

A-Z of Anti-Aging



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GPCME Conference – June 2012 – Rotorua



What's your plan to stop aging?



We Begin to Age the Moment We are Born...

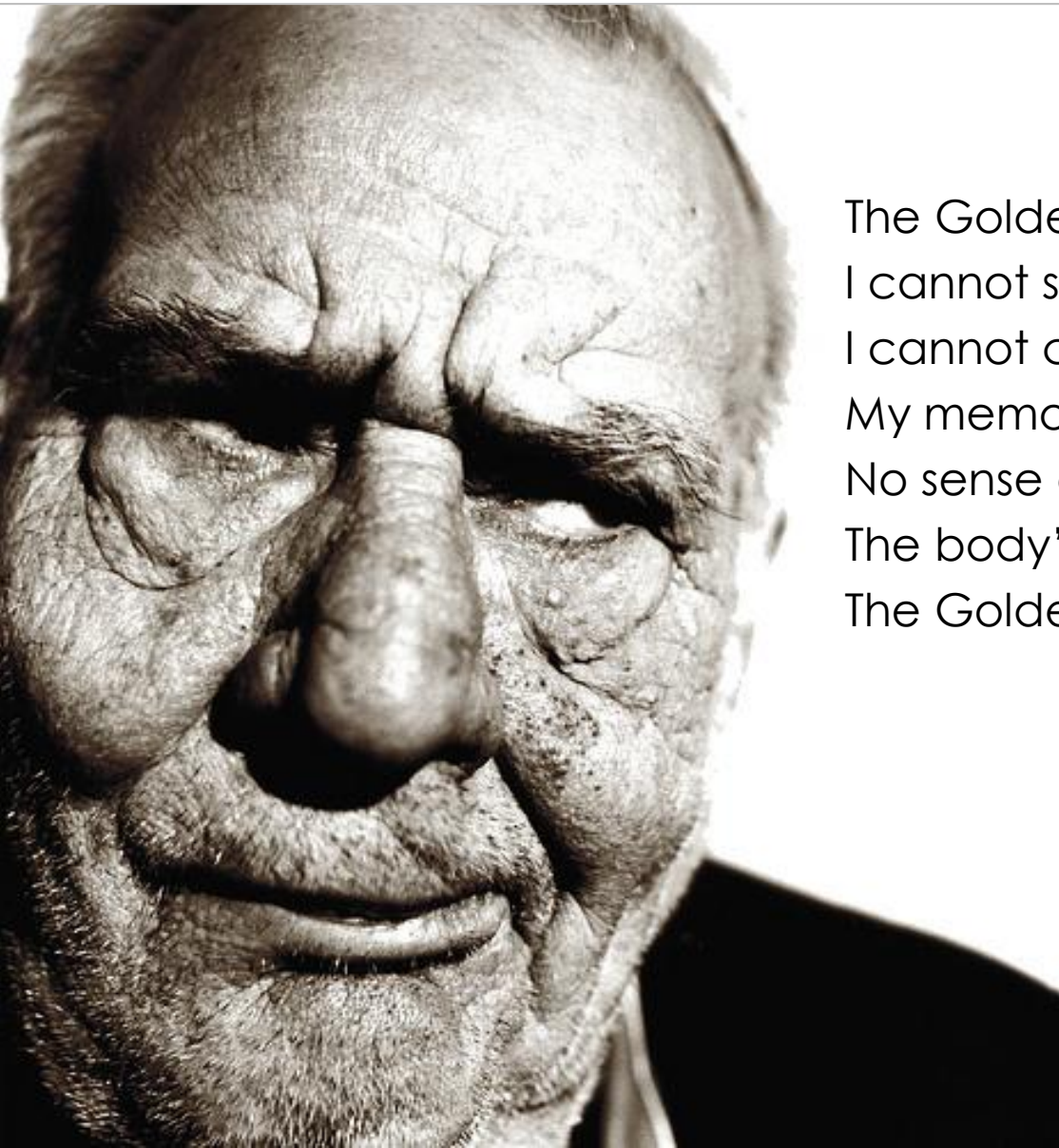


And, Time Sure Does Fly...



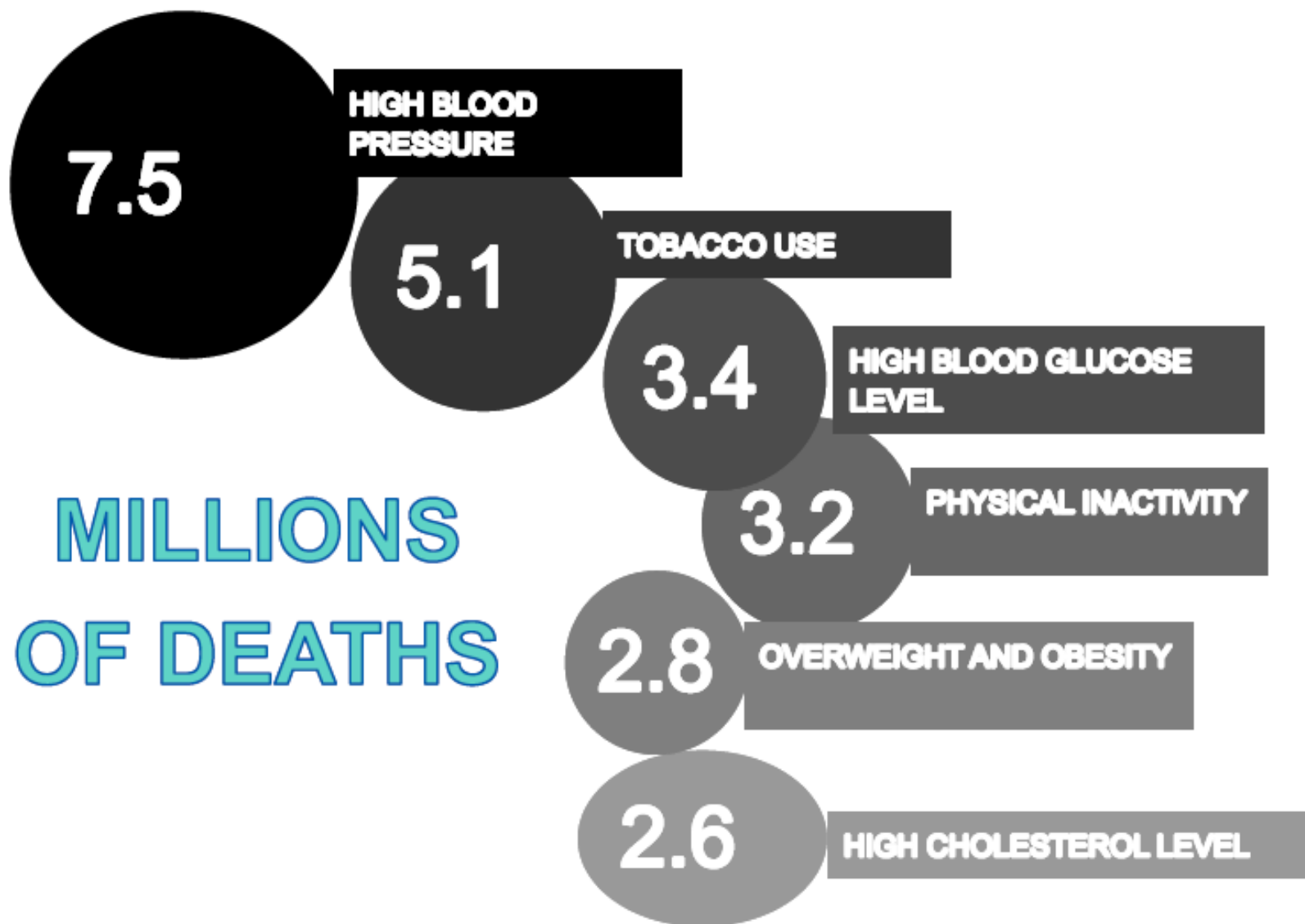


The Good 'Ole Golden Years...



The Golden years have come at last
I cannot see, I cannot pee
I cannot chew, I cannot screw,
My memory shrinks, my hearing stinks,
No sense of smell, I look like hell,
The body's drooping, got trouble pooping,
The Golden years have come at last...







Evidence of Failure

- Increases in incidence of obesity and diabetes and cardiovascular disease
- Childhood obesity, **1000% increase in type 2 diabetes**
- Increase in allergic, autoimmune, and inflammatory disorders
- Increase in digestive disorders (GERD)
- Increases in cancer incidence
- **Decrease in life expectancy of 2-5 years**



ORIGINAL ARTICLE

Long-Term Effects of Intensive Glucose Lowering on Cardiovascular Outcomes

The ACCORD Study Group*

ABSTRACT

BACKGROUND

The members of the writing group (Hertzel C. Gerstein, M.D., McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada; Michael E. Miller, Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Saul Geethu, M.D., Case Western Reserve University, Cleveland; Thomas A. Gaziano, M.D.,

Intensive glucose lowering has previously been shown to increase mortality among persons with advanced type 2 diabetes and a high risk of cardiovascular disease. This report describes the 5-year outcomes of a mean of 3.7 years of intensive glucose lowering on mortality and key cardiovascular events.

METHODS

As compared with standard therapy, the use of intensive therapy [glucose lowering] ...increased 5-year mortality. Such a strategy **cannot be recommended for high-risk patients with advanced Type 2 diabetes.**

N Engl J Med 2011;364:818-28.

N Engl J Med 2011;364:818-28.
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Diabetes and Insulin Resistance

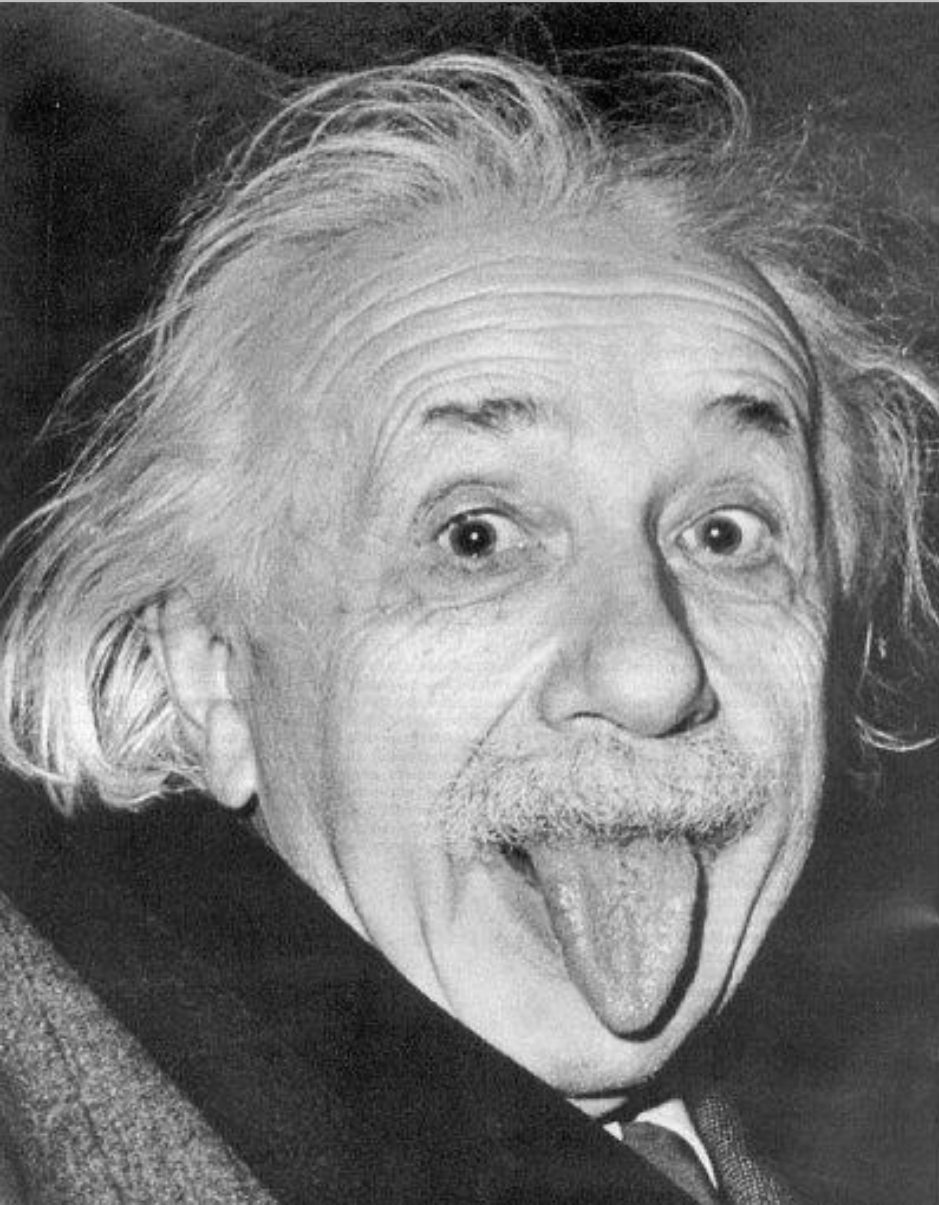
- Not a disease but a **systemic disorder**
- Multi-factorial etiology
- Treat causes or downstream symptoms?
- ACCORD study N Engl J Med. 2008 Jun 12;358(24)2545-59.
 - 10,000 diabetics intensive glucose control
 - Intensive treatment group had more deaths and heart attacks
- NAVIGATOR TRIALS: No benefit to risk factor reduction
- N Engl J Med. 2010 May 6;362(18):1748.



- Metaanalysis: statins increase risk of type 2 diabetes
 - 5 RCTs 32,752 non-diabetic participants follow-up of 4.9 years
 - 8.4% increase in diabetes
 - Worse in intensive dose patients
 - New ATP III guidelines – 40 million rx statins
 - **> 3.5 million new diabetics???**
 - JAMA. 2011;305(24):2556-2564.
- Women's Health Initiative:
 - **Statins increase diabetes risk 48%**
 - Arch Intern Med. 2012 Jan 23;172(2):144-52.



A Wise Man Once Said...



“We cannot solve our current problems with the same thinking we used to create them.”

-Albert Einstein



Traditional vs. Anti-Aging Medicine...

- Traditional medicine

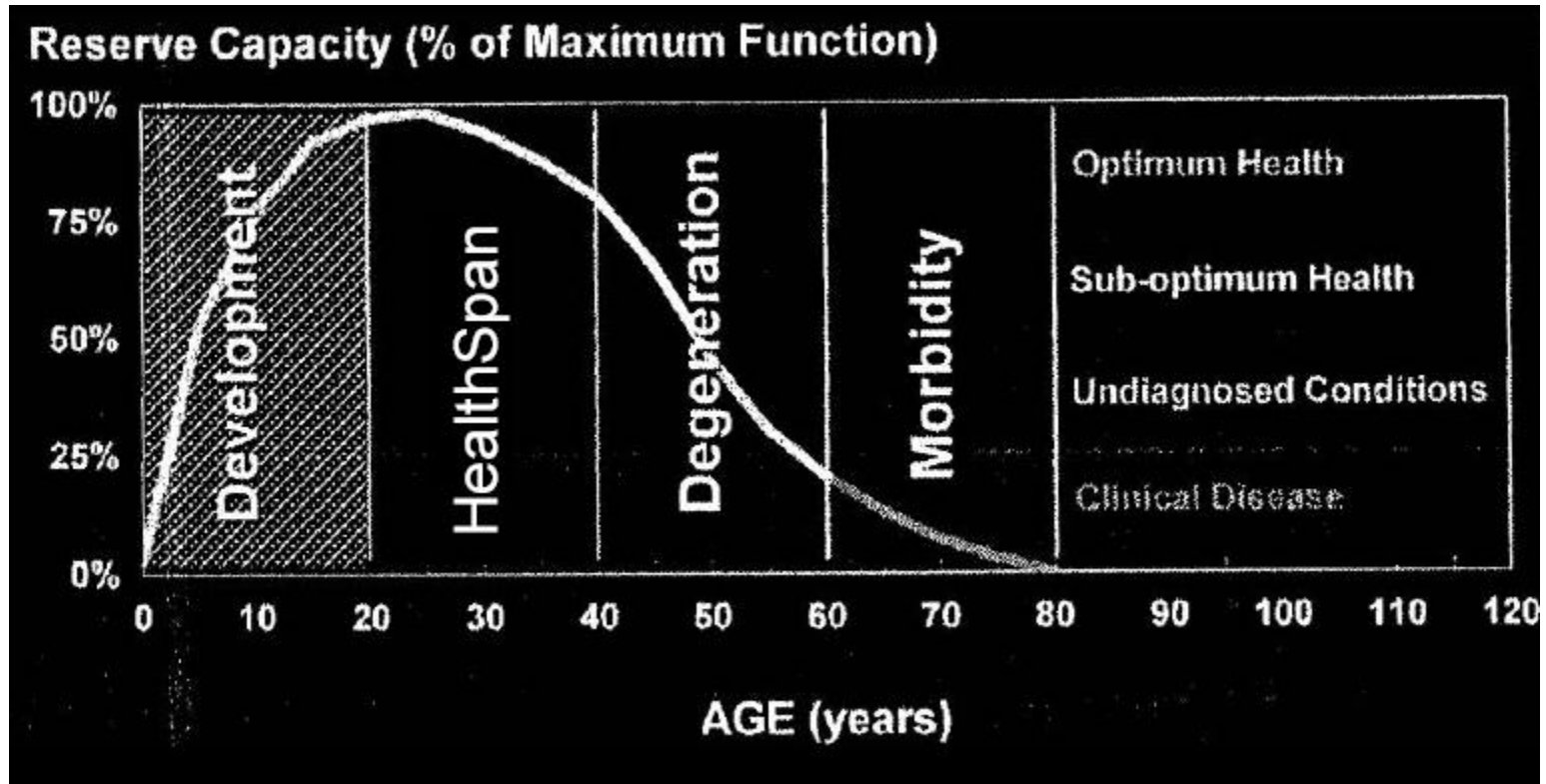
We can treat the outcomes of aging

- Anti-aging medicine

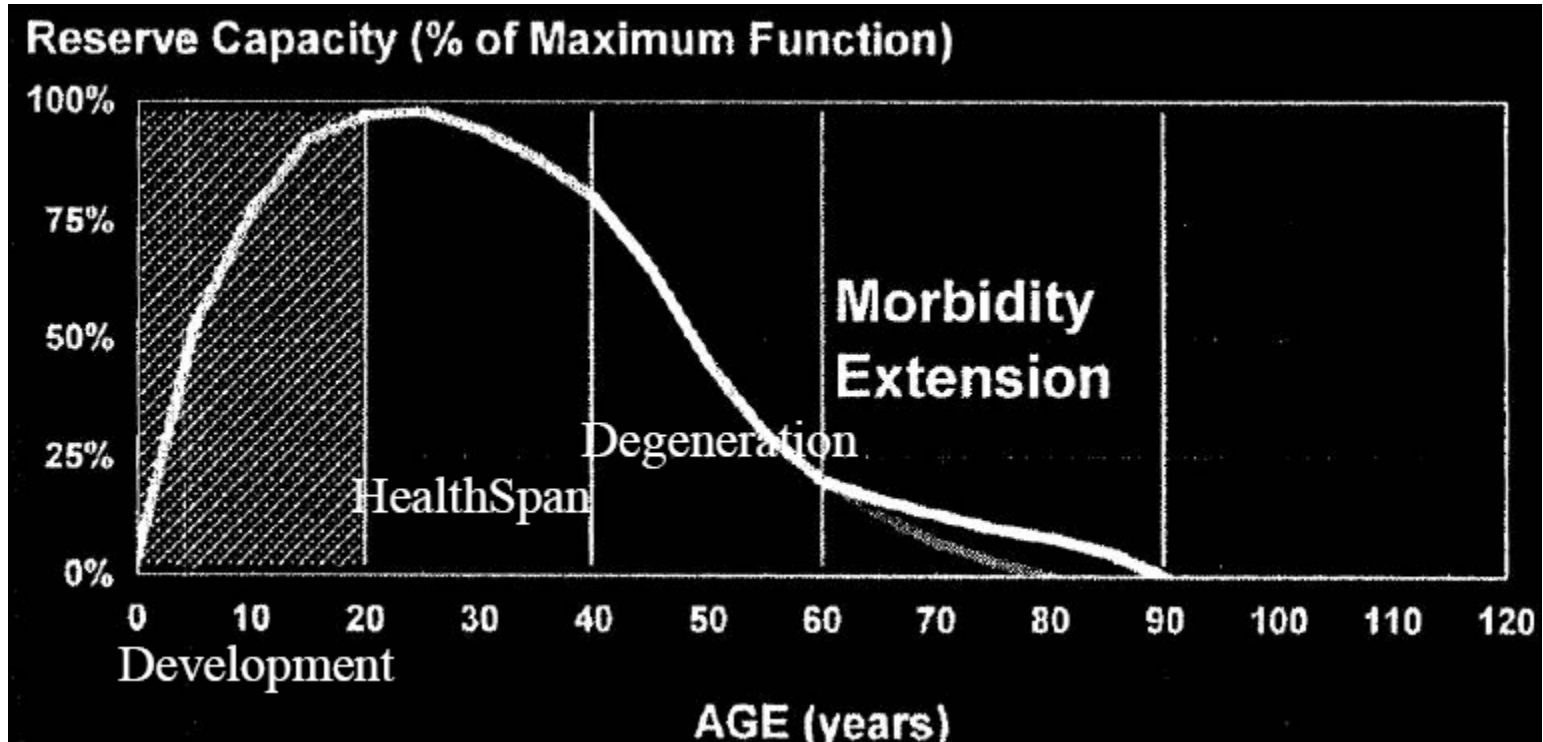
*We can change the **process** of aging in the first place*



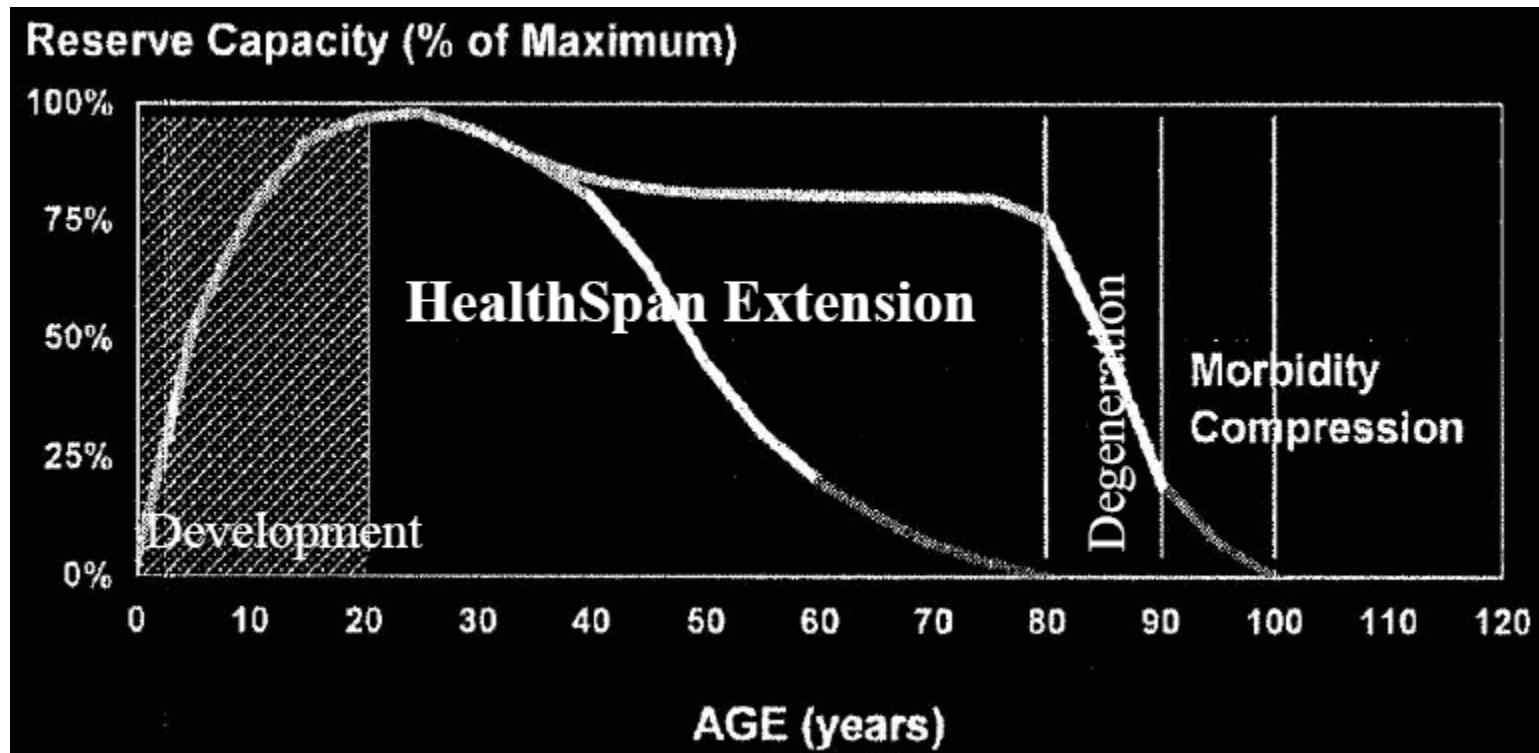
The HealthSpan Curve...



“Conventional Medicine” Prolongation of Morbidity...



Goal of Anti-Aging Medicine HealthSpan Extension, Morbidity Compression...



AAM maximizes chronological longevity while minimizing biological aging.



*Prevent the preventable &
delay the inevitable.*



3 Simple Rules to AAM...



1. Don't get sick.

2. Don't get old.

3. Don't die.



Anti-Aging Medicine IS...



- Optimal lifestyle documented by medical data
- Utilization of cutting edge technologies to detect, prevent & treat aging related disease
- Scientific
- Evidence Based
- Well Documented by peer-reviewed journals.



Anti-Aging Medicine is NOT...



- Reliant on Growth Hormone replacement therapy
- A type of “alternative” medicine
- Cosmetic medicine
- Elite medicine



Instead of Treating & Trying to Prevent...

- Coronary heart disease
- Cancer
- Dementia
- Insulin resistance (type II diabetes)
- Degenerative arthritis
- Degenerating body composition
- Osteoporosis
- Immune system decline
- Loss of libido & sexual function



Why not treat the cause?

Could there be one unifying cause?

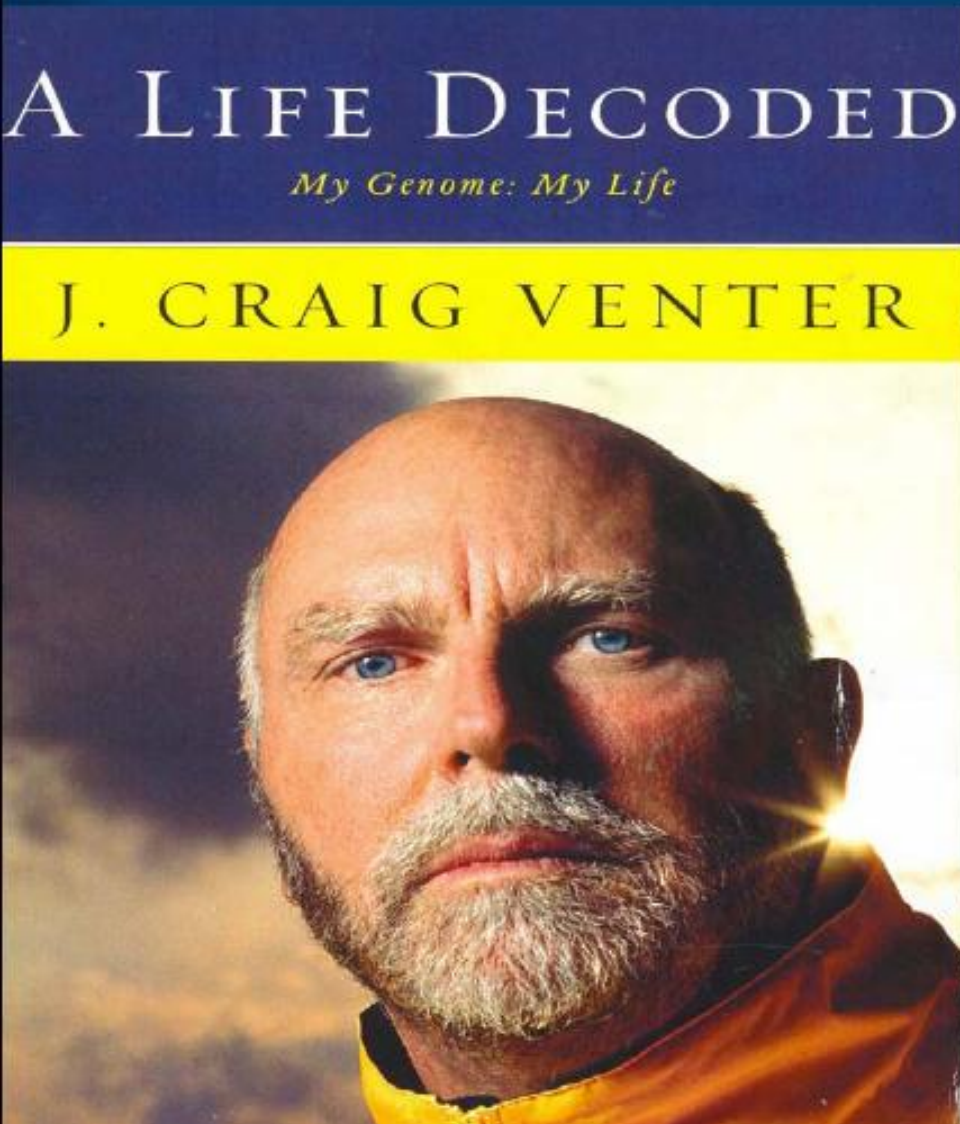


The Outcomes:

- Heart Disease Treatment in the USA
- 1.3 m angioplasties, \$48k each, \$60B in 2006
- 448,000 bypass, \$100k each, \$44B in 2006
- **Angioplasties and stents do not prolong life or** prevent heart attacks in stable patients (95% of those who receive them).
- N Engl J Med 2007 and JAMA recent JAMA article
- Bypass surgery prolongs life in less than 3% AND
- **Changing lifestyle could prevent at least 90% of all heart disease.**
- Lancet. 2004 Sep



What We Learned From the Human Genome Project



- The genome has far fewer genes than anticipated (20,000+)
- The variation of the genes is far greater than anticipated (3 million+ SNP's)
- Our phenotype results from genes and environment that works through our epigenome

Genetics? Exposome vs. Genome

- GWAS
 - Genome wide association studies
 - Less than 10% of risk
- Epigenetics
 - Prenatal – fetal origins of adult disease
- Early childhood programming and CVD and Diabetes
- The Lancet, Volume 378, Issue 9786, 9–15 July 2011, Pages 169-181



21st Century Medicine

- Emergence: How genes are translated into our health and disease patterns
- Exposome: How internal metabolic factors and environment influences on our gene expression
- Epigenetics: How our environment shapes our structure and function
- Nutrigenomics: How nutrients and phytochemicals speak to our genes
- Sociomics: How social networks influence health and disease



Chronic disease results from the *emergence* of a disturbed metabolism

Lifestyle and environment are the major factors altering gene expression that results in disturbed metabolism.



Recurrent Themes in Anti- Aging Medicine...

- Control of Inflammation (Cytokines, CRP)
- Control of Eicosanoid Hormones
- Control of Glucose & Insulin
- Control of Free Radicals, Homocysteine & AGE's
- Prevent & repair DNA damage
- Prevention of decline of Neuro-Endocrine-Immune system



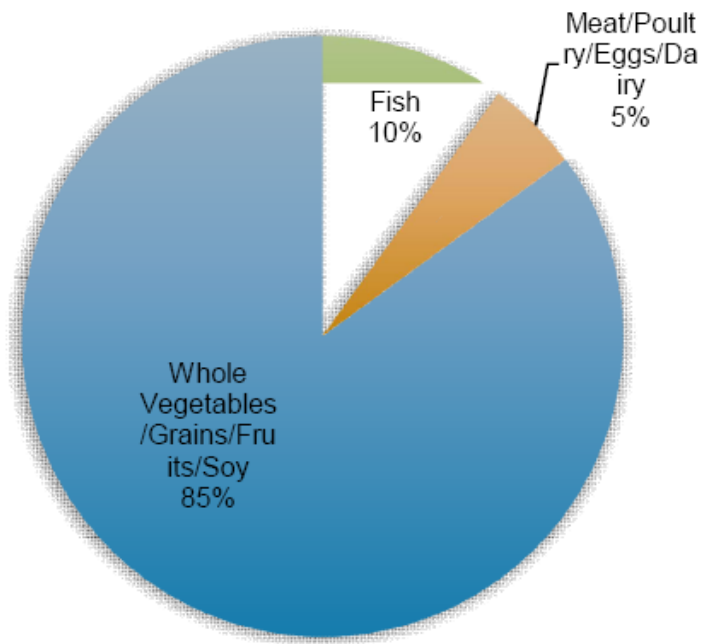
Lifestyle...

- 1st treatment in anti-aging medicine
- Diet, exercise, stress reduction
- Health does not come out of a pill or an injection

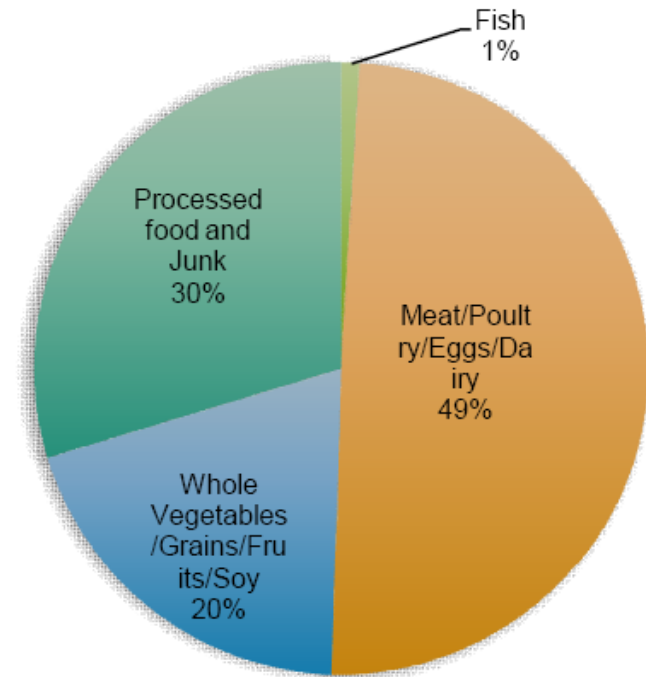


Eating... Pie Chart...

The Low Risk Eastern Way



The Western Way



Anti-Aging Medicine...

- “Zone” type diet
 - 40% carbohydrate*
 - 30% protein*
 - 30% fat*
- Less insulin secretion, fat storage, less glycation, inflammation
- No carbohydrate cravings
- Add omega-3 high dose fish oil for Eicosanoid control



-Cezanne



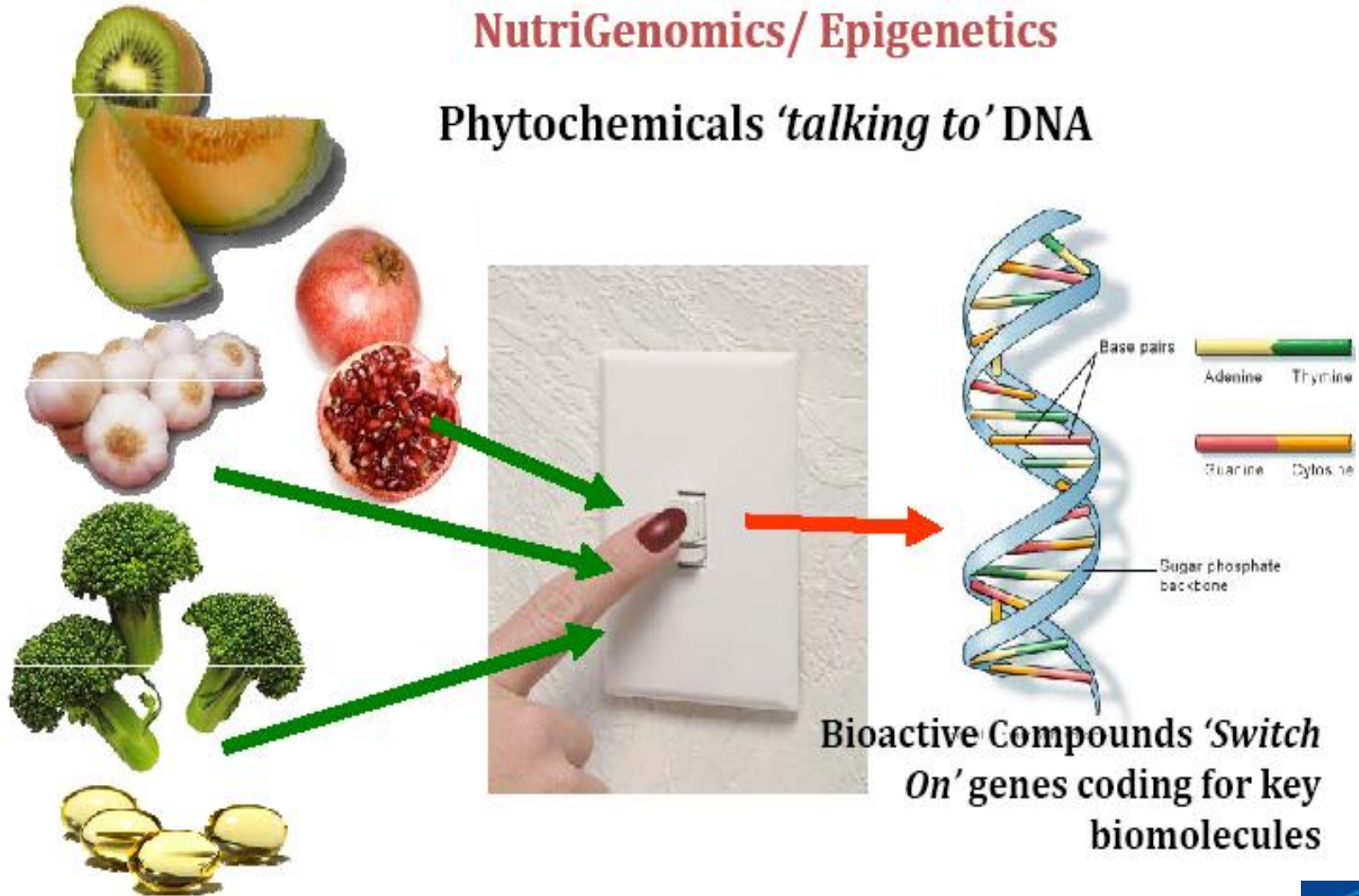
Zone Nutrition...

- Lifestyle not a diet
Diets don't work
- Easy to follow from gourmet restaurant to fast food
- Less insulin secretion
Less insulin resistance
Decreased fat storage
Improved lipid profile
Favourable Eicosanoid hormone balance
Vasodilation vs. constriction
Anti-inflammatory vs. inflammation



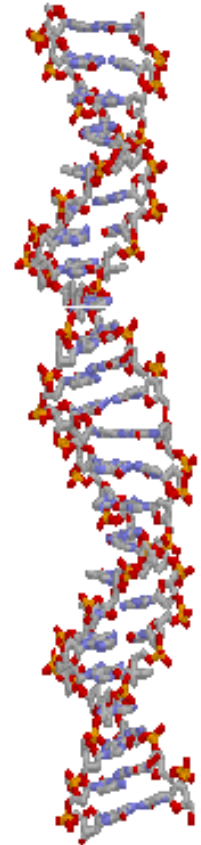
NutriGenomics/ Epigenetics

Phytochemicals *'talking to'* DNA



Transcription – Factor Pathways Mediating Nutrient–Gene interactions

Nutrient	Compound	Transcription factor
<i>Macronutrients</i>		
Fats	Fatty acids Cholesterol	PPARs, SREBPs, LXR, HNF4, ChREBP SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
<i>Micronutrients</i>		
Vitamins	Vitamin A	RAR, RXR
	Vitamin D	VDR
	Vitamin E	PXR
Minerals	Calcium	Calcineurin/NF-ATs
	Iron	IRP1, IRP2
	Zinc	MTF1
<i>Other food components</i>		
	Flavonoids	ER, NFkB, AP1
	Xenobiotics	CAR, PXR

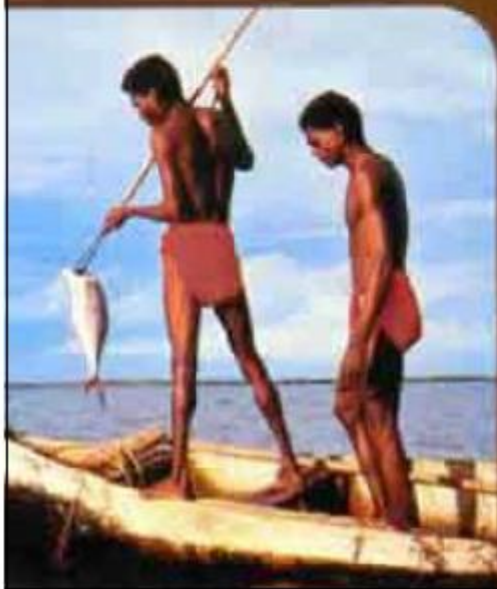


Muller M, Kersten S. Nat Rev 2003;4:315-322.





AUSTRALIAN ABORIGINES



Calorie Restriction



Full text article at
www.annalsnyas.org

Caloric restriction in primates and relevance to humans.

Roth GS, Ingram DK, Lane MA.

Laboratory of Neurosciences, Gerontology Research Center, National Institute on Aging,
National Institutes of Health, Baltimore, Maryland 21224, USA. geor@vax.grc.nia.nih.gov

Dietary caloric restriction (CR) is the only intervention conclusively and reproducibly shown to slow aging and maintain health and vitality in mammals. Although this paradigm has been known for over 60 years, its precise biological mechanisms and applicability to humans remain unknown. We began addressing the latter question in 1987 with the first controlled study of CR in primates (rhesus and squirrel monkeys, which are evolutionarily much closer to humans than the rodents most frequently employed in CR studies). To date, our results strongly suggest that the same beneficial "antiaging" and/or "antidisease" effects observed in CR rodents also occur in primates. These include lower plasma insulin levels and greater sensitivity; lower body temperatures, reduced cholesterol, triglycerides, blood pressure, and arterial stiffness, elevated HDL; and slower age-related decline in circulating levels of DHEAS. Collectively, these biomarkers suggest that CR primates will be less likely to incur diabetes, cardiovascular problems, and other age-related diseases and may in fact be aging more slowly than fully fed counterparts. Despite these very encouraging results, it is unlikely that most humans would be willing to maintain a 30% reduced diet for the bulk of their adult life span, even if it meant more healthy years. For this reason, we have begun to explore CR mimetics, agents that might elicit the same beneficial effects as CR, without the necessity of dieting. Our initial studies have focused on 2-deoxyglucose (2DG), a sugar analogue with a limited metabolism that actually reduces glucose/energy flux without decreasing food intake in rats. In a six-month pilot study, 2DG lowered plasma insulin and body temperature in a manner analogous to that of CR. Thus, metabolic effects that mediate the CR mechanism can be attained pharmacologically. Doses were titrated to eliminate toxicity, a long-term longevity study is now under way. In addition, data from other laboratories suggest that at least some of the same physiological/metabolic end points that are associated with the beneficial effects of underfeeding may be obtained from other potential CR mimetic agents, some naturally occurring in food products. Much work remains to be done, but taken together, our successful results with CR in primates and 2DG administration to rats suggest that it may indeed be possible to obtain the health- and longevity-promoting effects of the former intervention without actually decreasing food intake.

Publication Types:

* Review



Resveratrol...

- Resveratrol (3,5,4'-trihydroxystilbene) extends the lifespan of diverse species including:

Saccharomyces cerevisiae

Caenorhabditis elegans

Drosophila melanogaster

- In these organisms, lifespan extension is dependent on Sir2, a conserved deacetylase proposed to underlie the beneficial effects of caloric restriction.



Harvard study...



- Old mitochondria emit more free radicals, while the new ones convert energy in cells more cleanly (Like changing your old car for a powerful & environmentally friendly hybrid model).
- Resveratrol activates the anti-aging gene (SirT-1) which is normally activated by calorie restriction. A reported 31% increase in small mammal life span.



Physical Activity & Ageing...



Sarcopenia- muscle loss with ageing- is multifactorial with contributing factors that may include:

Loss of alpha-motor neuron input

Changes in anabolic hormones

↓ intake of dietary protein

↓ in physical activity



Muscle Mass Maintenance Recommendations...



- Protein requirements in older people should be maintained above 1 g/kg/d.
- Physical activity can significantly assist in reversing this deficit and may improve the regeneration potential of muscle fibre- as of skeletal muscle mass in elderly people.



Exercise...



- Can be 10-20 years younger than biological age with regular exercise: aerobic, anaerobic, flexibility
- Exercise promotes longevity & compression of disability into fewer years (Vita, *NEJM* 1998 Apr)
- ↑ production of GH
- ↑ Sense of well being & cognition
- ↓ Inflammation, CRP



Exercise, Antioxidants & Inflammation...

- Strenuous exercise increases inflammation, TNF-alpha & IL-1beta & IL-6.
- Trained athletes have less inflammatory response.
- Antioxidant treatment for 60 days eliminated increase in inflammatory markers.

Vassilakopoulos T et al. Antioxidants attenuate the plasma cytokine response to exercise in humans J Appl Physiol. 2003 Mar;94(3):1025-32.





“Every time I think of exercise, I lie down until the feeling passes.”

-Oscar Wilde



L-Carnitine/Physical Activity...

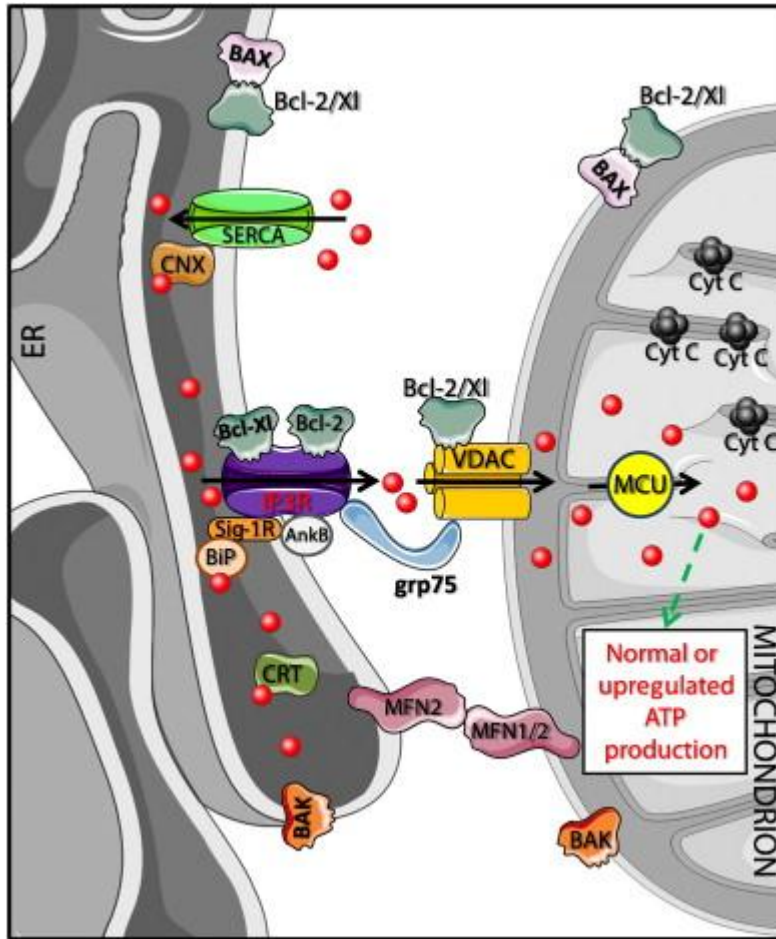
Old Rats

- Moderate physical exercise was effective in (a) limiting fat mass gain and (b) inducing an increase in the capacities of the soleus to oxidize fatty acids.
- Supplementation with L-carnitine at 30 mg/kg body weight for 12 weeks.
- Allowed the restoration of L-carnitine level in muscle cells.
- Restored muscle oxidative activity in the soleus.
- Induced positive changes in body composition:
 - ↓ *abdominal fat mass*
 - ↑ *muscle capabilities without any changes in food intake.*

J Gerontol A Biol Sci Med Sci. 2008;63(10):1027-33.



Maintaining Energy through Life...

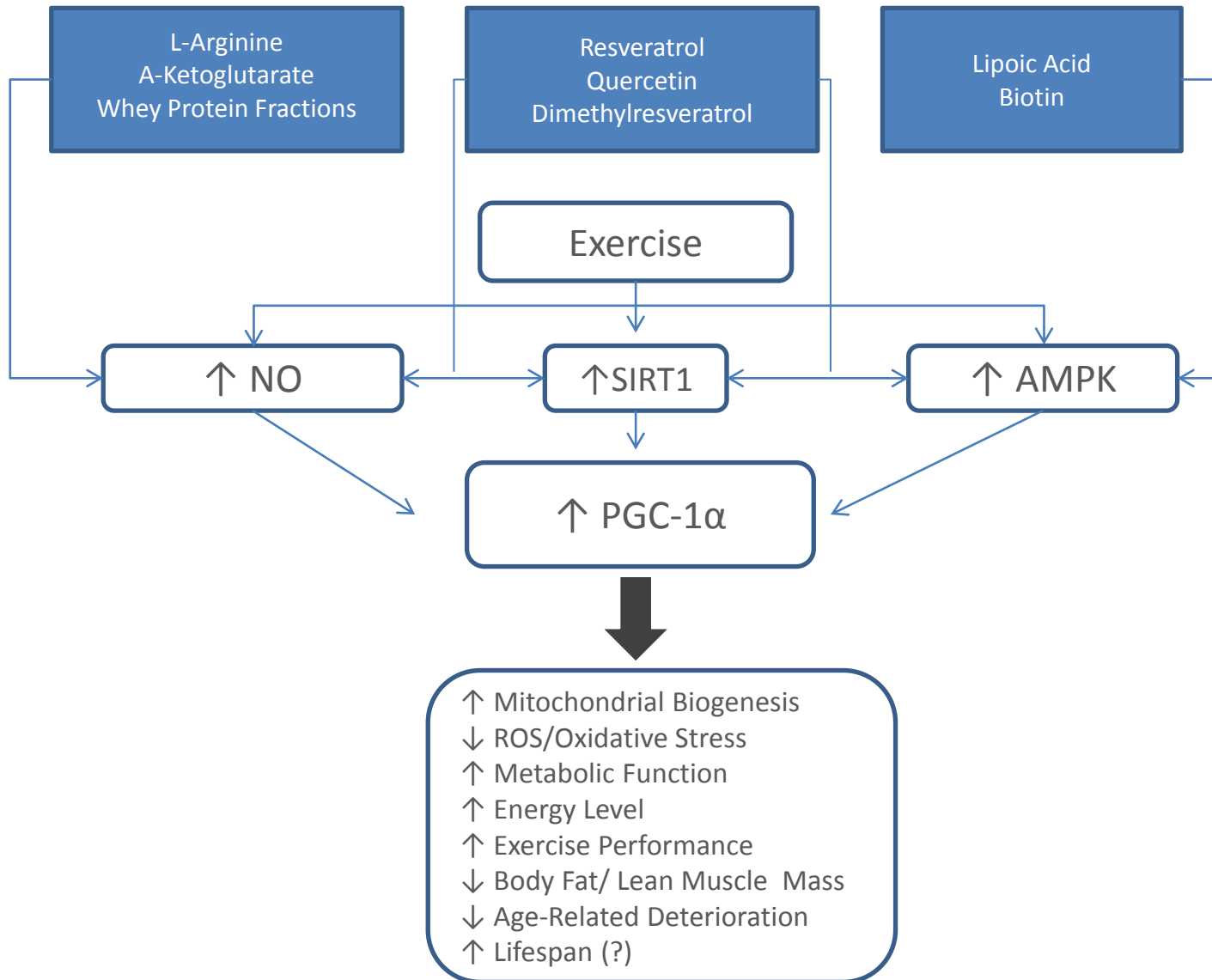


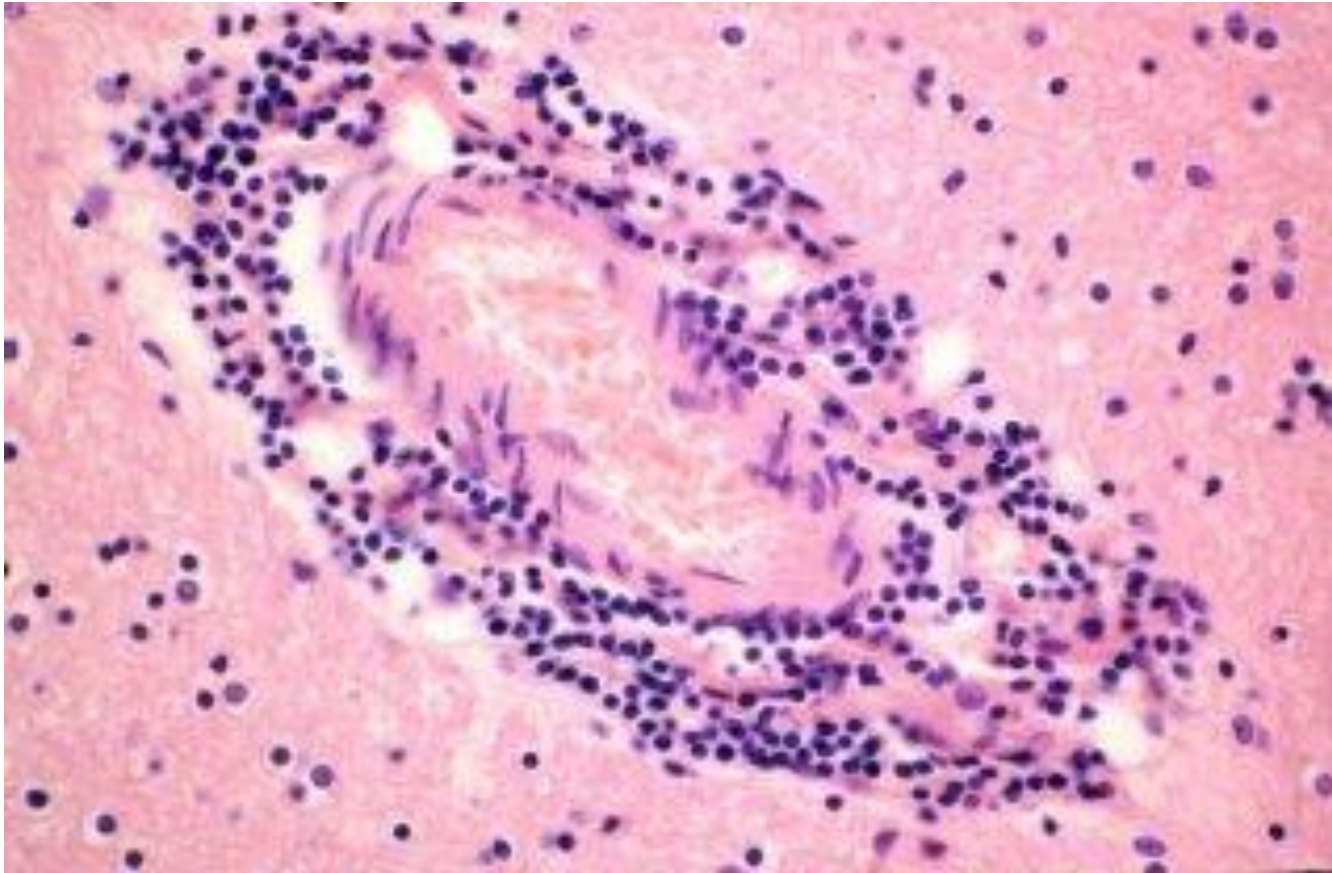
The Mitochondria Connection

- Produce useable energy in the form of ATP
- Exercise increases mitochondrial function & [mitochondrial biogenesis](#)
- Repeated metabolic demand on skeletal muscle activates PGC-1 α



Nutritional Supplement Approach to Stimulate Mitochondrial Biogenesis...





Chronic Inflammation



Unified Theory of Wellness...

- Chronic Inflammation is the cause & the effect of illness & the diseases of aging
- Anti-inflammation = Wellness



Inflammation Can Save Your Life...



- Acute inflammation is the body's response to injury or serious illness, infection, or stress (threat of serious injury etc.)
- Cytokines are released to defend the body



If a Shark Bites You, You Need Inflammation Right Now...



- Blood vessels constrict to stop bleeding
- Fibrinogen & clotting factors increase to stop bleeding
- White blood cells fight infection
- Pain reminds you “Don’t swim with sharks”



Acute inflammation keeps us alive,
Chronic inflammation kills us slowly,

*Why do we have all this inflammation
anyway?*



Antagonistic Evolutionary Benefit...

- What helped our Palaeolithic ancestors make it to reproductive age...is killing us now
- Insulin Resistance- helped store fat & survive famine
- Anti-inflammation resistance- helped survive acute infectious disease & trauma



Antagonistic Evolutionary Benefit...

- Lifestyle difference
- Today in NZ: sedentary, high carb, lower infections, stress from “perceived threats”
- Palaeolithic: active, high protein, more infections, stress from “really dangerous threats”



Where does Inflammation Come from?

- Antagonistic evolutionary benefit
- Infection
- LifestyleLack of Exercise, Visceral Fat

Stress

Diet: Glucose, Omega 6's, Trans Fats

Free Radicals, AGE's

Decreased Testosterone & Estrogen, Growth Hormone

Hypertension

- Anti-Inflammatory Cytokine Decrease (IL-10) with aging
Centenarians have high levels of IL-10
- Inflammatory Cytokine Increase(IL-6) with aging



Anti-Inflamm. Vrs. Inflamm...

Anti-Inflamm.

- ↓ CRP, IL-6, TNFα
- Omega 3
- ↓ Homocysteine
- ↑ B vitamins
- ↓ FR, ↑ Antioxidant
- Insulin Sensitivity
- Statins (side effects)
- NSAID's
- ↑ IL-10
- Youthful T, E2, E3, GH, M, DHEA
- Tranquillity

Inflamm.

- ↑ CRP, IL-6, TNFα
- Omega 6
- ↑ Homocysteine
- ↓ B vitamins
- ↑ FR, ↓ Antioxidant
- Insulin Resistance, DMtype2
- ASCVD, Syndrome X
- Arrhythmias, sudden death DEMENTIA
- Depression
- Cancer
- Osteoporosis
- Obesity
- Autoimmune
- Declining hormones
- Stress



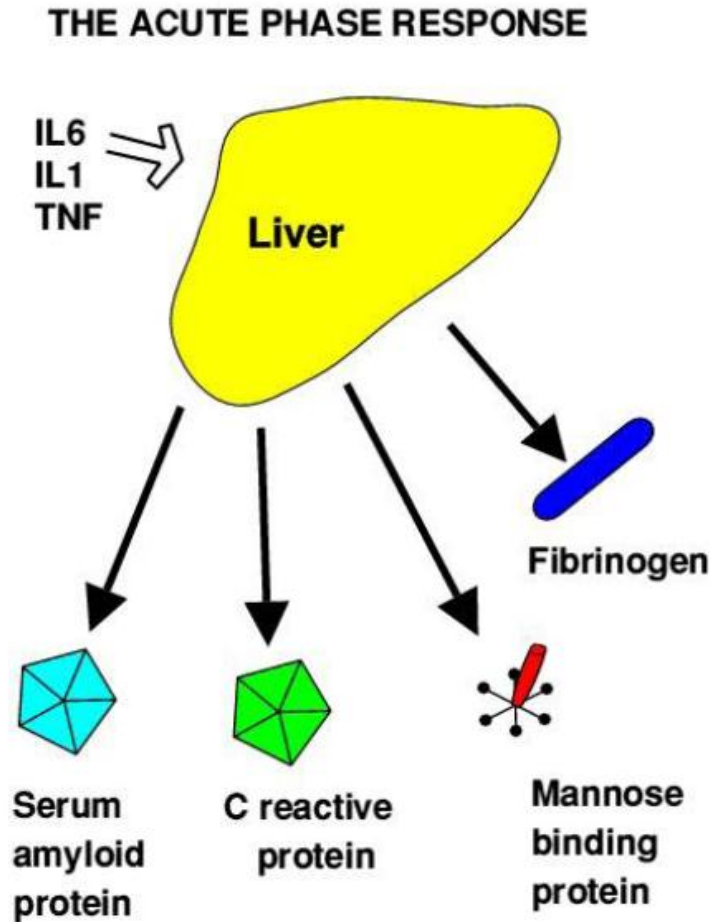
Calorie Restriction (CR) Decreases Inflammation...

- CR is the most documented method of extending lifespan & healthspan in all species studied
- CR decreases inflammatory cytokines

*Chung, H et al. Molecular Inflammation Hypothesis of Aging
Baedon the Anti-aging mechanism of Calorie Restriction.
Microscopy research & techniques 59:264-272 (2002)*



The Acute Phase Response...



- Inflammatory cytokines produced by white blood cells & other tissues
- Cytokines cause liver to produce Acute Phase proteins
- Gets animal ready for “combat” with enemies or micro-organisms



C-Reactive Protein...

- Risk factor for illness
- Produced in liver in response to inflammatory cytokines
- Can rise 1000 x with acute inflammation
- IL-6
- TNF α
- Others
- What is your CRP?



CRP Worse than LDL...



THE NEW ENGLAND JOURNAL OF MEDICINE

- Ridker PM et al. Comparison of C-reactive protein & low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events.

*New England Journal of Medicine 2002 Nov
14;347(20):1557-65*



CRP More than Just a Marker...

- Initially thought of as an inactive downstream marker of the inflammatory cascade, emerging evidence suggests that CRP may be directly involved in atherogenesis, & that arterial plaque can produce CRP, independent of traditional hepatic pathways.

Blake GJ et al. Inflammatory bio-markers & cardiovascular risk prediction. Intern Med 2002 Oct;252(4):283-94



Rheumatoid Arthritis & Cardiovascular Disease...

- Nurses health study > 100,000 pts
- RA = 2 x risk of MI (heart attack)
- Solomon DH et al. Cardiovascular morbidity & mortality in women diagnosed with rheumatoid arthritis

Circulation 2003 Mar 11;107(9):1303-7

- Why?



CRP & Cognitive Function...

- CRP- negative correlation with mental performance.
- Teunissen CE et al. Inflammation markers in relation to cognition in a healthy aging population.

J Neuroimmunol 2003 Jan;134(1-2):142-50



Alzheimer's & Inflammation...

- Elevated levels of inflammatory cytokines in blood vessels
- IL-6, IL-1beta, TNF α
- Grammas P et al. Inflammatory factors are elevated in brain microvessels in Alzheimer's disease

Neurobiol Aging. 2001 Nov-Dec;22(6):837-42.



Cytokines & Cognition...

- Brain is part of Neuro-endocrine-immune system, not isolated
- Systemic Inflammation effects Brain
- Brain can effect distant organs
- Cytokines affect cognition

*Wilson, CJ et al. Journal of the American Geriatrics Society
50:2041-2056, 2002*



CRP Predicts Dementia 25 Years Later...

- Schmidt R Early inflammation & dementia: a 25-year follow-up of the Honolulu-Asia Aging Study.

Ann Neurol. 2002 Aug;52(2):168-74.



Mortality and Gluten

JAMA. 2009;302(11):1171-1178

Small-Intestinal Histopathology and Mortality Risk in Celiac Disease

Jonas F. Ludvigsson, MD, PhD

Scott M. Montgomery, PhD

Anders Ekblom, MD, PhD

Lena Rosoth, BS

Fredrik Granath, PhD

CELIAC DISEASE IS AN IMMUNE-mediated disorder that is triggered by gluten exposure in genetically sensitive individuals, occurring in about 1% of the Western population.

With few exceptions,¹ research has shown an increased risk of death in celiac disease^{2,3} and in individuals with positive antiendomysial antibodies (EMA)⁴ or either EMA or antigliadin.⁵ However, several studies were not population-based⁶ or were limited by their focus on inpatients,⁷ less than 1000 individuals with celiac disease,^{1,2,8,9} or lack of inclusion of children.^{1,4,4}

The introduction of celiac disease serological markers has allowed screening of individuals with less marked symptoms; it is therefore possible that earlier studies (based on data until 2000)^{1,2,4,6,8,9,10} overestimate the risk of death in celiac disease.

While villous atrophy is usually required for the diagnosis of celiac disease, less is known about the long-term consequences of nonspecific small-intestinal inflammation without villous atrophy. Research on other inflammatory disorders suggests that inflammation may be associated with increased mortality,^{11,12} but this has not been investigated for nonspecific inflammation in the small intestine.

Some individuals have positive antibodies for normal small-intestinal mucosa, often referred to as having "latent" celiac

Context Studies of mortality in celiac disease have not taken small-intestinal histopathology into account.

Objective To examine mortality in celiac disease according to small-intestinal histopathology.

Design, Setting, and Patients Retrospective cohort study. We collected data from duodenal biopsy samples taken between July 1969 and February 2008 on celiac disease (Marsh stage 3; villous atrophy; n = 29 094 individuals) and inflammation (Marsh stage 1-2; n = 13 305) from all 28 pathology departments in Sweden. A birth cohort consisted of individuals with latent celiac disease from 8 university hospitals (n = 2719). Latent celiac disease was defined as positive celiac disease serology in individuals with normal mucosa (Marsh stage 0). Through linkage with the Swedish Total Population Register, we estimated the risk of death through August 31, 2008, compared with age- and sex-matched controls from the general population.

Main Outcome Measure All-cause mortality.

Results There were 3049 deaths among patients with celiac disease, 2947 with inflammation, and 188 with latent celiac disease. We found an increased hazard ratio (HR) for death in celiac disease (HR, 1.33; 95% confidence interval [CI], 1.23-1.45; median follow-up, 8.4 years), inflammation (HR, 1.72; 95% CI, 1.64-1.79; median follow-up, 7.2 years), and latent celiac disease (HR, 1.38; 95% CI, 1.14-1.58; median follow-up, 6.7 years). The absolute mortality rate was 16.4 (95% CI, 16.0-16.9) per 1000 person-years in celiac disease, 25.9 (95% CI, 25.5-26.3) in inflammation, and 6.7 (95% CI, 6.2-7.6) in latent celiac disease. Excess mortality was 2.6 per 1000 person-years in celiac disease, 10.8 in inflammation, and 1.7 in latent celiac disease. This risk increase was also seen in children, excluding the first year of follow-up. HRs decreased somewhat.

Conclusion Risk of death among patients with celiac disease, inflammation, or latent celiac disease is modestly increased.

JAMA. 2009;302(11):1171-1178.

www.jama.com

disease.¹³ Although villous atrophy in small-intestinal biopsy has been the gold standard for celiac disease diagnosis,^{14,15} it has been argued that small-intestinal biopsies, under certain circumstances, be replaced by celiac disease serology.¹⁶ Positive celiac disease serology has been linked to increased mortality⁴; however, the predictive value and long-term consequences of celiac disease serology in individuals with normal mucosa are unknown.

We used nationwide histopathology data to examine the overall risk of death in individuals with celiac disease and inflammation. Through regional data linkage, we were also able to examine mortality in latent celiac disease.

METHODS

This retrospective cohort study estimated mortality in celiac disease according to small-intestinal histopathology. Nationwide histopathology data were matched with mortality data from government agencies in Sweden.

Authors Affiliations: Department of Pediatrics (Dr Ludvigsson), Uppsala University Hospital, Uppsala; Department of Medicine, Karolinska Institutet, Stockholm; Institute for Life Sciences, Montgomery, Boston, and Granath and Ekblom, and Department of Primary Care and Social Medicine, Oxford Group Hospital, Ipswich College, Ipswich, England (Dr Montgomery). Corresponding Author: Jonas F. Ludvigsson, MD, PhD, Department of Pediatrics, Uppsala University Hospital, Östra 141 86, Sweden (jonas.ludvigsson@pediatrics.uu.se).

See also p 1225 and Patient Page.

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Reprinted JAMA, September 16, 2009;302(11):1171-1178

- Latent celiac - positive antibodies or inflammation without villous atrophy
- 19-35% increased risk of cardiovascular disease
- 41 to 132% increased risk of malignancy

Leaky Gut Diabetes

Obes Rev. 2011 Jun;12(6):449-58.

Review

Leaky gut and diabetes mellitus: what is the link?

S. de Kort, D. Keszthelyi and A. M. Masclee

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Received 4 October 2010; revised 8 November 2010; accepted 12 November 2010

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Summary

Diabetes mellitus is a chronic disease requiring lifelong medical attention. With hundreds of millions suffering worldwide, and a rapidly rising incidence, diabetes mellitus poses a great burden on healthcare systems. Recent studies investigating the underlying mechanisms involved in disease development in diabetes point to the role of the dysregulation of the intestinal barrier. Via alterations in the intestinal permeability, intestinal barrier function becomes compromised whereby access of infectious agents and dietary antigens to mucosal immune elements is facilitated, which may eventually lead to immune reactions with damage to pancreatic beta cells and can lead to increased cytokine production with consequent insulin resistance. Understanding the factors regulating the intestinal barrier function will provide important insight into the interactions between luminal antigens and immune response elements. This review analyses recent advances in the mechanistic understanding of the role of the intestinal epithelial barrier function in the development of type 1 and type 2 diabetes. Given our current knowledge, we may assume that reinforcing the intestinal barrier can offer and open new therapeutic horizons in the treatment of type 1 and type 2 diabetes.

Keywords: barrier function, diabetes mellitus, gastrointestinal tract, insulin resistance.

Obesity reviews (2011)

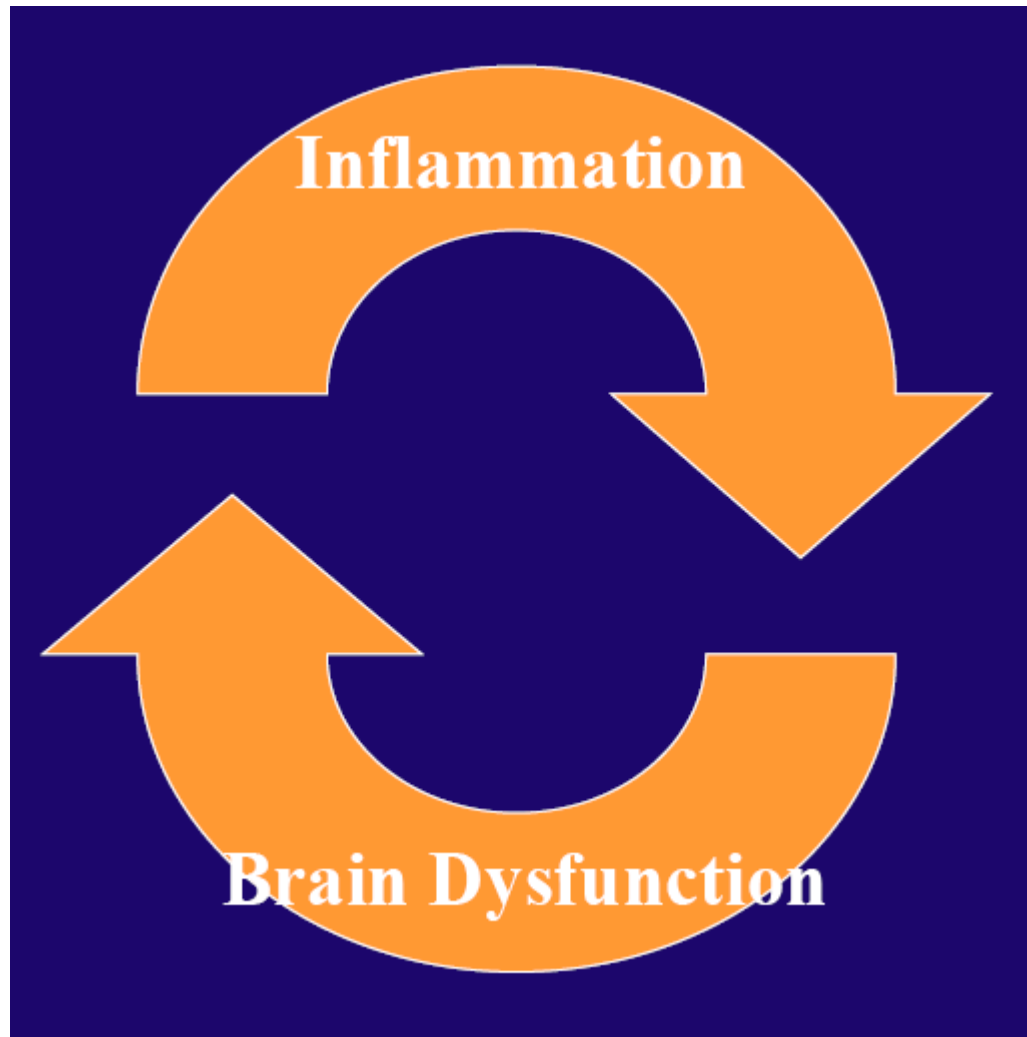
Introduction

According to the reports of the World Health Organization (WHO), globally an estimated 225 million people are suffering from diabetes mellitus (1). Without further actions or interventions, this number is likely to double by the year 2035. In the past decades, the prevalence of both type 1 and type 2 diabetes mellitus has dramatically increased, resulting from changes in diet, reduced physical activities and exposure to certain environmental factors described in the 'hygiene' and 'overload' hypotheses (2). Currently, as type 1 and type 2 diabetes are multifactorial diseases, genetic factors consisting of multiple susceptibility genes as well as environmental influences contribute to disease development. In a number of countries, type 2 diabetes mellitus has become the most prevalent type of diabetes in children (3). The dramatic rise in prevalence will have impact on the

socioeconomic perspective of the population. For instance, the WHO estimates that in the coming 5 years, China will lose over 100 billion dollars income because of heart disease, stroke and diabetes (1).

Diabetes affects the gut: there is ample evidence that diabetes mellitus affects gastrointestinal morphology and function. Conversely, the gut affects diabetes: several recent publications provide evidence that an altered bowel function contributes to the pathogenesis of diabetes mellitus. In this respect, the intestinal barrier is particularly relevant with focus on intestinal permeability (IP), immune response and intestinal microbiota. Intestinal barrier function is compromised in various gastrointestinal disorders such as inflammatory bowel disease, celiac disease, non-alcoholic steatohepatitis/non-alcoholic fatty liver disease (NASH/NAFLD) and irritable bowel disease, but also in autoimmune and systemic diseases (4). This review explores the

- Impaired intestinal permeability
- Access of infectious agents and dietary antigens to mucosal immune elements
- Immune reactions with damage to pancreatic beta cells
- Increased cytokine production and insulin resistance.

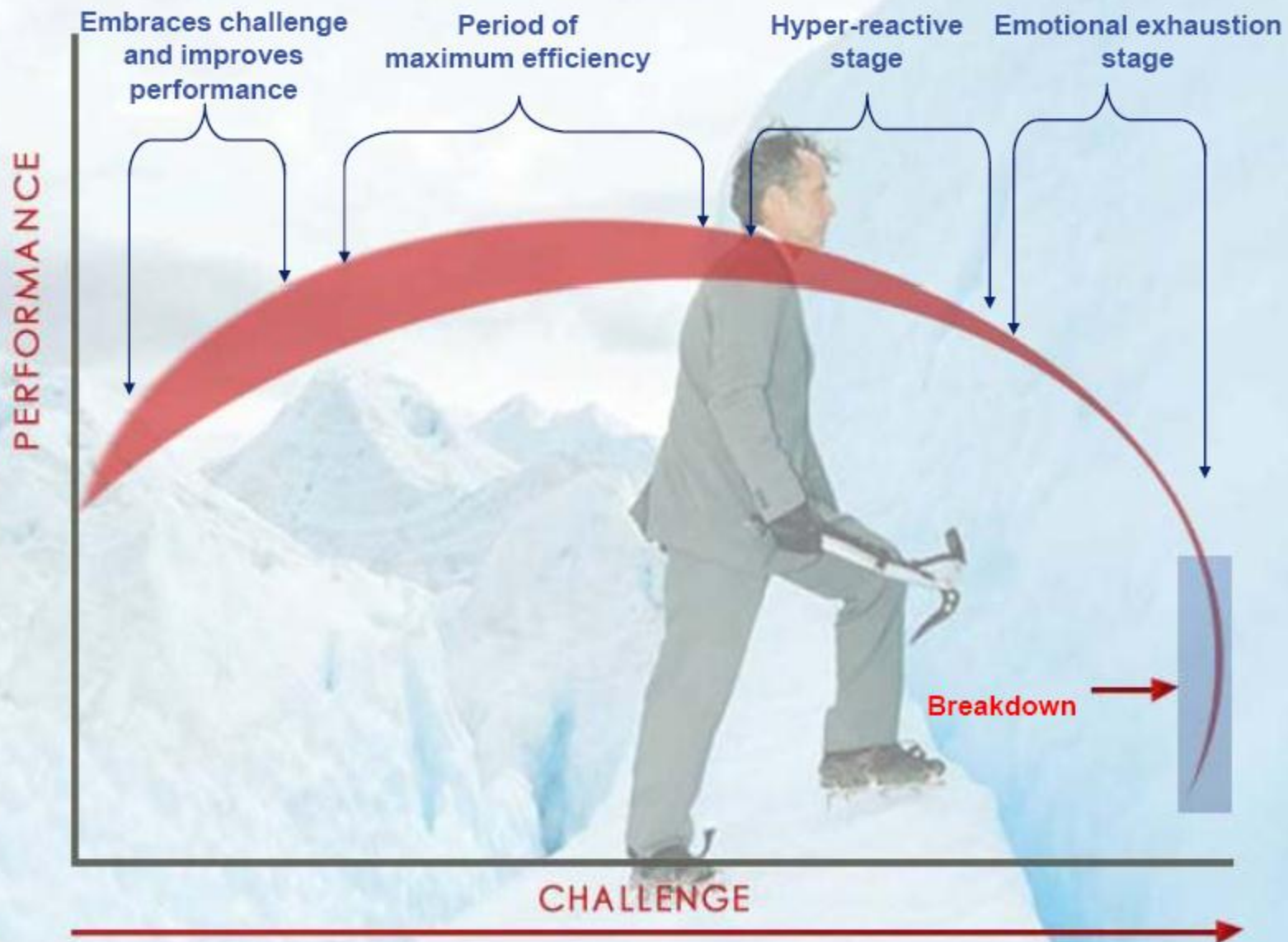


Stress

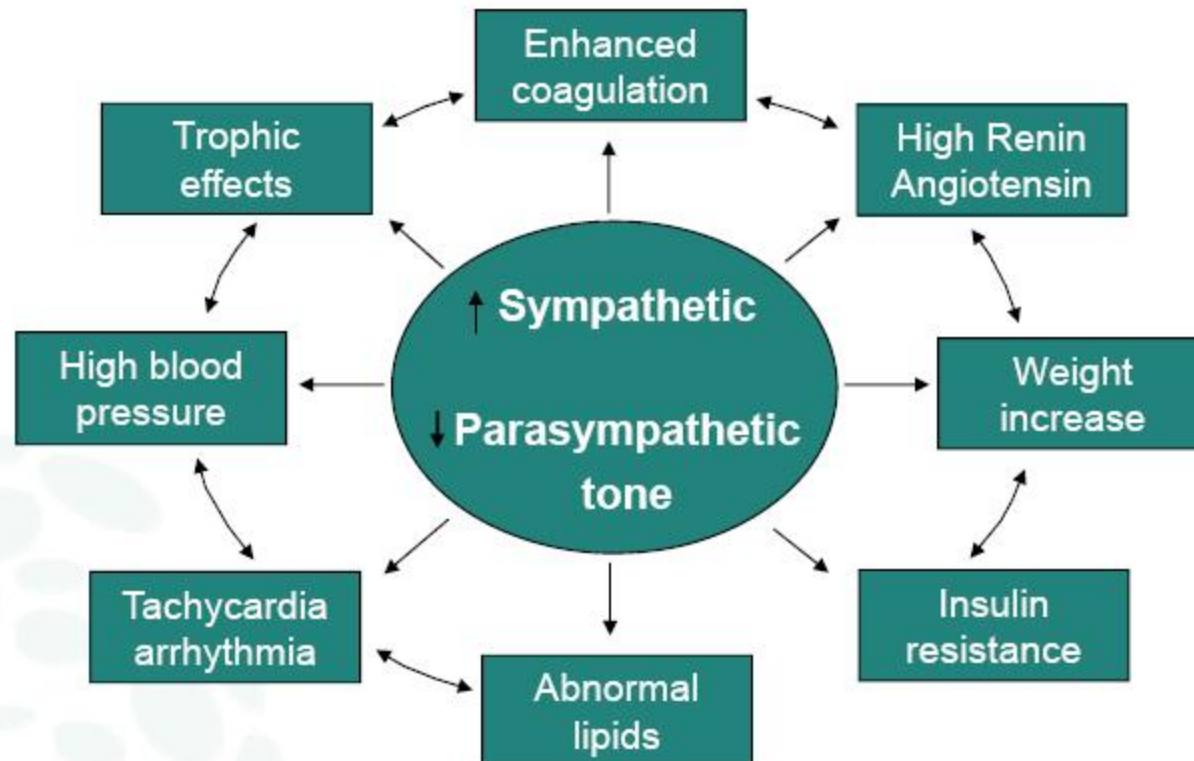


75 to 90% of all visits to health care providers result from **stress-related disorders.**





The Stress Response



Psychoneuroimmunology...

Psychoneuroimmunology and Psychosomatic Medicine: Back to the Future

- Proinflammatory cytokine production can be directly stimulated by negative emotions & stressful experiences

Janice K. Kiecolt-Glaser

Psychosomatic Medicine 64:15–28 (2002)

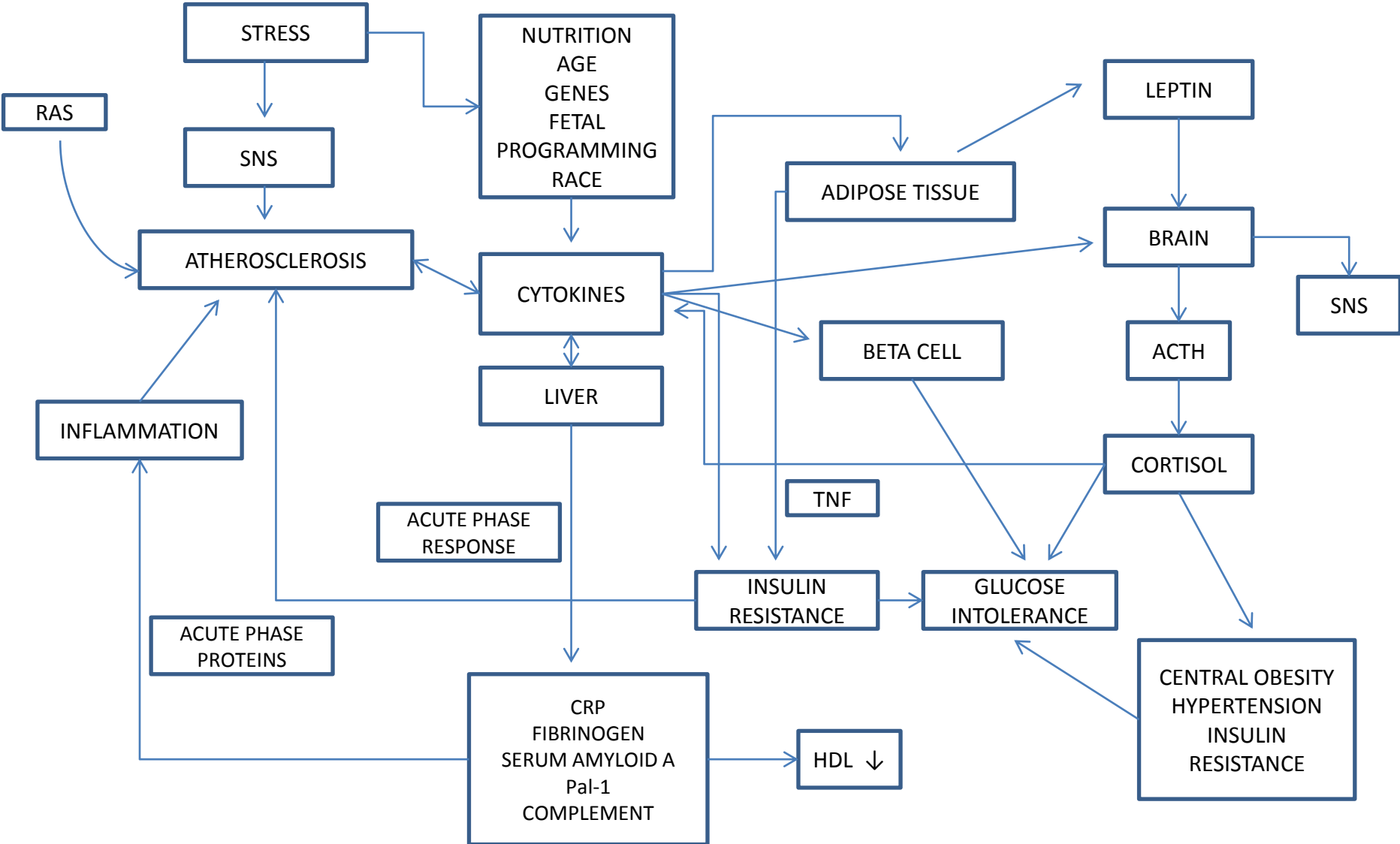


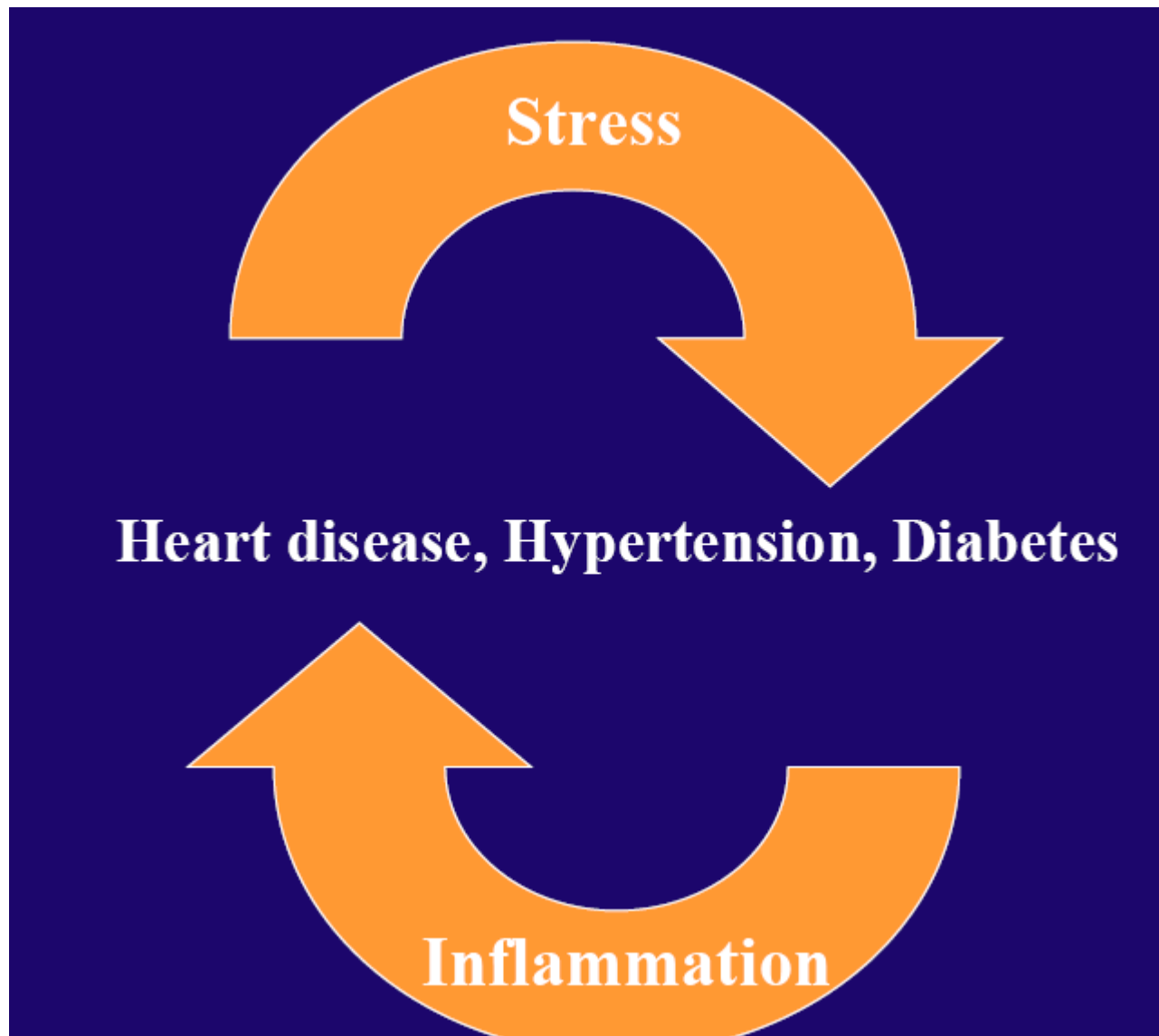
Stress, Diabetes, Heart Disease...

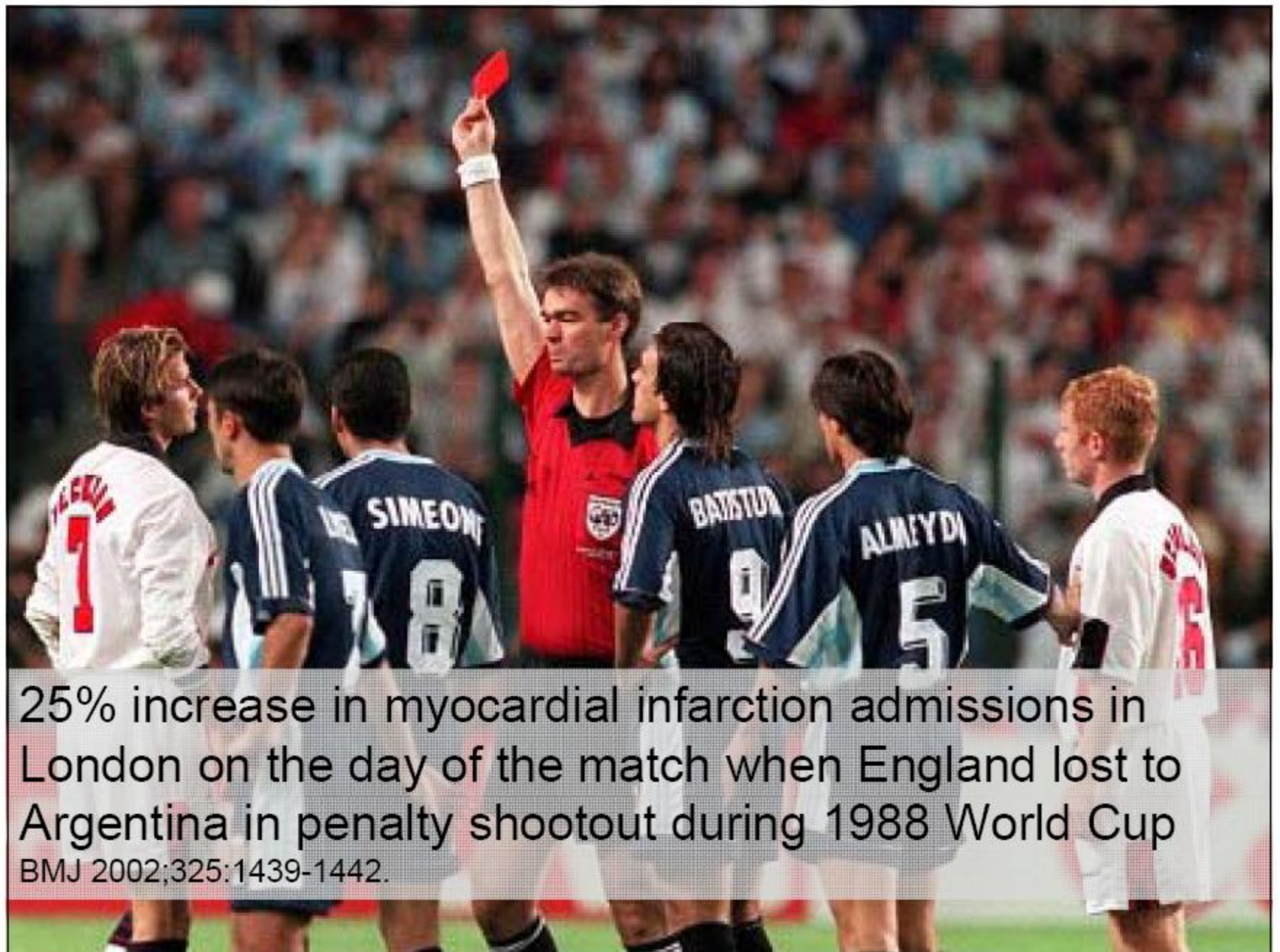
- Visceral obesity correlated with IL-6 TNF alpha & CRP
- Black PH The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes & metabolic syndrome X.

Brain Behav Immun. 2003 Oct;17(5):350-64.









25% increase in myocardial infarction admissions in London on the day of the match when England lost to Argentina in penalty shootout during 1988 World Cup

BMJ 2002;325:1439-1442.

Warning Signs

- 
- Loss of focus and mental clarity
 - Lack of ability to relax and sleep
 - Loss of self esteem
 - Feeling tired and on edge/Anger

Turning Stress Into Strength



- Exercise: Preferable in Nature
- Guided Imagery
- Meditation and Yoga
- Breath Work
- Mudras and Mantras
- Practice Appreciation
- Don't Make Assumptions
- Get Plenty of Sleep
- Avoid Excess Caffeine
- Practice Effective Communication
- Remember The Serenity Prayer
- Love and Social Support



Darwin said...



"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change."

How Do We Neutralize the Stress Response



- Breathing controls the nervous system. With each inhalation, the HR increases.
- With each exhalation, the heart rate slows down.



Social Connection and The HPA Axis



The social environment can have a buffering effect on stress. The same stressor that when given to an animal who is alone increases plasma cortisol by 50%, does not increase the cortisol level at all when the animal is surrounded by familiar companions.

Levine S., Lysons DM, Schatzberg AF. Psychobiological consequences of social relationships. *Ann NY ACAD Sci.* 1997; 807:210-218.



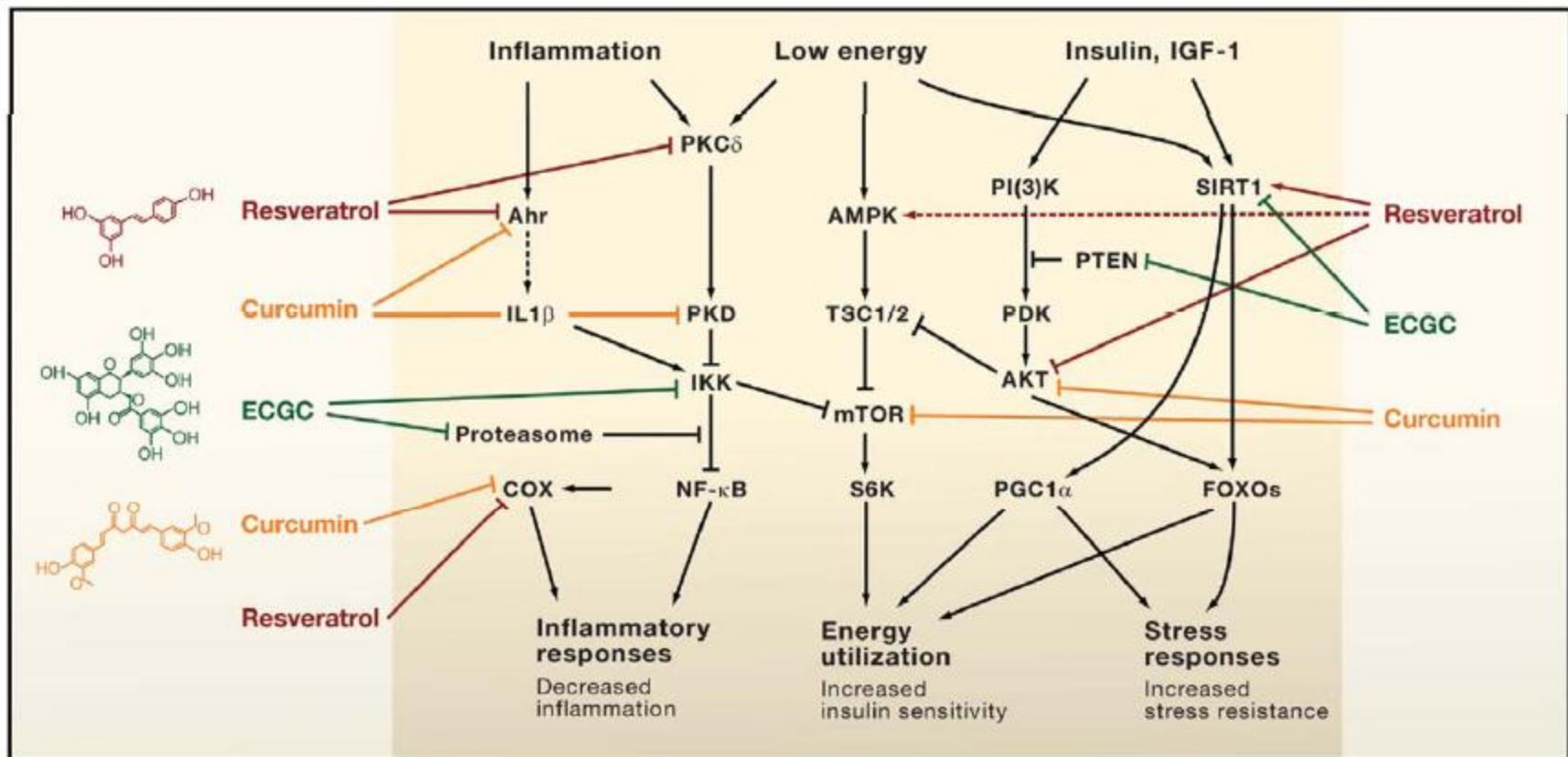
Group Support in Metastatic Breast Cancer - Outcomes



- **Women in support groups showed less depression, anger, and anxiety**
- Women in support groups lived twice as long (18 months compared to 9 months) as controls!
 - Spiegel, D et al, The Lancet, 1989, ii:888-91

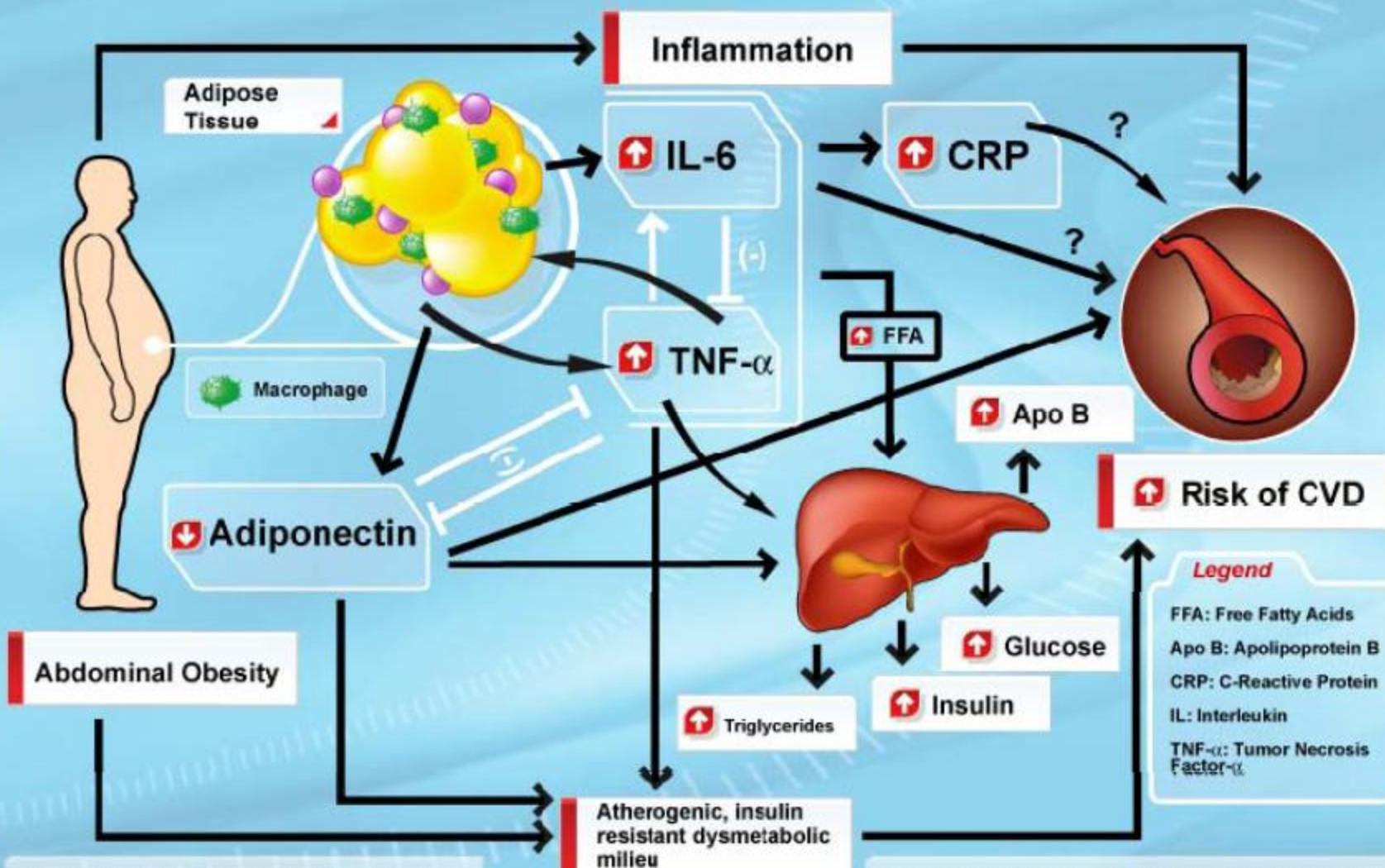


Inflammation-Energy-Stress Pathways are Linked



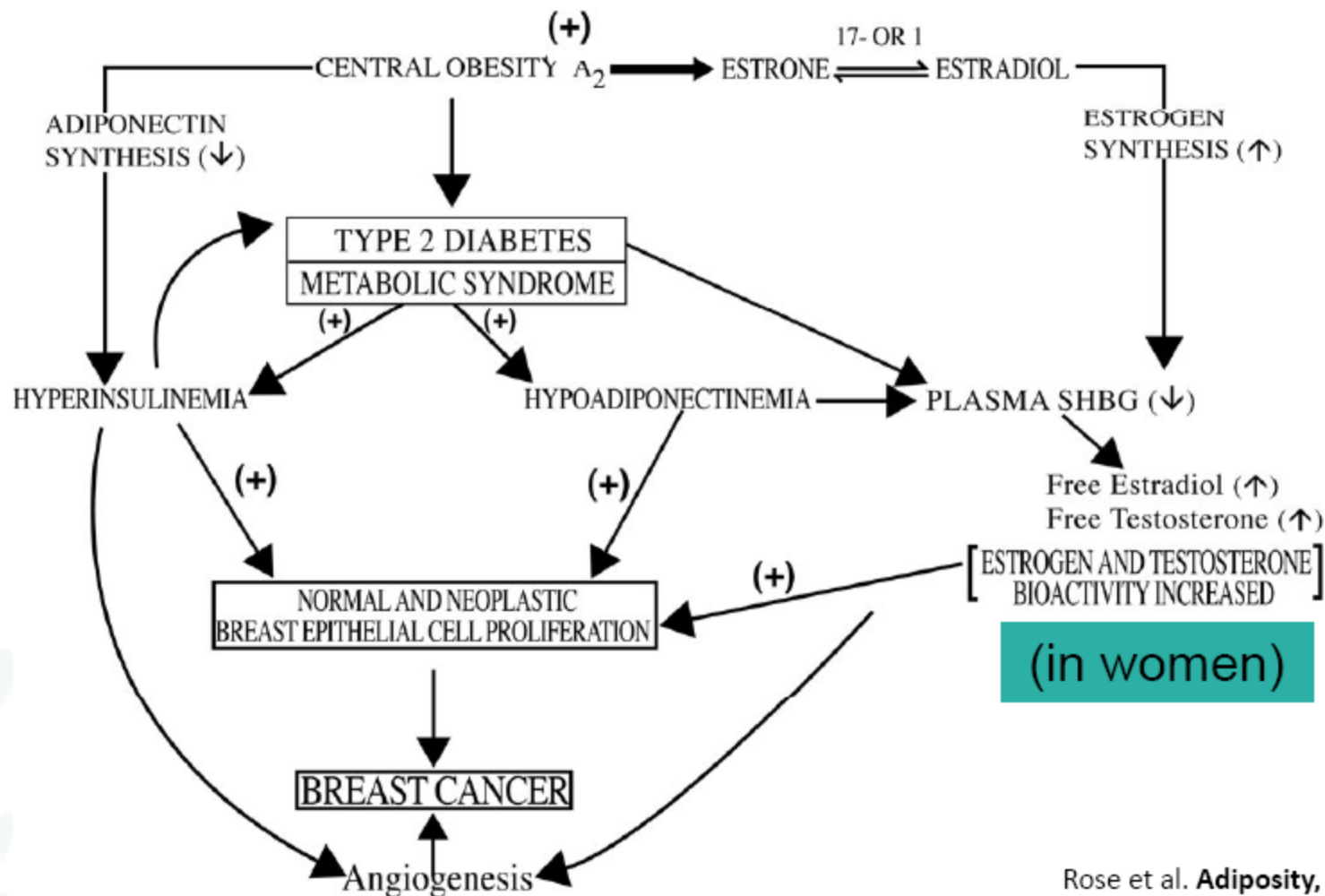
Howitz KT, Sinclair DA. Xenohormesis: sensing the chemical cues of other species. *Cell*. 2008 May 2;133(3):387-91.

INFLAMMATION: THE LINK BETWEEN ABDOMINAL OBESITY AND GLOBAL CARDIOMETABOLIC RISK (CVD RISK)



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

Adapted from Després JP Int J Obes Metab Disord 2003; 27: S22-4



(in women)

Insulin imbalance → Hormone imbalance

Rose et al. **Adiposity, the Metabolic Syndrome, and Breast Cancer** in African-American and White American Women, Endocrine Reviews, 2007.

Aging Causes Inflammation Youthful Hormones Protect...

- IL-6 proinflammatory cytokine
- Stays low in youth except for trauma, infection, stress
- Testosterone & Estrogens downregulate IL-6 gene expression

Ershler, WB et al. AGE-ASSOCIATED INCREASED INTERLEUKIN-6 GENE EXPRESSION, LATE-LIFE DISEASES, & FRAILITY Annu. Rev. Med. 2000. 51:245–270



Environmental Toxins...



- Many of the Chronic Degenerative Diseases that we now are seeing more & more, can be attributed to the effects of continual & accumulative exposure to Xenobiotic Chemicals.
- We are ALL Victims of the Greatest Uncontrolled & Unauthorized Clinical Trial to which Humanity has EVER been exposed.



Environmental Toxins...



400+ Chemicals have been identified in Human Tissues:

48 in Breast Milk

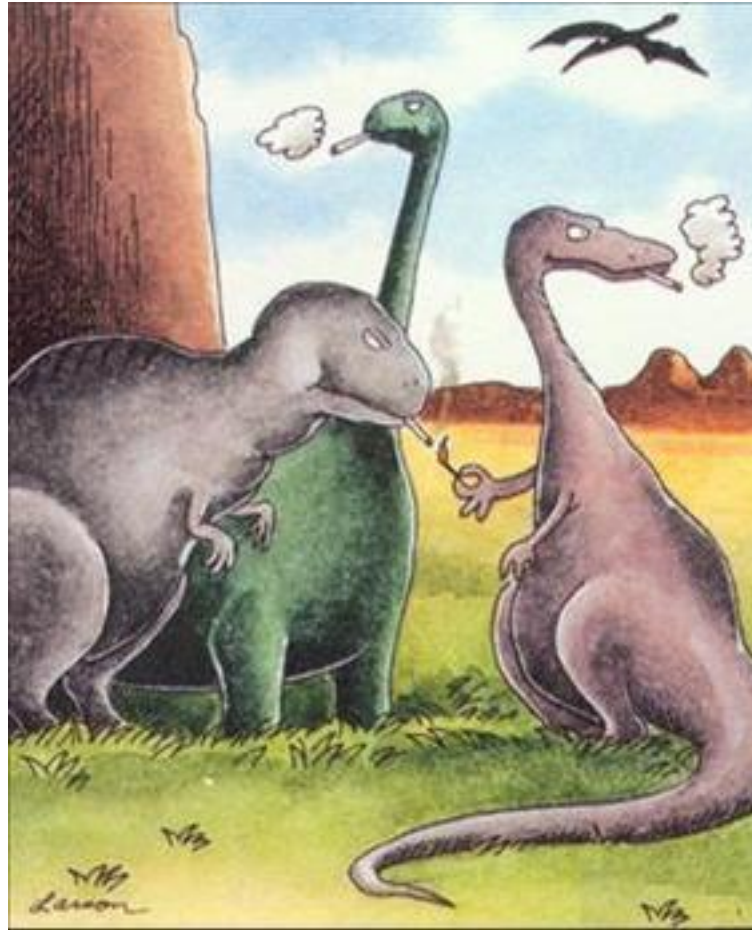
40 in Fat Tissue

73 in Liver

250 in Plasma



The Real Reason Dinosaurs became Extinct...



Lead and CVD

Circulation 2006;114:138-1399

Epidemiology

Blood Lead Below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) and Mortality Among US Adults

Andy Menke, MPH; Paul Muntner, PhD; Vecihi Batuman, MD; Ellen K. Silbergeld, PhD; Eliseo Guallar, MD, DrPH

Background—Blood lead levels above 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) in adults have been associated with increased risk of cardiovascular, cancer, and all-cause mortality. The objective of the present study was to determine the association between blood lead levels below 0.48 $\mu\text{mol/L}$ and mortality in the general US population.

Methods and Results—Blood lead levels were measured in a nationally representative sample of 33 946 adult participants of the Third National Health and Nutrition Examination Survey recruited in 1988 to 1994 and followed up for up to 12 years for all-cause and cause-specific mortality. The geometric mean blood lead level in study participants was 0.12 $\mu\text{mol/L}$ (2.58 $\mu\text{g/dL}$). After multivariate adjustment, the hazard ratios (95% CI) for comparisons of participants in the highest tertile of blood lead (≥ 0.17 $\mu\text{mol/L}$, [≥ 3.62 $\mu\text{g/dL}$]) with those in the lowest tertile (<0.09 $\mu\text{mol/L}$, [<1.94 $\mu\text{g/dL}$]) were 1.25 (1.04 to 1.51; P_{trend} across tertiles=0.002) for all-cause mortality and 1.55 (1.08 to 2.24; P_{trend} across tertiles=0.003) for cardiovascular mortality. Blood lead level was significantly associated with both myocardial infarction and stroke mortality, and the association was evident at levels >0.10 $\mu\text{mol/L}$ (≥ 2 $\mu\text{g/dL}$). There was no association between blood lead and cancer mortality in this range of exposure.

Conclusions—The association between blood lead levels and increased all-cause and cardiovascular mortality was observed at substantially lower blood lead levels than previously reported. Despite the marked decrease in blood lead levels over the past 3 decades, environmental lead exposures remain a significant determinant of cardiovascular mortality in the general population, constituting a major public health problem. (Circulation. 2006;114:1388-1394.)

Key Words: risk factors ■ mortality ■ cardiovascular diseases ■ myocardial infarction ■ stroke

Blood lead levels above 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) have been associated with increased risks of cardiovascular, cancer, and all-cause mortality in several occupational cohorts. In the general population, Luthberg and Silbergeld¹ also reported significant relationships between blood lead levels above 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) and cardiovascular, cancer, and all-cause mortality.

Editorial p 1347

Clinical Perspective p 1394

Environmental lead exposures in the United States have generally declined since the mid-1970s, largely because of the phase-out of lead in gasoline, which was finalized in 1996. In addition, lead-based paints were restricted in use, and a voluntary program removed lead solder from food cans.^{2,3} Among US adults, the geometric mean blood lead level decreased from 0.23 $\mu\text{mol/L}$ (4.73 $\mu\text{g/dL}$) in 1970 to 0.08 $\mu\text{mol/L}$ (1.6 $\mu\text{g/dL}$) in 1999 to 2002. Currently, 99% of US adults have blood lead levels below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$).⁴ To the best of our knowledge, the association of

blood lead levels below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) with mortality end points has never been investigated.

The purpose of the present analysis was to evaluate the association of blood lead levels below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) with all-cause and cause-specific mortality in the general US population. To do so, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) Mortality Study, a cohort study based on a nationally representative sample of US adults in which blood lead was measured in 1988 to 1994, with participants followed up for up to 12 years.

Methods

Study Population

NHANES III was a stratified, multistage probability survey designed to select a representative sample of the civilian, noninstitutionalized US population.⁵ Overall, 16 000 adults 20 years of age and older completed the NHANES III interview and examination between 1988 and 1994. After the exclusion of 2482 participants who were missing data for blood lead, 707 participants with blood lead ≥ 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) and 1494 participants who were missing other

- Low level exposure blood lead > 2 ug/dl
- 55% increase CVD
- 89% increase in MI
- 151% increase stroke
- Affects 39% of population

Rapid Insulinotropic Action of Low Doses of Bisphenol-A on Mouse and Human Islets of Langerhans: Role of Estrogen Receptor β

Sergi Soriano¹, Paloma Alonso-Magdalena¹, Marta García-Arévalo¹, Anna Novials², Sarheed J. Muhammed³, Albert Salehi², Jan-Ake Gustafsson⁴, Ivan Quesada¹, Angel Nadal^{1*}

1 Instituto Biogerontológico y CSER de Diabetes y Enfermedades Metabólicas Asociadas (IGBDEM), Universidad Miguel Hernández de Elche, Elche, Alicante, Spain, **2** Institut D'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and CSERCBM, Barcelona, Spain, **3** Department of Clinical Sciences, Lund University, Malmö, Sweden, **4** Department of Cell Biology and Biochemistry, Center for Nuclear Receptors and Cell Signaling, University of Houston, Houston, Texas, United States of America

Abstract

Bisphenol-A (BPA) is a widespread endocrine-disrupting chemical (EDC) used as the base compound in the manufacture of polycarbonate plastics. It alters pancreatic β -cell function and can be considered a risk factor for type 2 diabetes in rodents. Here we used ER β 2/2 mice to study whether ER β is involved in the rapid regulation of K_{ATP} channel activity, calcium signals and insulin release elicited by environmentally relevant doses of BPA (1 nM). We also investigated these effects of BPA in β -cells and whole islets of Langerhans from humans. 1 nM BPA rapidly decreased K_{ATP} channel activity, increased glucose-induced $[Ca^{2+}]_i$ signals and insulin release in β -cells from WT mice but not in cells from ER β 2/2 mice. The rapid reduction in the K_{ATP} channel activity and the insulinotropic effect was seen in human cells and islets. BPA actions were stronger in human islets compared to mouse islets when the same BPA concentration was used. Our findings suggest that BPA behaves as a strong estrogen via nuclear ER β and indicate that results obtained with BPA in mouse β -cells may be extrapolated to humans. This supports that BPA should be considered as a risk factor for metabolic disorders in humans.

Citation: Soriano S, Alonso-Magdalena P, García-Arévalo M, Novials A, Muhammed SJ, et al. (2012) Rapid Insulinotropic Action of Low Doses of Bisphenol-A on Mouse and Human Islets of Langerhans: Role of Estrogen Receptor β . PLoS ONE 7(2): e31109. doi:10.1371/journal.pone.0031109

Editor: Kathrin Mader, University of Bremen, GERMANY

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Full
Gen
an
col
Con
* Se

Intro

Bis
prod
fundi
endo
factor
Rece
BPA

show high BPA levels in urine samples (4.20 ng/ml or 18 nM) [6]. Moreover, an association between urinary levels of BPA, obesity and insulin resistance in middle-aged and elderly Chinese adults has been recently described [6]. The range of BPA levels found in humans is from 0.7 to 20 nM [7,8]. To support the evidence that BPA may be a risk for the development of diabetes it is critical to study its effect on human tissues involved in glucose and lipid metabolism, including the endocrine pancreas which is key in glucose homeostasis.

The Islet of Langerhans is the physiological unit of the endocrine pancreas. It is a group of 1500–3000 cells of five different types [9–11], and the most abundant are β -cells. The main function of β -cells is the biosynthesis and release of insulin in response to neurotransmitters, hormones and nutrients, the most important being glucose. The secretory response of β -cells depends

membrane potential, a $[Ca^{2+}]_i$ oscillatory pattern originates [15–19], which triggers a pulsatile insulin secretion [17–19]. In addition to the K_{ATP} -dependent process of insulin secretion there is a K_{ATP} -independent process which involves cAMP-dependent phosphorylation [20,21].

Beta cells express estrogen receptor α (ER α), estrogen receptor β (ER β) and the G-protein coupled receptor (GPR30), also named GPER1 [22,23]. The use of genetically modified mice has revealed the role of these estrogen receptors [23]. ER α is involved in the regulation of pancreatic insulin biosynthesis in response to both E2 and BPA. Remarkably, nanomolar concentrations of either BPA or E2 act via extranuclear ER α to activate ERK1/2 and regulate insulin content [24]. This action involves the activation of the transcription factor NeuroD1 [25]. In addition, activation of extranuclear ER β by physiological concentrations of E2 rapidly

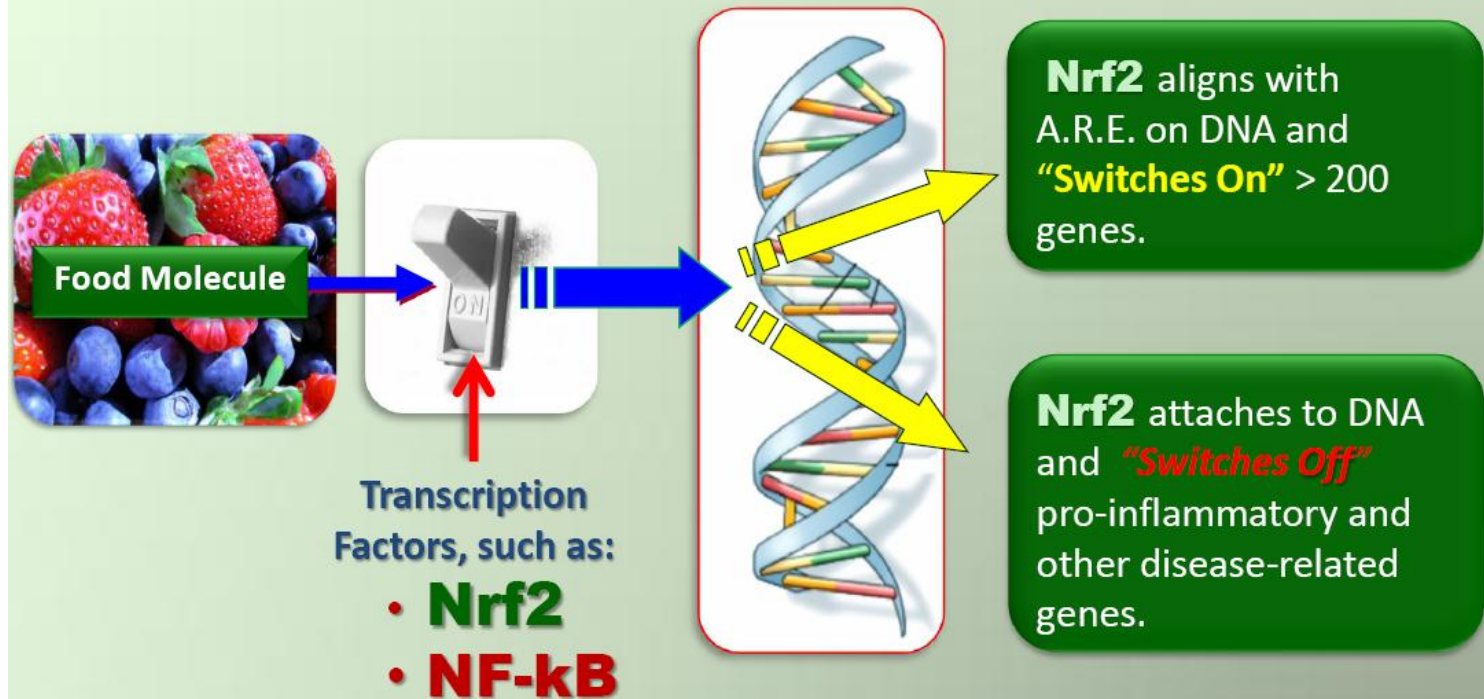
Insulinogenic Effect of Low Doses of Bisphenol A on Human Islet Cells
PLOS ONE 7(2): e31109.

Treatment of Toxicity...

- Avoid Exposure
- Detoxification
- Increased Excretion



'Nutrigenomic' molecules at work



Nutrigenomic biomolecules **'Switch On'** cytoprotective genes and **'Switch Off'** pro-inflammatory genes.

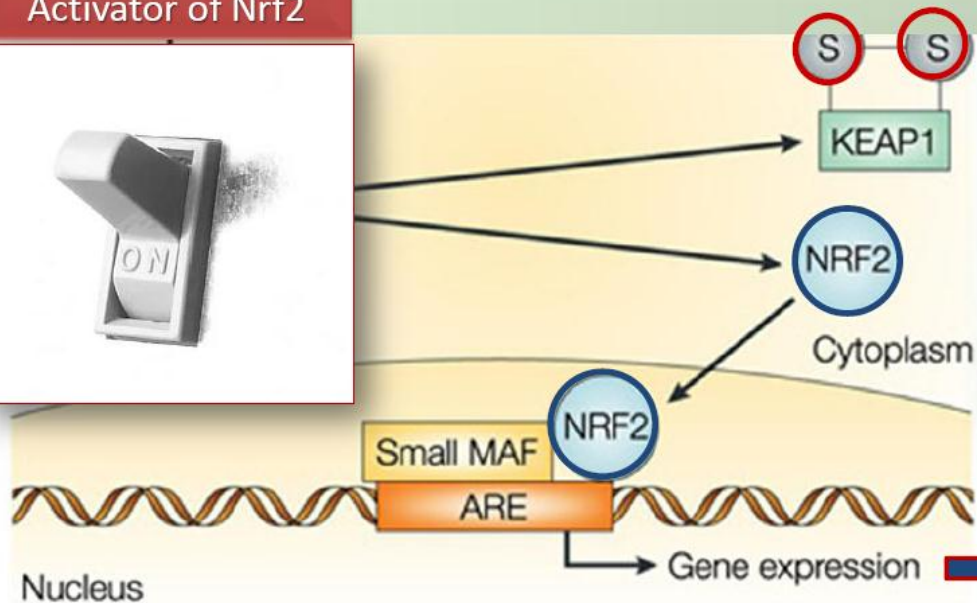


How does Nrf2 activate cellular defences?

1994

Pro-oxidant

Activator of Nrf2



Sulforaphane as
most potent
phytochemical
activator of
Nrf2.

2011 - Christine Houghton©

Nrf2 activates > 200 cytoprotective genes



Rx for Longevity...

- Principles:

Control Oxidative Stress

Decrease Inflammation

Detoxification

Endocrine Rejuvenation

Smart Nutrient



In a Nutshell...

- Lifestyle

Zone Type Calorie Diet

Exercise

Stress Reduction



Key Supplements to Decrease Inflammation...



- Fish Oils



- Curcumin



Key Supplements to Reduce Oxidative Stress...

- B Vitamins
- Antioxidants
- Polyphenols
- Glutathione- NRF2 Activator



Endocrine Rejuvenation...

- Youthful bio-identical hormones
- Treat a “deficiency disease”
- Improve Quality of Life
- Decrease Inflammation
- Do not increase cancer risk
- Do not increase heart disease risk
- Are a matter of personal choice
- Must be given by the correct route
- Are a “work in progress”



Endocrine Rejuvenation...

Balanced Hormone Optimization

- All hormones restored to 25-30 year old level & monitored by regular serum levels
- Natural (Bioidentical) hormones
 - *Identical molecular structure to hormones produced by human female or male.*
 - *Not xeno hormones or horse hormones*
- Synthetically produced



Endocrine Rejuvenation...

Balanced Hormone Optimization

- Growth hormone
- DHEA, Pregnenolone, Melatonin
- Testosterone in men & women
 - Estrogens & Progesterone in women (Bio-identical hormones) Not Premarin or Provera (MPA)*
- Thyroid (T3 & T4, not just T4)



Endocrine Rejuvenation...

GH Replacement Improves

- Brain
- Bone
- Atherosclerosis
- Heart Function
- Immune System
- Body Composition
- Exercise Capacity
- Wound Healing
- Well Being
- Quality of Life
- Cosmetic Appearance



Endocrine Rejuvenation...

Testosterone Replacement in men improves:

- Libido
- Erectile function
- Mood, depression
- Memory, Alzheimer's
- Angina, Heart disease
- Type 2 diabetes
- Muscle mass, Fat, Bone
- Inflammation
- Quality of life



Middle Age...



You know you have arrived when you are asked to suck in your middle & you already have!



Smart Nutrients for Brain Function...

- Acetyl-L-Carnitine
- Phosphatidyl Serine
- Ashwagandha
- Others





“Irving, remember when
we used to chase
after young ‘chicks’
like that?”

“Oh, sure, I remember
doing it....I just can’t
remember *why!*”



With a bit of care....



*Your body will last
you a lifetime.*



What Do I Do in Anti-Aging Medicine?

- Design customized preventive medicine programs with our patients
- Advanced lab testing
- Nutrition
- Exercise
- Stress reduction
- Neutraceuticals
- Inflammation control
- Bio-identical youthful hormones



My Anti-Aging Plan...

- Diet
- Exercise
- Sunshine – Vitamin D connection
- Stress Reduction – Meditation



My Anti-Aging Plan (continued)...

- Avoid Toxins – smoking, alcohol, drugs
- Nrf2 Activator



Nutritional Support...



- Functional Foods - OptiCleanse



- ProOmega D



- Mito Resus Kit



- CoQ10, Smart Nutrients



- Osaplex for bone/collagen support



We are becoming increasingly aware that...



- Beauty is achieved from the inside out
- The current medical system is a sickness system, not a health system
- There is great potential for optimising our health and performance
- We can prevent disease and slow ageing
- As a society, we must invest in wellness
- We are PERSONALLY responsible for our own health and well-being





“My personal experience has been that treating the symptoms of the degenerative diseases of modern living, e.g. Type 2 diabetes, obesity, high blood pressure did not restore my health.

I have now changed my lifestyle with no processed foods or sugars and refined flour, but added beneficial foods and exercise programs along with a nutritional and hormonal program, designed by Dr. Karl.

I am now medication free and feel the best I have in the last 30 years.”

-Rodney Hide



Fountain of Youth...



dr.karl@wellnesscentre.co.nz



Resources

- Alternative Medical Review Journal
- Textbook of Nutritional Medicine by Dr. Alan Gaby

