplasmic antibodies (ANCAs) are directed against a number of antigens located in the cytoplasm of neutrophils.

ANCA testing currently distinguishes between cytoplasmic ANCA (cANCA) and perinuclear ANCA (pANCA).

A positive cANCA test result indicates the presence of antibodies to the enzyme proteinase 3. The cANCA test has high specificity and sensitivity for the detection of Wegener's granulomatosis. (A rare disorder)

The pANCA test targets myeloperoxidase, an antigen frequently associated with microscopic polyangiitis and necrotizing glomerulonephritis. However, the sensitivity of pANCA for these diseases is quite low. Although pANCA has been identified in several rheumatic autoimmune diseases, the sensitivity and specificity are quite low.
Less Used Antibody Tests

- Anti-dsDNA (Anti Double Stranded DNA)
- Anti-ssDNA
- Anti-histone
- Anti-Sm SLE
- Anti-U1 snRNP SLE
- Anti-ribosome SLE
- Anti-Jo1
Functional Laboratory Assessments

- Detoxification Markers
- Pesticide Levels
- Organochlorine Baseline
- RBC Micronutrients (e.g., Selenium, Copper, Zinc)
- Female Hormone Panel
- LFTs, Particularly GGT
- Consider SNPs for COMT & MTHFR
- Food Allergies
Testing for Endocrine Disruptors

### 0740 Phthalates and Parabens

<table>
<thead>
<tr>
<th>Phthalates</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEHP</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MEH</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MEOP</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MEP</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### 0762 Volatile Solvents - Whole Blood

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>Not Detected</td>
<td>0.26 ppm</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>24.54</td>
<td>0.11 ppm</td>
</tr>
<tr>
<td>Styrene</td>
<td>Not Detected</td>
<td>0.12 ppm</td>
</tr>
<tr>
<td>Toluenes</td>
<td>Not Detected</td>
<td>0.88 ppm</td>
</tr>
<tr>
<td>m,p-Xylene</td>
<td>Detected</td>
<td>0.4 - 1.3 ppm</td>
</tr>
</tbody>
</table>

### 0790 Chlorinated Pesticides - Serum

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDE</td>
<td>12.90</td>
<td>-</td>
</tr>
<tr>
<td>DDT</td>
<td>Not Detected</td>
<td>-</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>Detected</td>
<td>-</td>
</tr>
<tr>
<td>Heptachlor Epoxide</td>
<td>Not Detected</td>
<td>-</td>
</tr>
<tr>
<td>Hexachloroethene (HCB)</td>
<td>Not Detected</td>
<td>-</td>
</tr>
<tr>
<td>Mirex</td>
<td>Not Detected</td>
<td>-</td>
</tr>
<tr>
<td>Crypyliodane</td>
<td>Detected</td>
<td>-</td>
</tr>
<tr>
<td>trans, trans-Chlordane</td>
<td>Not Detected</td>
<td>-</td>
</tr>
<tr>
<td>Chloroform</td>
<td>180</td>
<td>-</td>
</tr>
<tr>
<td>Hexane</td>
<td>134</td>
<td>-</td>
</tr>
<tr>
<td>2-Methylpentane</td>
<td>49.1</td>
<td>-</td>
</tr>
<tr>
<td>3-Methylpentane</td>
<td>74.9</td>
<td>-</td>
</tr>
<tr>
<td>Isolurane</td>
<td>7.76</td>
<td>-</td>
</tr>
</tbody>
</table>

For interpretive information, visit [www.metametrix.com](http://www.metametrix.com) and select the downloads tab.

For interpretive information, visit [http://www.metametrix.com/test-manu/profiles](http://www.metametrix.com/test-manu/profiles)

# Nutritional Modulation of Estrogen

<table>
<thead>
<tr>
<th>Step</th>
<th>Clinical Markers</th>
<th>Nutritional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Input</td>
<td>Evaluate T &amp; E Levels, Evaluate EDCs, BMI</td>
<td>Decrease aromatization with phytochemicals (isoflavins, tea catechins, pomegranate, licorice flavinoids, resveratrol, hop flavinoids, flax lignans, grapeseed extract); Reduce contact with EDCs; Reduce body weight and toxin load with detox/body comp program</td>
</tr>
<tr>
<td>Phase I</td>
<td>Evaluate 2:16αOH; SNPs for CYP450 Enzymes</td>
<td>Increase cruciferous vegetable consumption (indole-3-carbinol), flax lignans, isoflavones, omega-3 fatty acids; Decrease omega-6 fatty acids</td>
</tr>
<tr>
<td>Protection</td>
<td>Evaluate 4OH and 16αOH</td>
<td>Increase antioxidants: vitamins E, A, and C, mixed carotenoids, biologinoids, selenium, curcumin, N-acetylcysteine, green tea catechins (polyphenols), lycopene, alpha-lipoic acid</td>
</tr>
<tr>
<td>Methylation</td>
<td>Check homocysteine levels; MTHFR SNP; 2-MeOHE</td>
<td>Folic acid, B12, B6, trimethylglycine</td>
</tr>
<tr>
<td>Excretion</td>
<td>Evaluate E levels</td>
<td>Lipotropic factors (choline, vitamins B6 &amp; B12, folic acid) for bile synthesis; Probiotics; Increase fiber &amp; decrease fat</td>
</tr>
<tr>
<td>Tissue Availability</td>
<td>Evaluate E levels</td>
<td>Phytoestrogens (lignans, isoflavones); Dietary factors such as fiber &amp; fat may influence</td>
</tr>
</tbody>
</table>
Acetaminophen Usage Patterns and Concentrations of Glutathione and γ-Glutamyl Transferase in Alcoholic Subjects

Charles F. Seifert, Pharm.D., FCCP, and Douglas C. Anderson, Pharm.D.

Study Objectives. To determine if subjects with chronic alcoholism are predisposed to acetaminophen-induced hepatotoxicity, and to determine the contributing factors.

Design. Prospective cohort study.


Subjects. One hundred eighty-eight subjects who answered "yes" to at least one of the four questions on the CAGE (Cut down-Annoyed-Guilty-Eye opener) questionnaire for identifying alcoholism, and 10 healthy volunteers (controls).

Conclusions. A significantly higher proportion of daily drinkers were regular (29.2% [43/154]) vs 11.8% [14/121], p=0.0497) as well as abusers (14.7% [5/34], p=0.0237) of acetaminophen compared with nondaily drinkers. Alanine transaminase (ALT) levels were significantly increased in subjects with depleted glutathione concentrations (2.33 mmol/L, 95% confidence interval [CI]: 1.74–2.69 mmol/L) compared with those of alcoholic subjects with normal GGT concentrations (5.97 mmol/L, 95% CI: 4.39–7.03 mmol/L, p=0.0001) and healthy volunteers (6.59 mmol/L, 95% CI: 4.79–9.65 mmol/L, p=0.0002). A significant inverse correlation was also noted between the GGT concentration and the plasma total glutathione concentration (r = -0.62, p<0.0001). None of the 188 subjects met all preset criteria for hepatotoxicity.

Conclusions. Daily drinkers were more than twice as likely as nondaily drinkers to be regular daily acetaminophen users and abusers. Alcoholic subjects with elevated GGT concentrations had significantly lower plasma total glutathione concentrations, and plasma total glutathione concentrations inversely correlated with GGT concentrations. Elevated GGT concentrations may be a clinical marker of depleted glutathione in alcoholic subjects. Acetaminophen-induced hepatotoxicity appears to be uncommon in alcoholic subjects, despite the 31.9% (60/188 patients) who took doses that are potentially hepatotoxic.

Key Words: acetaminophen, liver, glutathione, γ-glutamyl transferase, GGT, alcoholism, hepatotoxicity.


“Elevated GGT concentrations in serum may be a clinical marker of depleted glutathione in alcoholic subjects.”

Pharmacotherapy 2007; 27: 1473-82
Genes vs Environment

“The lifetime risk of breast cancer among female mutation carriers is presently 82%. Risks appear to be increasing with time. Before 1940 it was 24%. Lack of physical exercise and obesity in adolescence may be important modulating factors for risk in carriers.”
Epigenetics in Women’s Health Care

Some environmental changes that have been linked to epigenetic changes include starvation, folic acid, and various chemical exposures. There are periods in an organism's life cycle in which the organism is particularly susceptible to epigenetic influences; these include fertilization, gametogenesis, and early embryo development. These are also windows of opportunity for interventions during the reproductive life cycle of women to improve maternal-child health. Exposure to heavy metals and endocrine disruptors, such as bisphenol A and phthalates, has been shown to affect the epigenetic memory of an organism. Their long-term effects are unclear at this point, but many ongoing studies are attempting to elucidate the pathophysiological effects of such gene-environment interactions.
DNA methylation and histone modifications could be affected leading to large spatial and temporal changes in gene regulation. Other epigenetic processes, such as the influence of the ionic milieu around chromatin and DNA supercoiling stresses may be suspected also. The newly described role of microRNAs in control of gene expression is important by promoting or suppressing autoreactivity in AID. As a consequence control of cellular processes is affected becoming conducive, for example, to the development of autoreactive lymphocytes in systemic lupus erythematosus, synoviocyte proliferation in rheumatoid arthritis, or neural demyelination in multiple sclerosis. Application of epigenetics to AID is in its infancy and requires new hypotheses, techniques, tools, and collaborations between basic epigenetic researchers and autoimmune researchers in order to improve our comprehension of AID. From this will arise new therapeutics, means for early intervention, and prevention.
Phase II Catechol Estrogen Degradation

E2 & Estrone

CYP1A1

2-OHE1

CYP3A4

16α-OHE1 (carcinogenic)

4-OHE1

Quinones (carcinogenic)

Phase II Estrogen Excretion

COMT “methylated”

Protective Compound 2-methoxy-E1

reduced

Estriol

COMT “methylated” to 4-methoxy-E1

Neutralized to mercapturate

GST Neutralized
ROS overproduced by 4-OHE(2) increased the nuclear translocation of nuclear-factor kappaB (NF-kappaB) and its DNA binding through induction of IkappaB kinase alpha (IKKalpha) and IKKbeta activities.

...Low activity of COMT leads to higher levels of depurinating estrogen-DNA adducts that can induce mutations and initiate cancer.

Our study clearly indicates that COMT gene expression plays a critical role in modulating the hormonal and carcinogenic effects of E(2) and CEs and, consequently, modifies the risk for E(2)-induced endometrial cancer.

...The COMT genotype remained the most significant determinant for breast cancer development and was associated with a 4-fold increase in risk (95% confidence interval, 1.12-19.08).
Active Phase II Enzymes Subject to SNPs

• MTHFR: Methyltetrahydrofolate reductase
• COMT: Catechol-O-methytransferase
• NAT: N-acetyl transferase (fast/slow)
• GST: Glutathione S transferase
• SOD: Superoxide dismutase
• SULT: Sulfatase
• UGT: UDP-Glucuronyltransferase
Estrogen &
Phase II Detoxification

- **Sulfation**
  - Sulfated-estrogen hormones can have sulfate molecule cleaved off by sulfotransferase enzymes (SULT) --> estrogen activated

- **Methylation**
  - Production of 2-MeOH provides protection from dangerous estrogen metabolites
  - Test methylation adequacy by testing serum Hcy
  - Treat with B vitamins (B6, B12, folic acid)

- **Glucuronidation**
  - UDP-glucuronosyltransferase (UGT)
  - Glucuronidated estrogen passes through the bile
  - Bacteria producing B-glucuronidase, estrogen is reabsorbed
  - Adequate fiber and D-glucarate will improve glucuronidation and excretion of estrogens
What is the similarity and difference between:

- CAM / Anti-Aging Docs
- Functional Medicine Docs
- DABCI Docs
AI Disease

Key Points

• AI diseases are overlapping phenomena rather than distinct entities

• Approaching AI diseases as a maladaptive process rather than a consequence of bad genes opens the door to a wide range of treatment strategies

• Innate immunity plays a much larger role in AI disease than previously appreciated

• Tolerance to microbes plays a major role in maintaining tolerance to self

• In addition to defending against pathogens, the innate immune system responds to environmental triggers, including diet & toxins. This interaction occurs largely on epithelial & mucosal surfaces
Organ Reserve vs Thumbtacks

- Rest
- Exercise
- Health
- Supportive Relationships
- Healthy Diet
- Hormone Balance
- Clean Environment

- Insomnia
- Inactivity/Foggy Brain
- Illness / Chronic Infections
- GI Disorders/ Dysbiosis
- High Stress
- Poor Diet
- Insulin Resistance/ Obesity
- Toxic Environment
Foods That Modify Estrogen Metabolism

- Cruciferous Vegetables: Broccoli, Cabbage, Brussel/broccoli sprouts
- Fresh Greens & Vegetables (Assorted Colors)
- Herbs & Spices
- Legumes: Beans, Tofu, Soymilk, Miso, Tempeh, Steamed Soy Beans (Edamame), Garbanzo
- Fresh Fruit: Berries
- Raw Seeds & Nuts: Flax Seeds
- Whole Grains: Quinoa, Millet, Brown Rice or Rye Berries
- Quality Protein: Fish (Wild salmon, Haddock), Hormone-Free Grass-Fed Meats
- Oils: Flax Seed (ALA, Omega-3), Olive, Sesame
If It Looks Like A Brain...

“According to the US Department of Agriculture National Nutrient Database, walnuts also contain essential fatty acids as well as a number of other potentially neuroprotective constituents, including gamma-tocopherol (vitamin E), folate, melatonin, phytosterols, and numerous antioxidant polyphenols.”

Willis et al. Am J Clin Nutr 2009; 89(suppl):1602S-6S.
Foods High In Methionine

- Beans
- Legumes
- Onions
- Garlic
<table>
<thead>
<tr>
<th>Active</th>
<th>Per 3 T</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (from mixed carotenoids &amp; retinol)</td>
<td>2500 IU</td>
<td>Overall system support</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>200 IU</td>
<td>Overall system support</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>40 mcg</td>
<td>Bone support</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>50 mg</td>
<td>Methylation support; Neurotransmitter synthesis support</td>
</tr>
<tr>
<td>Folate (5-methyl THF, folate)</td>
<td>800 mcg</td>
<td>Methylation support</td>
</tr>
<tr>
<td>Vitamin B12 (methyl &amp; cyanocobalamin)</td>
<td>30 mcg</td>
<td>Methylation support</td>
</tr>
<tr>
<td>Isoflavones (red clover &amp; kudzu)</td>
<td>100 mg</td>
<td>Phytoestrogens, ER binding modulation, Enhances synthesis of SHBG</td>
</tr>
<tr>
<td>Curcuminoid Complex (95%)</td>
<td>210 mg</td>
<td>Chemopreventative</td>
</tr>
<tr>
<td>Rosemary Leaf Extract (5.1-7.6%)</td>
<td>200 mg</td>
<td>Chemopreventative</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>2 mg</td>
<td>Weak phytoestrogen; In vitro support of inhibition of DNA adduct formation; CYP3A 4 inhibitor</td>
</tr>
<tr>
<td>Trimethylglycine</td>
<td>200 mg</td>
<td>Methylation support</td>
</tr>
<tr>
<td>Chrysin</td>
<td>90 mg</td>
<td>Natural aromatase inhibitor; chemopreventative; CYP1A1 &amp; CYP1A2 inhibitor; increase glucuronidation by inducing UDP-glucuronosyltransferase 1A1 (UGT1A1), which might reduce the bioavailability of dietary carcinogens</td>
</tr>
</tbody>
</table>

www.naturaldatabase.com, Accessed 8/29/10
Nutritional Modulation of PGs

• Short term, PRN- Hops-based anti-inflammatory (Take with FOOD!)
• Long term- Replace high levels of arachidonic acid in cell membranes with the series-3 anti-inflammatory PG precursors, omega-3s.
• Provide series-1 anti-inflammatory PG precursors, gamma-linolenic acid (evening primrose, blank currant, & starflower oils)
Identifying Phytochemicals as SKRMS (Selective Kinase Response Modulators) that Influence Insulin Signaling
Nutritional Therapy to Balance Estrogen

How to deal with excess estrogen in the body:

• Balance (endogenous & exogenous) estrogen input
• Promote a healthy ratio of Phase I estrogen metabolites
• Protect cells from Phase 1 estrogen metabolites
• Promote healthy methylation (Phase II)
• Encourage healthy intestinal excretion
• Ensure balance bioavailability to tissues through SHBG & receptor tissue binding
Therapies for a Low 2:16-α OHE Ratio

- Cruciferous Vegetables (Broccoli, Cabbage, Cauliflower)
- Indole 3-Carbinol (I3C) or diindolymethane (DIM)
- Flaxseed (Lignans)
- Soy Isoflavones (Genistein, Daidzein)
- Fish Oils (Omega-3 Fatty Acids)
- Reduce Dietary Fat, Increase Dietary Fiber
- Rosemary, Kudzu, Turmeric
Estrogen Receptors (ERs)

• Estrogens bind to one of the two specific ERs, ER-α and ER-β
• ER-α and ER-β are products of different genes and exhibit tissue-and-cell-type specific expression
• When co-expressed, ER-β has an inhibitory action on ER-α mediated gene expression and in many instances opposes the actions of ERα
• Different forms of estrogen may bind to receptor differently, E2 most active
Estrogens

17β-estradiol (E2)

• Most potent estrogen
• Major estrogen secreted by the ovaries in premenopausal women
• Less available in postmenopausal women
• In postmenopausal women, E2 originates from E1 (reversible reaction) or from testosterone via aromatization in peripheral tissues such as adipose
• Stimulates growth and development of female reproductive tissues (breasts, vagina, uterus)
Estrogens

Estrone (E1)

- Estrone sulfate is the most abundant circulating estrogen in non-pregnant women
- E1-S is converted to estrone within estrogen target tissues such as ovary, placenta, skin, brain, endometrium, bone, & blood
- Predominant circulating estrogen in menopause; bound primarily to albumin rather than SHBG
- E1 is the second most potent estrogen after E2. It is made from either adrenal androstenedione via aromatization in peripheral tissues such as adipose, or from estradiol (reversible reaction)
- E1-S, estrone, and estradiol provide an approximation of total estrogenicity in the body
In summary, the inhibitory effects of Resv are the sum of three factors. One is the induction of NQO1 that provides a decrease in estrogen quinones and an increase in catechol estrogen. The second factor is the inhibition of CYP1B1 expression, which decreases the formation of 4-catechol estrogens. The third factor is the antioxidant properties of Resv that reduce the estrogen semiquinones to catechol estrogens, as indirectly determined in vitro.

Nature’s Color Wheel

- **Red**: Lycopene, Capsanthin
- **Yellow/Orange**: Beta-carotene, Beta-cryptoxanthin
- **White**: Allicin, Favorol
- **Green**: Chlorophyll, Lutein
- **Blue/Purple**: Anthocyanin, Quercetin
# White Phytochemicals

<table>
<thead>
<tr>
<th>Phytonutrient</th>
<th>Benefits</th>
<th>Found in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allicin*</td>
<td>Boosts immunity; helps lower high cholesterol; helps control high blood pressure; reduces the risk of heart attacks; reduces the risk for spread of cancer (particularly stomach and colon cancer)</td>
<td>Garlic, onions, leeks, scallions, chives</td>
</tr>
</tbody>
</table>
# Blue-Purple Phytochemicals

<table>
<thead>
<tr>
<th>Phytonutrient</th>
<th>Benefits</th>
<th>Found in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthocyanins*</td>
<td>Reduce the risk of cancer; powerful antioxidants; reduce the risk of age-related memory loss; help control high blood pressure; reduce the risk of diabetes complications; reduce the risk of heart attacks; reduce the risk of Alzheimer’s disease</td>
<td>Blueberries, blackberries, purple grapes, black currants, elderberries</td>
</tr>
<tr>
<td>Phenolics*</td>
<td>Powerful antioxidants; may slow some of the effects of aging.</td>
<td>Dried plums (prunes), raisins, plums, eggplant</td>
</tr>
</tbody>
</table>

*Provided by the National Cancer Institute, www.Saday.gov
# Yellow-Green Phytochemicals

<table>
<thead>
<tr>
<th>Phytonutrient</th>
<th>Benefits</th>
<th>Found in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutein* /Zeaxanthin</td>
<td>Helps maintain good vision; reduces the risk of cataracts or macular degeneration.</td>
<td>Kale, spinach, leafy greens (turnip, collard, mustard), romaine lettuce, broccoli, green peas, kiwifruit, honeydew melon</td>
</tr>
<tr>
<td>Indoles*</td>
<td>Reduce the risk of cancer (particularly breast and prostate cancers); reduce the risk of tumor growth in cancer patients.</td>
<td>Broccoli, cabbage, brussels sprouts, bok choy, arugula, Swiss chard, turnips, rutabaga, watercress, cauliflower, kale</td>
</tr>
<tr>
<td>Chlorophyll</td>
<td>Powerful antioxidant</td>
<td>All green vegetables</td>
</tr>
<tr>
<td>Folate</td>
<td>Methylation; cell growth.</td>
<td>Leafy greens</td>
</tr>
</tbody>
</table>

*Provided by the National Cancer Institute, www.Saday.gov*
# Orange phytochemicals

<table>
<thead>
<tr>
<th>Phytonutrient</th>
<th>Benefits</th>
<th>Found in</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-carotene</strong></td>
<td>Powerful antioxidant; boosts immunity; reduces risk for cancer; reduces risk of heart attacks; helps maintain good vision.</td>
<td>Carrots, sweet potatoes, pumpkin, butternut squash, cantaloupe, mangos, apricots, peaches</td>
</tr>
<tr>
<td><strong>Bioflavonoids</strong></td>
<td>Powerful antioxidants; Works with vitamin C to reduce the risk of heart attacks, reduce the risk of cancer, and to help maintain strong bones/teeth, healthy skin, and good vision.</td>
<td>Oranges, grapefruit, lemons, tangerines, clementines, peaches, papaya, apricots, nectarines, pears, pineapple, yellow raisins, yellow pepper</td>
</tr>
</tbody>
</table>

*Provided by the National Cancer Institute, www.Saday.gov
## Red phytochemicals

<table>
<thead>
<tr>
<th>Phytonutrient</th>
<th>Benefits</th>
<th>Found in</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lycopene</strong></td>
<td>Reduces the risk of prostate, breast, and skin cancer; reduces the risk of heart attacks</td>
<td>Tomato-based products (tomato juice, spaghetti sauce, tomato soup, tomato paste), watermelon, pink grapefruit, fresh tomato, guava</td>
</tr>
<tr>
<td><strong>Anthocyanins</strong></td>
<td>Reduce the risk of cancer; powerful antioxidants; help control high blood pressure; reduce the risk of diabetes complications; reduce the risk of heart attacks, reduce the risk of Alzheimer’s disease</td>
<td>Red raspberries, sweet cherries, strawberries, cranberries, beets, red apples (with skin), red cabbage, red onion, kidney beans, red beans</td>
</tr>
<tr>
<td><strong>Astaxanthin</strong></td>
<td>Potent antioxidant, particularly for the liver; Gastroprotective effects; Immune stimulant; Chemoprotectant.</td>
<td>Microalgae, yeast, salmon, trout, krill, shrimp, crayfish, crustaceans,</td>
</tr>
</tbody>
</table>

*Provided by the National Cancer Institute, www.5aday.gov*
Clinical Takeaways: AI Disease

• Address Underlying Inflammation
  • Remove Offenders
    • Diet (Gluten, Casein, Allergens)
    • Toxins
    • Stress
  • Reduce Inflammation with Safe, Effective, Anti-inflammatory Nutrients
    • Anti-inflammatory Medical Food Powder
    • Fish Oils
    • Probiotics
    • Vitamin D
    • Phytonutrients
• Examine Estrogen / Androgen Metabolites
Treatment of AI Disease

- Remove Neuro-Endocrine Disruptors
- 4 Rs
- Gluten-Free Casein-Free Mediterranean Diet
- Supplements as Indicated by Testing
  - Omega 3
  - Magnesium
  - Dhea
  - Anti-Inflammatory Herbs
  - Proteolytic Enzymes
  - Probiotics
  - Nrf2 Mod
  - Vitamin D
  - Iodine
  - Thyroid / Progesterone
  - Methylfolate/B12
  - MSM,
  - Hyaluronic Acid
  - Glucosamine...
VISCERAL EVALUATION

GB
GE
F
PY
SO
DJF
ICV
Case Study

Shenelle
Age 24

- Diagnosed 4 years ago with Grave’s
- 4 years Methimazole 20mg 2xday
- 2/2011 Presented with medium goiter, extreme fatigue, anxiety, dysmenorrhea, off meds while waiting for radioactive iodine
- Free T3 was 7.3
- Thyroid Peroxidase was >600
- Cortisol was 4.2
- Total Cholesterol was 102
- ANA was 1:1280 speckled pattern
- Mother has just diagnosed with RA (was told she had fibromyalgia)
Shenelle
Age 24

- GFCF Anti-Inflammatory food plan with increase fat (fish + egg yolk)
- Potassium iodine, Herbal remedies (Bladderwrack, Curcumin, Kudzu, Rosemary)
- EPA/DHA, Anxiety support
- Adrenal support- Thyroid & Adrenal
- Methimazole 20mg x2 on 3/2011
- Methimazole 5mg x2 on 6/2011 (her Free T3 is now 2.3)
- 6/2011 Goiter 60% gone, did not have to give natural progesterone which I usually give to older Grave’s patients, & her cycles are regulating
- Thyroid, Cortisol, Cholesterol tested every 5 weeks
Shanon C
38 y/o Female

- Recurrent multiple kidney stones bilat since age 9
  Passing stones monthly – 6 lithotripsy– 3 extractions
  Exacerbation with each pregnancy, Over 60 KUB
- IBS onset age 30
- HBP onset age 20 – Propanolol 10mg
- Migraines with PMS- daily Excedrin
- Esophageal birth defect corrected 2007
Case Study

Shanon C
02/03/2009

- Severe kidney pain, nausea, vomiting, diarrhea, migraine, reflux, generalized pain.
- 25 lbs overweight
- SAD diet
- Pulse 90
- BP: 130/80
- Abdomen: All Quadrants tender
Shanon C
Initial visit 01/15/2009

- Positive ANA 1:320 speckled
- BUN: 17 (5-18)
- Creatinine: 0.99 (.4-1)
- Free T3: 2.6 TSH: 0.9
- Potassium: 5.1
- Eosinophils: 7.9
Shanon C

- Gluten free / dairy free Autoimmune diet
- Kidney stones: Taurine, Magnesium, Malic acid, Vitamin D, Herbal kidney mix
- IBS: Probiotics, GI herbal support, Bentonite, fish oils, visceral manipulations.
- Last lithotripsy March 2009 for old stones (was scheduled in January)
- Last Excedrin taken January 20th 2009
Case Study

Shanon C

- Last Excedrin taken January 20th 2009
- Last lithotripsy March 2009 for old stones in the Kidneys, not Ureters (was scheduled in January)
- KUB in May 2009 no new stones
- Next KUB scheduled in November 2009
- Patient compliant with supplementation
- 50 % compliance on diet (Back on Gluten but still dairy free)
AI Disease: A Maladaptive Process?

Definition of Intelligence: “Faculty of adapt”

“...ability to adapt effectively to the environment, either by making a change in oneself or by changing the environment or finding a new one... intelligence is not a single mental process, but rather a combination of many mental processes directed toward effective adaptation to the environment.”

-Encyclopedia Britannica
Are Women Not Adapting?

1. We have to adapt our environment to us
2. We have to adapt ourselves to our environment
Adapt Our Environment to Us

Public Health Changes

- Education in Nutrition (school/work)
- Food Labeling (GMO/Organic)
- Research in Immune & Neuro Endocrine Disruptors
- Food Grading
- Environmental Activism
- Gene Hygiene
Adapt Ourselves to Our Environment

Personal Changes

- Hectic schedules / Stress
- Less is More
- Part Time Employment
- Make Time for Exercise / Fun / Nature
- One or Both Partners Must Cook
- Teach Kids to Cook
Peace

Non Peace
The sooner the ratio is reversed, the better for mankind and the planet.
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A PDF of this presentation is available at:
DrWellhausen.com/DC