Med diet dosetti 14 dicembre 2009

by

Adolfo Panfili

IS MED DIET THE DIETS GRAAL?

What is the Mediterranean Diet?

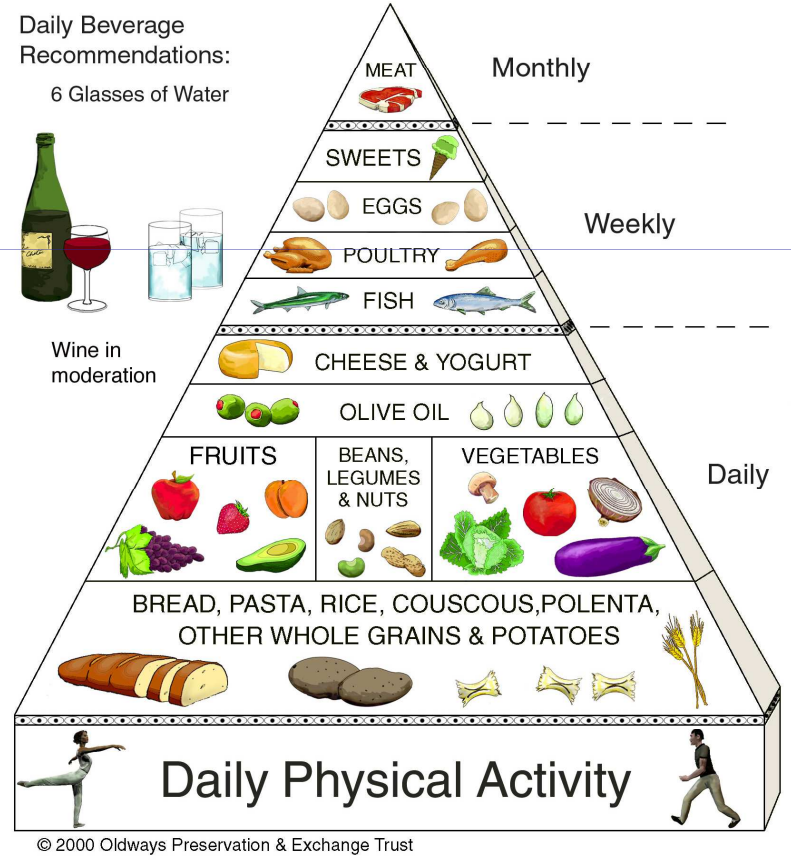
- Based on traditional foods of the 16 countries bordering the Mediterranean Sea
- Higher in monounsaturated fats
- More fresh food – less processed
- Proven benefits for all ages

  even those over 70

What are the proven benefits?

- Lyon Heart Study
  - Reduced death from repeat heart attacks by 50-70%
- HALE Study
  - In those age 70-90, reduced death from all causes 23% through diet changes alone
  - Add regular activity, no smoking and moderate drinking, 65% lower mortality rate
- Study by Esposito et al.
  - decreased metabolic syndrome and cardiovascular disease

What is Med Diet?



Things at the bottom should be done or consumed more often

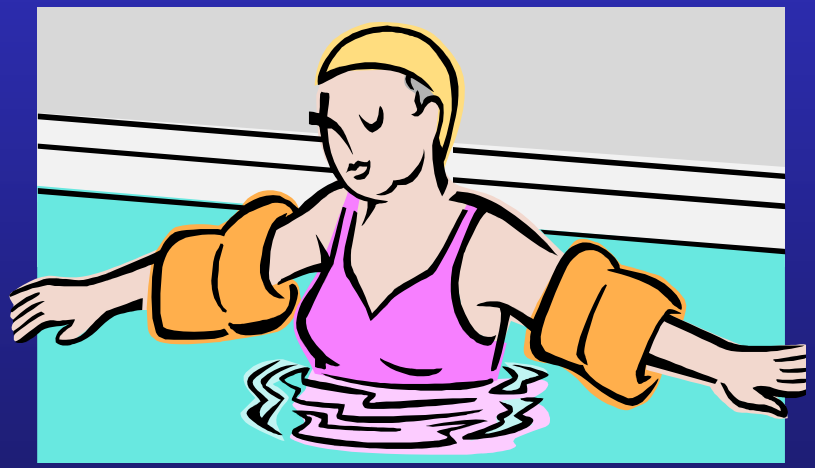
Things at the top should be consumed less often

Mediterranean Diet Pyramid

- Things at the bottom should be done or consumed more often
- Things at the top should be consumed less often

Daily Activity

- Do at least 30 minutes of moderate activity daily
- Can be structured activity
- Can be part of daily living activities



1° FALSE PILLAR OF MED DIET

Eat more whole grains and starchy vegetables

- Consume whole grain breads, cereals, rice and pasta
- Enjoy potatoes, corn, sweet potatoes, winter squash and other starchy vegetables

Eat lots of fruits and vegetables

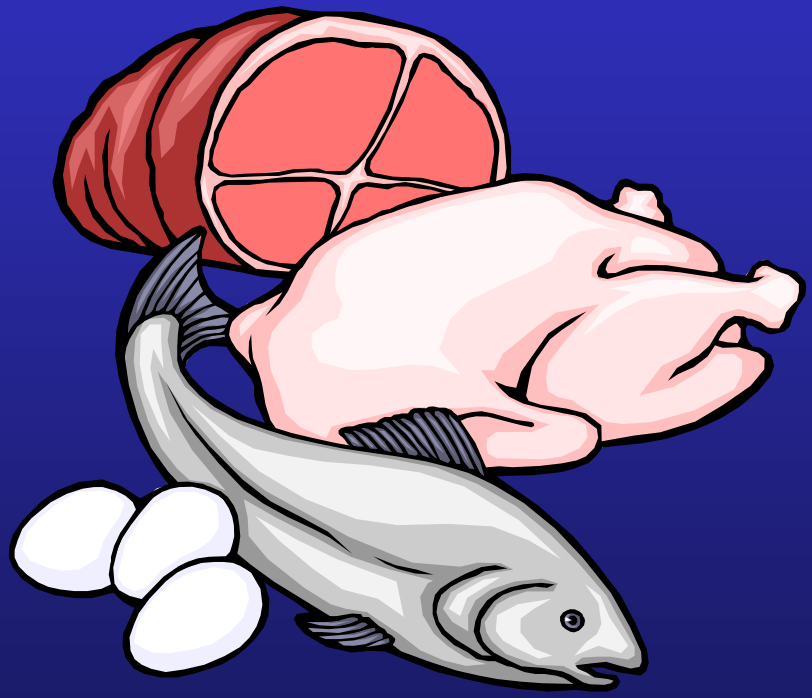
- Eat lots of fruits and vegetables daily
- Have beans, legumes and nuts daily – watch portions

Also Eat Daily in Small Amounts

- Olive oil and olives
- Cheese and yogurt

Use sparingly

- Weekly
  - Fish
  - Skinless poultry
  - Eggs
  - Sweets
- Monthly
  - Red meat

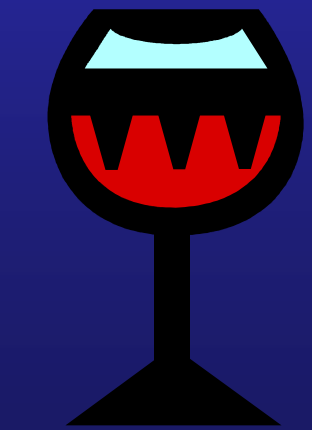


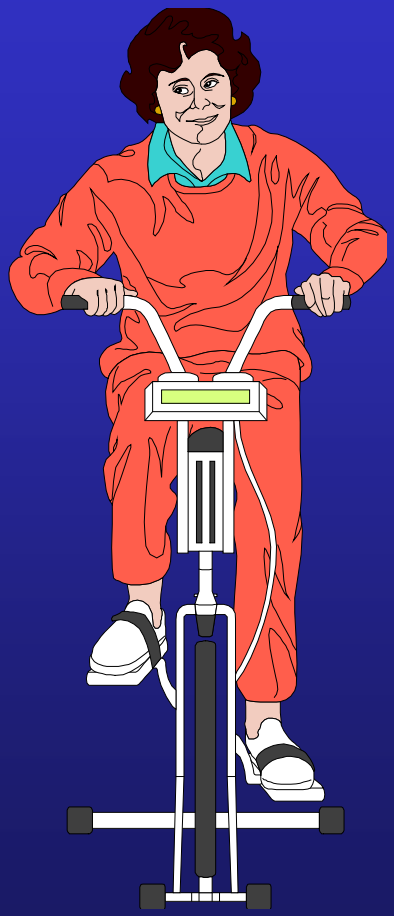
Beverages

- At least 6 cups of water per day
- If drink, use red wine in moderation

Diet Works Best with

- No smoking
- Moderate daily physical activity
- Moderate alcohol intake



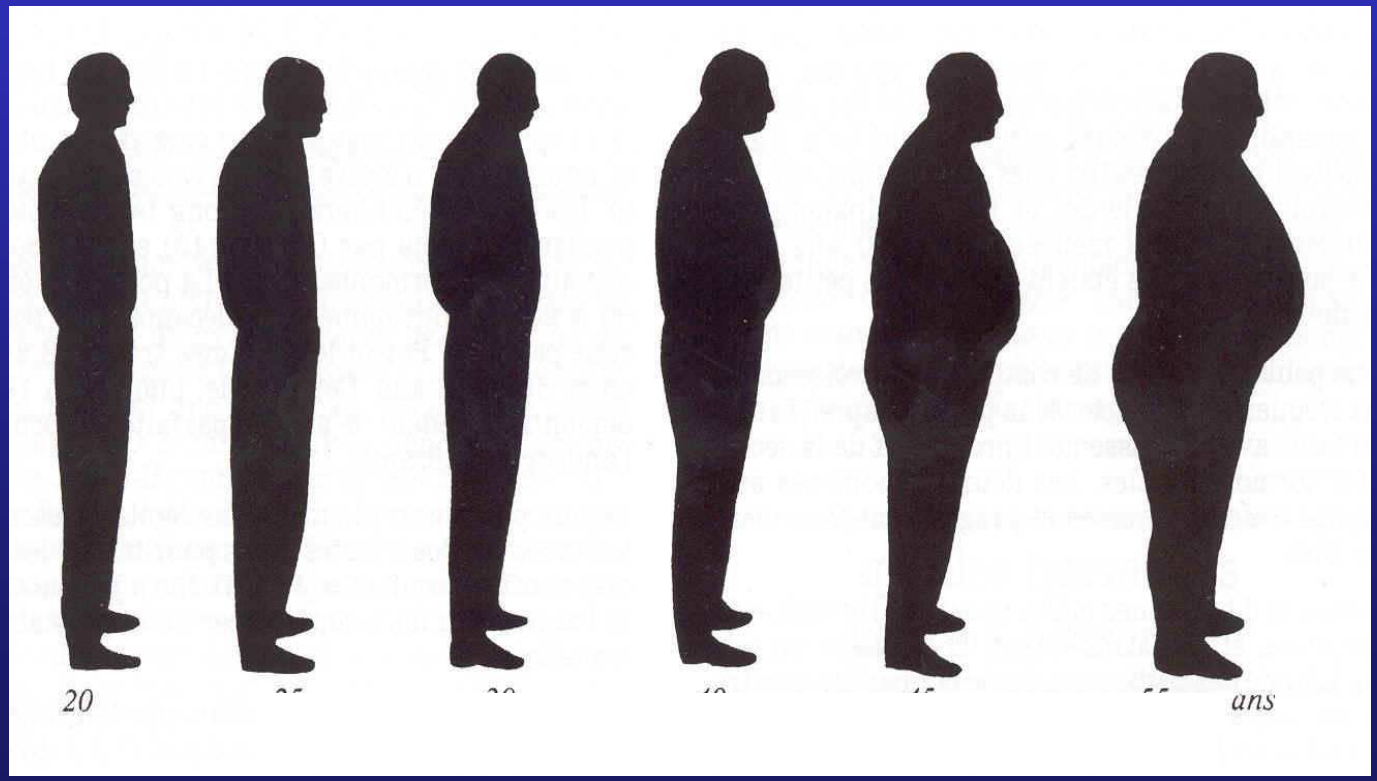


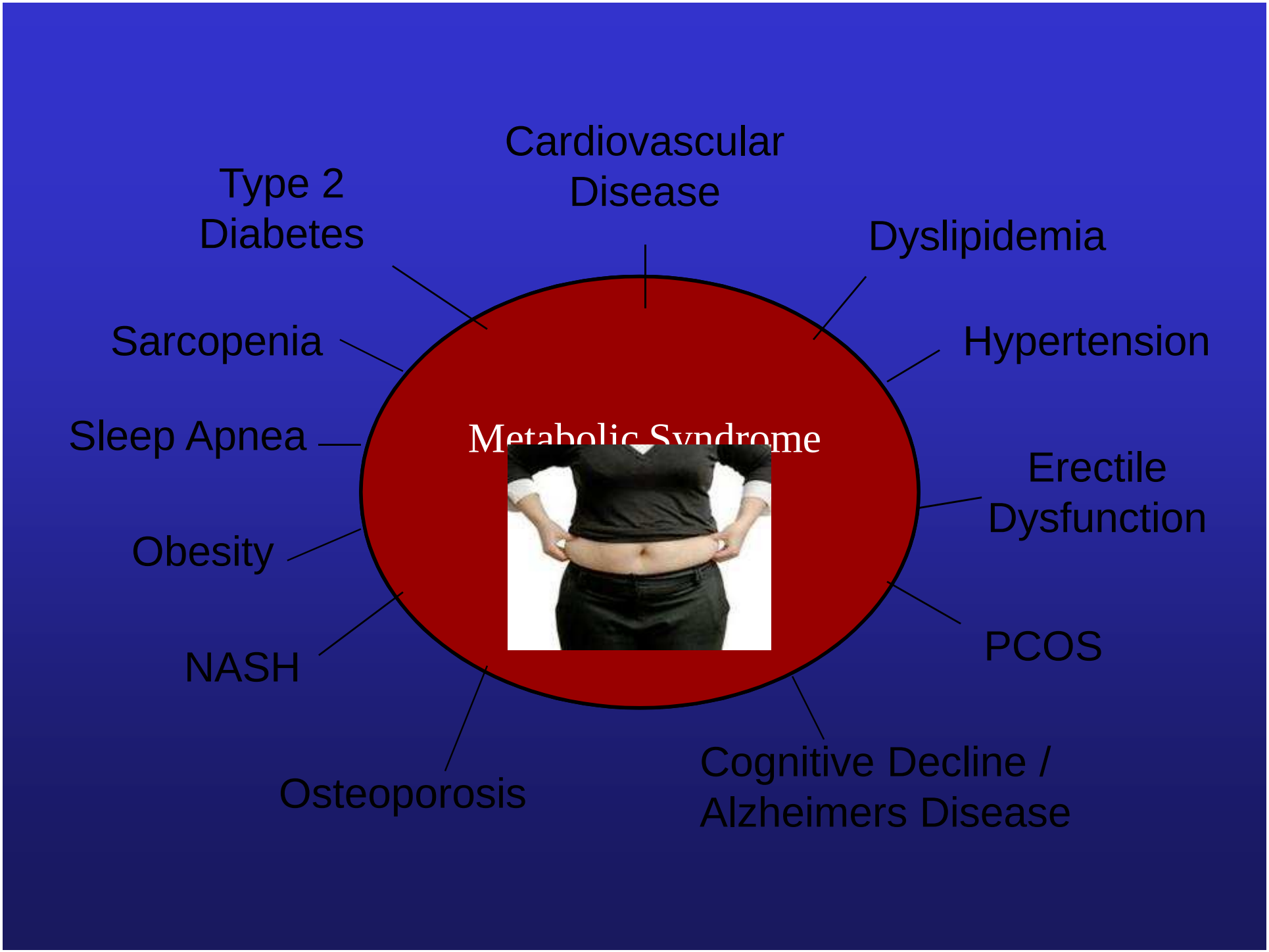
For whom the bell tolls?

John Donne
(London, 1572 –1631) Meditation 17

"No man is an island, entire of itself; every man is a piece of the continent, a part of the main. If a clod be washed away by the sea, Europe is the less, as well as if a promontory were, as well as if a manor of thy friend's or of thine own were. Any man's death diminishes me, because I am involved in mankind; and therefore never send to know for whom the bell tolls; it tolls for thee..."

Over a lifetime of **“illegitimate”** (dietary) signals, **symptoms** develop, symptoms evolve into **chronic conditions**.




Cardiovascular Disease
Type 2 Diabetes
Dyslipidemia
Sarcopenia
Hypertension
Sleep Apnea
Metabolic Syndrome
Erectile Dysfunction
Obesity
PCOS
NASH
Osteoporosis
Cognitive Decline / Alzheimers Disease

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STATE-OF-THE-ART PAPER

Dietary Strategies for Improving Post-Prandial Glucose, Lipids, Inflammation, and Cardiovascular Health

James H. O'Keefe, MD, Neil M. Gheewala, MS, Joan O. O'Keefe, RD
Kansas City, Missouri

The highly processed, calorie-dense, nutrient-depleted diet favored in the current American culture frequently leads to exaggerated supraphysiological post-prandial spikes in blood glucose and lipids. This state, called post-prandial dysmetabolism, induces immediate oxidant stress, which increases in direct proportion to the increases in glucose and triglycerides after a meal. The transient increase in free radicals acutely triggers atherogenic changes including inflammation, endothelial dysfunction, hypercoagulability, and sympathetic hyperactivity. Post-prandial dysmetabolism is an independent predictor of future cardiovascular events even in nondiabetic individuals. Improvements in diet exert profound and immediate favorable changes in the post-prandial dysmetabolism. Specifically, a diet high in minimally processed, high-fiber, plant-based foods such as vegetables and fruits, whole grains, legumes, and nuts will markedly blunt the post-meal increase in glucose, triglycerides, and inflammation. Additionally, lean protein, vinegar, fish oil, tea, cinnamon, calorie restriction, weight loss, exercise, and low-dose to moderate-dose alcohol each positively impact post-prandial dysmetabolism. Experimental and epidemiological studies indicate that eating patterns, such as the traditional Mediterranean or Okinawan diets, that incorporate these types of foods and beverages reduce inflammation and cardiovascular risk. This anti-inflammatory diet should be considered for the primary and secondary prevention of coronary artery disease and diabetes. (J Am Coll Cardiol 2008;51:249–55) © 2008 by the American College of Cardiology Foundation

Systemic inflammation is increasingly recognized as an ... CAD. Dietary and lifestyle factors play a central role in the

Experimental and epidemiological studies indicate that eating patterns such as the traditional Mediterranean and Okinawan diets, that incorporate minimally processed, high-fiber, plant-based foods such as vegetables and fruits, whole grains, legumes and nuts along with fish oil,, cinnamon, other phytochemicals and exercise will markedly blunt post-prandial dysmetabolism and inflammation".
J Am College Cardiology 2008; 51: 249-55.

Current Dietary Guidelines for the Metabolic Syndrome

- USDA Dietary Guidelines for Americans
- American Dietetic Association
- American Heart Association
- National Heart, Lung, and Blood Institute
- National Cholesterol Education Program
  - Therapeutic Lifestyle Changes
- Dietary Approaches to Stop Hypertension
- American Diabetes Association

No firm consensus on the most appropriate dietary recommendations exists for

Metabolic Syndrome

So, the question is:

How do you define those patients with insulin resistance who are candidates for cardiovascular disease from those who are candidates for diabetes or other manifestations of metabolic syndrome?

Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies

Naveed Sattar, Alex McConnachie, A Gerald Shaper, Gerard J Blauw, Brendan M Buckley, Anton J de Craen, Ian Ford, Nita G Forouhi, Dilys J Freeman, J Wouter Jukema, Lucy Lennon, Peter W Macfarlane, Michael B Murphy, Chris J Packard, David J Stott, Rudi G Westendorp, Peter H Whincup, James Shepherd, S Goya Wannamethee

Summary

Background Clinical use of criteria for metabolic syndrome to simultaneously predict risk of cardiovascular disease and diabetes remains uncertain. We investigated to what extent metabolic syndrome and its individual components were related to risk for these two diseases in elderly populations.

Methods We related metabolic syndrome (defined on the basis of criteria from the Third Report of the National Cholesterol Education Program) and its five individual components to the risk of events of incident cardiovascular disease and type 2 diabetes in 4812 non-diabetic individuals aged 70–82 years from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). We corroborated these data in a second prospective study (the British Regional Heart Study [BRHS]) of 2737 non-diabetic men aged 60–79 years.

Findings In PROSPER, 772 cases of incident cardiovascular disease and 287 of diabetes occurred over 3·2 years. Metabolic syndrome was not associated with increased risk of cardiovascular disease in those without baseline disease (hazard ratio 1·07 [95% CI 0·86–1·32]) but was associated with increased risk of diabetes (4·41 [3·33–5·84]) as was each of its components, particularly fasting glucose (18·4 [13·9–24·5]). Results were similar in participants with existing cardiovascular disease. In BRHS, 440 cases of incident cardiovascular disease and 105 of diabetes occurred over 7 years. Metabolic syndrome was modestly associated with incident cardiovascular disease (relative risk 1·27 [1·04–1·56]) despite strong association with diabetes (7·47 [4·90–11·46]). In both studies, body-mass index or waist circumference, triglyceride, and glucose cutoff points were not associated with risk of cardiovascular disease, but all five components were associated with risk of new-onset diabetes.

Lancet 2008; 371: 1927–35
Published Online
May 22, 2008
DOI:10.1016/S0140-6736(08)60602-9

See Comment page 1892

Faculty of Medicine (Prof N Sattar FRCPath, D J Freeman PhD, Prof P W Macfarlane DSc, Prof C J Packard DSc, Prof D J Stott MD, Prof J Shepherd MD) and Robertson Centre for Biostatistics (A McConnachie PhD, Prof I Ford PhD), University of Glasgow, Glasgow, UK; MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrookes Hospital, Cambridge, UK (N G Forouhi FFPH); Department of Pharmacology

"Metabolic syndrome and its components are associated with type 2 diabetes but have weak or no association with vascular risk in elderly populations, suggesting that attempts to define criteria that simultaneously predict risk for both cardiovascular disease and diabetes are unhelpful".

Lancet 2008; 371: 1972-79.

Metabolic syndrome—what is the clinical usefulness?

"More research is needed to understand the cause of risk-factor clustering and the pathogenesis of insulin resistance".

metabolic syndrome for predicting diabetes. They also show that a diagnosis of the metabolic syndrome has

factors of cardiovascular disease are found more often in combination than chance would dictate. Thus identi-

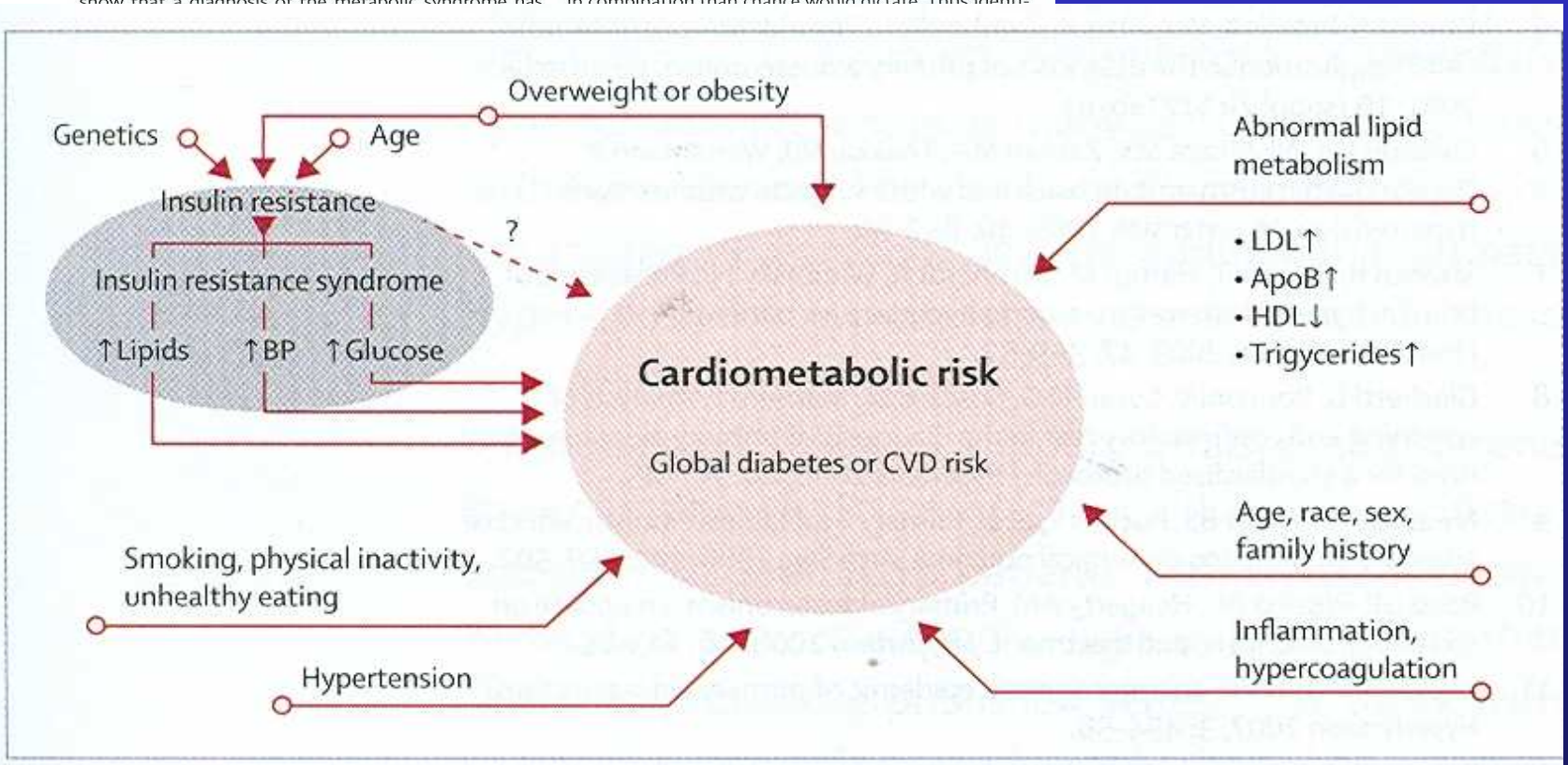

Figure: **Factors contributing to cardiometabolic risk[12]**

ApoB=apolipoprotein B. BP=blood pressure. CVD=cardiovascular c

Lancet 2008; 371: 1892.

Nutrition & Metabolism BioMed Central

Enhancement of a modified Mediterranean-style, low glycemic load diet with specific phytochemicals improves cardiometabolic risk factors in subjects with metabolic syndrome and hypercholesterolemia in a randomized trial

Nutrition & Metabolism 2008, **5**:29 doi:10.1186/1743-7075-5-29

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Abstract

As the worldwide dietary pattern becomes more westernized, the metabolic syndrome is reaching epidemic proportions. Lifestyle modifications including diet and exercise are recommended as first-line intervention for treating metabolic syndrome. Previously, we reported that a modified Mediterranean-style, low glycemic load diet with soy protein and phytosterols had a morefavorable impact than the American Heart Association Step 1 diet on cardiovascular disease(CVD) risk factors. Subsequently, we screened for phytochemicals with a history of safe use that were capable of increasing insulin sensitivity through modulation of protein kinases, and

identified hops *rho* iso-alpha acid and acacia proanthocyanidins. The objective of this study was to investigate whether enhancement of a modified Mediterranean-style, low glycemic load diet (MED) with specific phytochemicals (soy protein, phytosterols, *rho* iso-alpha acids and proanthocyanidins; PED) could improve cardiometabolic risk factors in subjects with metabolic sy

Lerman, Minich, Tripp and Bland, Nutrition and Metabolism 2008; 5: 29-34.

Clinical and Laboratory Assessment Summary

- Serum Triglycerides elevated (greater than 130)
- Serum HDL depressed (males <40; females<50)
- Serum Triglyceride to HDL ratio greater than 4:1
- Elevated C reactive protein (<0.9)
- Hemoglobin A1c greater than 5.5%
- Elevated serum liver enzymes (AST/ALT)
- Elevated Percent Body Fat
- Elevated Waist to Hip ratio (greater than 1)
- Elevated Waist circumference (men>40inch; women>35)
- Elevated Systolic and/or Diastolic Blood Pressure (greater than 130/85)
- Elevated Apo B and Reduced Apo A1 (Above 0.6)
- Elevated serum Asymmetrical Dimethylarginine (ADMA)
- Elevated serum Lipoprotein-associated Phospholipase A2 (PLAX)

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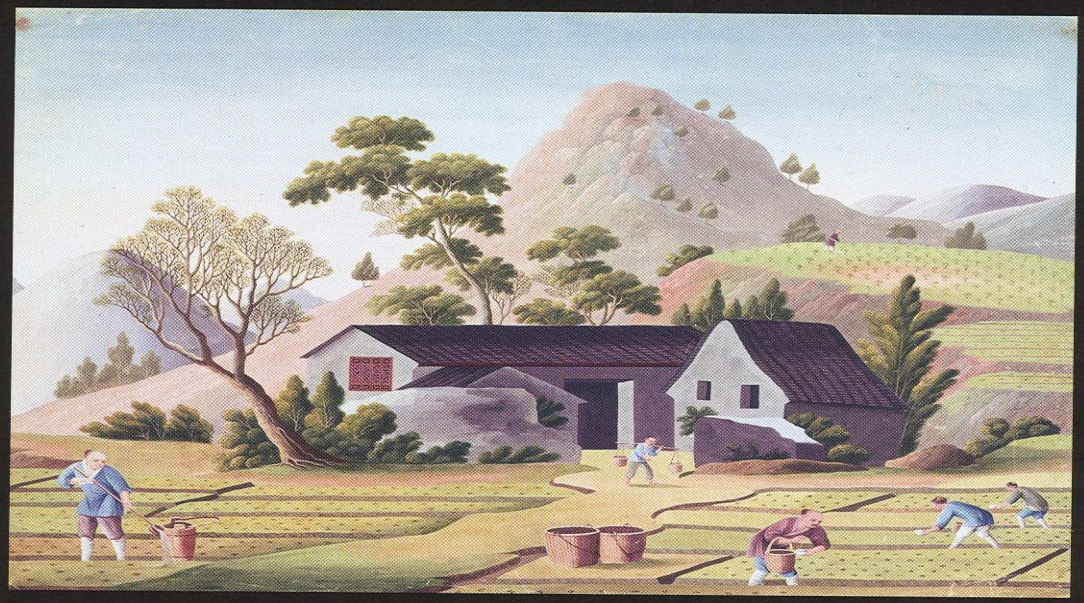


DIETARY MANAGEMENT OF THE METABOLIC SYNDROME BEYOND MACRONUTRIENTS

Lead Article

Dietary management of the metabolic syndrome beyond macronutrients

Deanna M Minich and Jeffrey S Bland

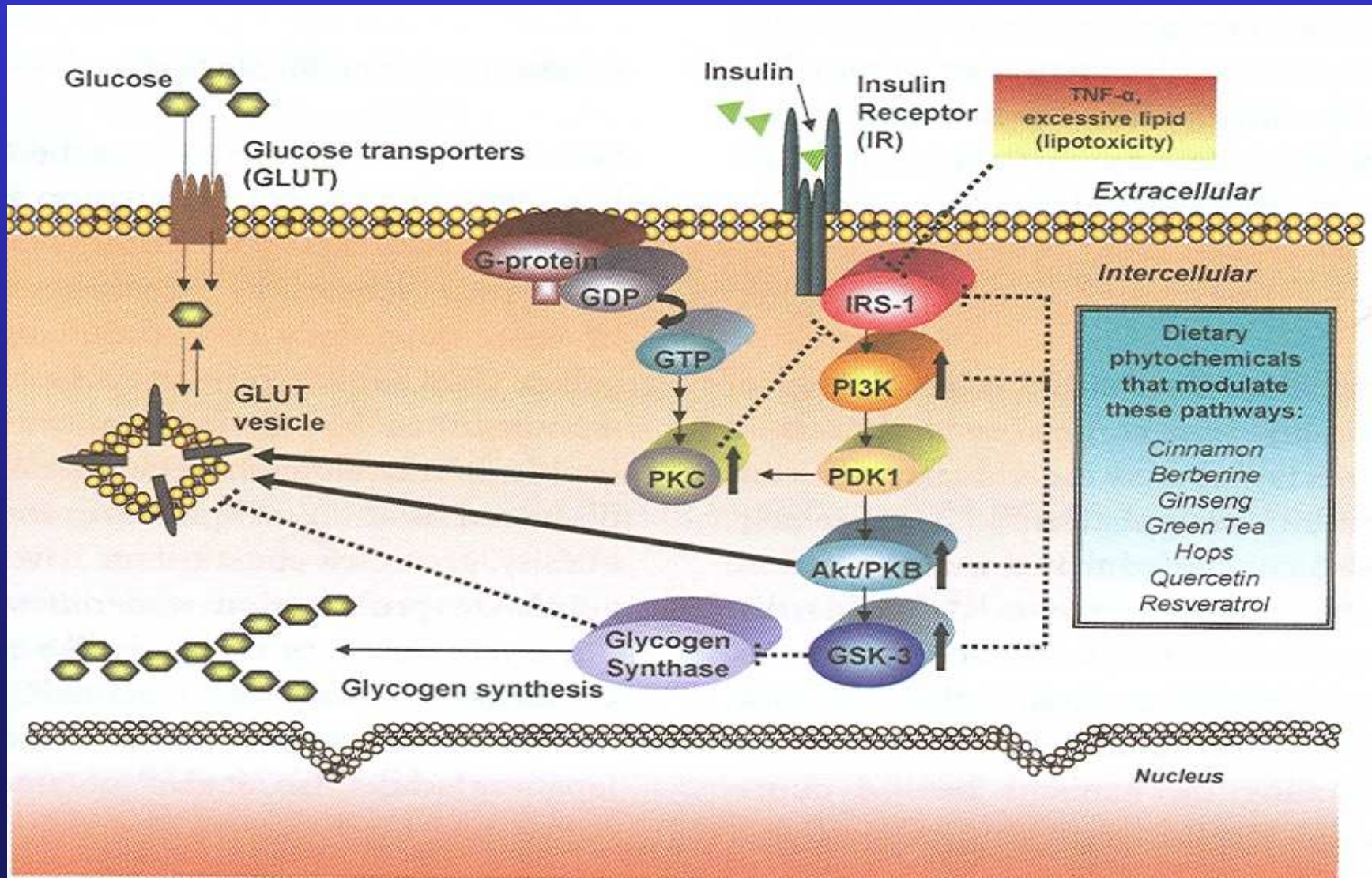
Due to the complexity of chronic conditions like the metabolic syndrome (MetS), tailored dietary approaches beyond macronutrient ratio modification may be necessary to effectively address metabolic measures. Mounting data on whole foods-based, phytochemical-abundant dietary patterns, such as the Mediterranean diet, reveal that they contain constituents, such as phytochemicals, that may be beneficial for treating MetS. The role of food-based phytochemicals on underlying mechanisms of MetS, specifically as they impact insulin signaling, has yet to be investigated thoroughly. This review discusses various dietary approaches for MetS, with a focus on certain foods and dietary phytochemicals known to impact insulin signaling.

"Mounting data on whole foods-based, phytochemical-abundant dietary patterns, such as the Mediterranean diet, reveal that they contain phytochemicals that may be beneficial for treating MetS".

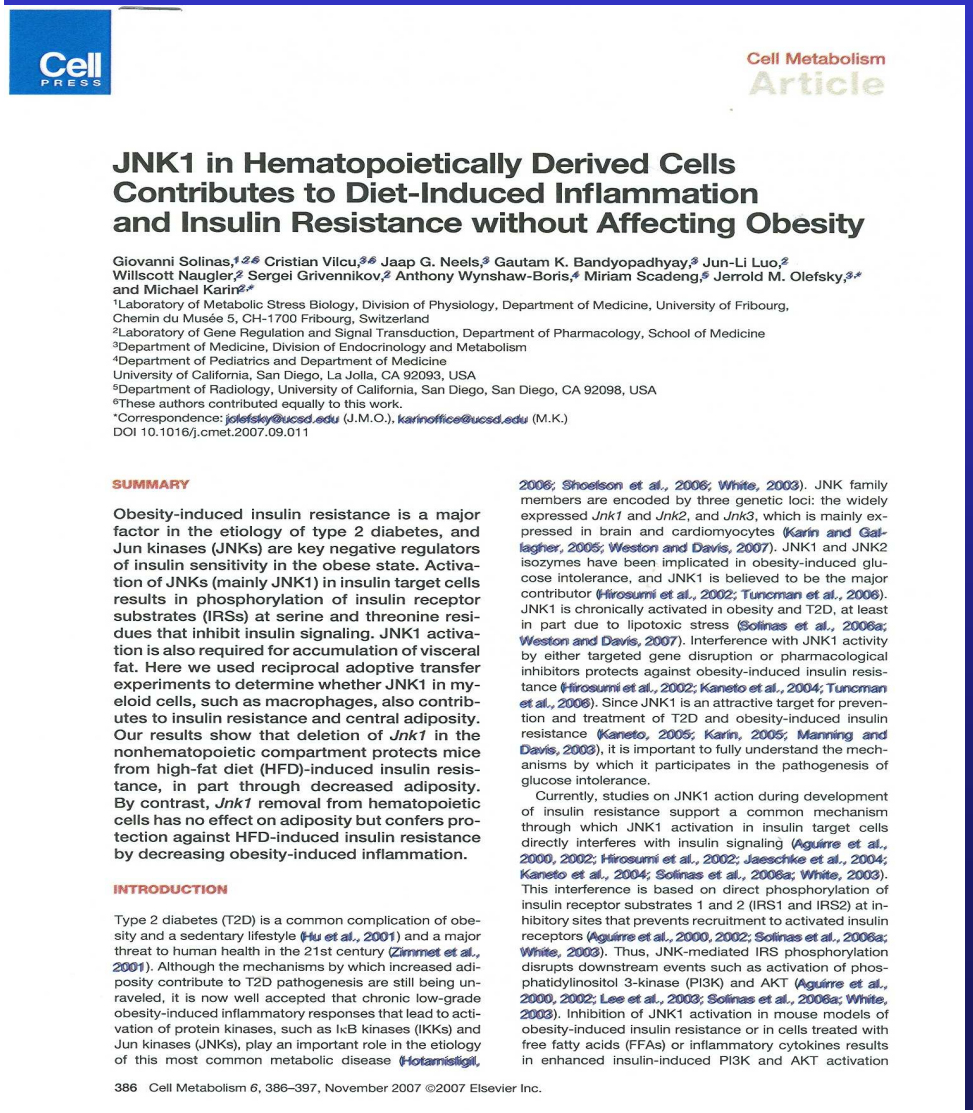
Minich and Bland, Nutrition Reviews, August 2008

doi:10.1111/j.1753-4887.2008.00075.x
Nutrition Reviews® Vol. 66(8):429–444

Role of Phytochemicals on Insulin Signaling



Inflammation, not Obesity, Causes Insulin Resistance



Cell PRESS

Cell Metabolism
Article

JNK1 in Hematopoietically Derived Cells Contributes to Diet-Induced Inflammation and Insulin Resistance without Affecting Obesity

Giovanni Solinas,[1,2,6] Cristian Vilcu,[3,6] Jaap G. Neels,[3] Gautam K. Bandyopadhyay,[3] Jun-Li Luo,[2] Willscott Naugler,[2] Sergei Grivennikov,[2] Anthony Wynshaw-Boris,[4] Miriam Scadeng,[5] Jerrold M. Olefsky,[3,*] and Michael Karin[2,*]

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DOI 10.1016/j.cmet.2007.09.011

SUMMARY

Obesity-induced insulin resistance is a major factor in the etiology of type 2 diabetes, and Jun kinases (JNKs) are key negative regulators of insulin sensitivity in the obese state. Activation of JNKs (mainly JNK1) in insulin target cells results in phosphorylation of insulin receptor substrates (IRSs) at serine and threonine residues that inhibit insulin signaling. JNK1 activation is also required for accumulation of visceral fat. Here we used reciprocal adoptive transfer experiments to determine whether JNK1 in myeloid cells, such as macrophages, also contributes to insulin resistance and central adiposity. Our results show that deletion of *Jnk1* in the nonhematopoietic compartment protects mice from high-fat diet (HFD)-induced insulin resistance, in part through decreased adiposity. By contrast, *Jnk1* removal from hematopoietic cells has no effect on adiposity but confers protection against HFD-induced insulin resistance by decreasing obesity-induced inflammation.

INTRODUCTION

Type 2 diabetes (T2D) is a common complication of obesity and a sedentary lifestyle (Hu et al., 2001) and a major threat to human health in the 21st century (Zimmet et al., 2001). Although the mechanisms by which increased adiposity contribute to T2D pathogenesis are still being unraveled, it is now well accepted that chronic low-grade obesity-induced inflammatory responses that lead to activation of protein kinases, such as IκB kinases (IKKs) and Jun kinases (JNKs), play an important role in the etiology of this most common metabolic disease (Hotamisligil, 2006; Shoelson et al., 2006; White, 2003). JNK family members are encoded by three genetic loci: the widely expressed *Jnk1* and *Jnk2*, and *Jnk3*, which is mainly expressed in brain and cardiomyocytes (Karin and Gallagher, 2005; Weston and Davis, 2007). JNK1 and JNK2 isozymes have been implicated in obesity-induced glucose intolerance, and JNK1 is believed to be the major contributor (Hirosumi et al., 2002; Tuncman et al., 2006). JNK1 is chronically activated in obesity and T2D, at least in part due to lipotoxic stress (Solinas et al., 2006a; Weston and Davis, 2007). Interference with JNK1 activity by either targeted gene disruption or pharmacological inhibitors protects against obesity-induced insulin resistance (Hirosumi et al., 2002; Kaneto et al., 2004; Tuncman et al., 2006). Since JNK1 is an attractive target for prevention and treatment of T2D and obesity-induced insulin resistance (Kaneto, 2005; Karin, 2005; Manning and Davis, 2003), it is important to fully understand the mechanisms by which it participates in the pathogenesis of glucose intolerance.

Currently, studies on JNK1 action during development of insulin resistance support a common mechanism through which JNK1 activation in insulin target cells directly interferes with insulin signaling (Aguirre et al., 2000, 2002; Hirosumi et al., 2002; Jaeschke et al., 2004; Kaneto et al., 2004; Solinas et al., 2006a; White, 2003). This interference is based on direct phosphorylation of insulin receptor substrates 1 and 2 (IRS1 and IRS2) at inhibitory sites that prevents recruitment to activated insulin receptors (Aguirre et al., 2000, 2002; Solinas et al., 2006a; White, 2003). Thus, JNK-mediated IRS phosphorylation disrupts downstream events such as activation of phosphatidylinositol 3-kinase (PI3K) and AKT (Aguirre et al., 2000, 2002; Lee et al., 2003; Solinas et al., 2006a; White, 2003). Inhibition of JNK1 activation in mouse models of obesity-induced insulin resistance or in cells treated with free fatty acids (FFAs) or inflammatory cytokines results in enhanced insulin-induced PI3K and AKT activation

- Activated macrophages release proinflammatory substances that, in turn, stimulate kinase receptors on cells resulting in altered insulin signaling
- This process is independent of obesity
- Cell Metabolism 2007; 6: 386-97.

Atherogenic Dyslipidemia Associated with Metabolic Syndrome and Insulin Resistance

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Dallas, Texas

Atherogenic dyslipidemia, a component of metabolic syndrome, is characterized by high levels of apolipoprotein B (apo B)–containing lipoproteins, including very-low-density lipoprotein remnants and small low-density lipoprotein particles, and reduced levels of high-density lipoprotein cholesterol. Although the National Cholesterol Education Program Adult Treatment Panel III includes elevations in blood pressure and plasma glucose in the definition of metabolic syndrome, the broader scope of metabolic syndrome includes proinflam-

"Atherogenic dyslipidemia, a component of metabolic syndrome, is characterized by high levels of apolipoprotein B-containing lipoproteins, including LDL remnants and small LDL parts, and a reduced level of HDL lipoprotein cholesterol".

Clin Cornerstone 2006; 8: s21.

minogen activator inhibitor-1 and fibrinogen.[1]

Atherogenic dyslipidemia manifests predominantly as elevated levels of very-low-density lipoprotein (VLDL) remnants and small low-density lipoprotein (LDL) particles, as well as reduced levels of high-density lipoprotein cholesterol (HDL-C).[1] Elevated LDL cholesterol (LDL-C) is not a characteristic of atherogenic dyslipid-

Atherogenic dyslipidemia manifests predominantly as elevated levels of VLDL remnants and small LDL particles, as well as reduced levels of HDL-C.

International Journal of Obesity (2007) 1–7

0307-0565/07 $30.00
www.nature.com/ijo

ORIGINAL ARTICLE

Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension and diabetes, independent of markers of central obesity and inflammation

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[1]*Department of Cardiology, Turkish Society of Cardiology, Turkey;* [2]*Department of Public Health, Cerrahpaşa Medical Faculty, Istanbul University, Turkey;* [3]*Biology Department, Yıldız Technical University, İstanbul, Turkey;* [4]*Medical Faculty Cardiology Section, Düzce University, Düzce, Turkey and* [5]*Department of Cardiology, S. Ersek Center for Cardiovascular Surgery, İstanbul, Turkey*

Objectives: To investigate the role of serum apolipoprotein (apo) B levels in predicting metabolic syndrome (MS), hypertension, atherogenic dyslipidemia and type II diabetes.
Methods: Prospective evaluation of 1125 men and 1223 women, aged 28–74 years, participating in the survey 1997/1998 who had serum apo B determinations and were followed-up for a mean 5.9 years. Tertiles of apo B were formed by cut points by 120 and 95 mg/dl. MS was defined by modified ATPIII criteria.
Results: Apo B values exhibited no significant difference among sexes. Low-density lipoprotein (LDL)-cholesterol and triglycerides were their leading determinants on linear regression analysis. By logistic regression analyses, the top versus bottom apo B tertile predicted significantly newly developing MS in both sexes separately with two-fold relative risks (RRs) ($P<0.02$) and the development of high triglyceride/low high-density lipoprotein-cholesterol dyslipidemia with nearly threefold RRs ($P=0.001$), after adjustment for waist circumference, C-reactive protein (CRP), physical activity grade and family income category. Development of hypertension was predicted only in women by the apo B top tertile (fully adjusted RR 1.71 [95% CI 1.001; 2.92]), while the significance of the prediction regarding age-adjusted diabetes in women (RR 1.86 [95% CI 1.04; 3.36]) attenuated after adjustment for the stated confounding factors.
Conclusions: Apo B concentrations, which reflect the number of small, dense LDL particles in plasma, are a significant predictor of cardiometabolic risk among adults with a high prevalence of MS, independent of waist circumference and CRP.
International Journal of Obesity advance online publication, 13 February 2007; doi:10.1038/sj.ijo.0803552

Keywords: apolipoprotein B; central obesity; diabetes mellitus; dyslipidemia; hypertension; metabolic syndrome

"Apo B which reflect the number of small, dense LDL particles in plasma, is a signficant predictor of cardiometabolic risk among adults with a high prevalence of metabolic syndrome, independent of waist circumference or hsCRP".

Inter J Obesity 2007; 10: 1-7.

Journal of Internal Medicine 2006; **259**: 493–519 doi:10.1111/j.1365-2796.2006.01643.x

SYMPOSIUM

The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy – a review of the evidence

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From the [1]King Gustaf V Research Institute, Karolinska Institute, Stockholm; [2]AstraZeneca, Södertälje; [3]Department of Medicine, Karolinska Institute, Epidemiological Unit, Stockholm; and [4]CALAB Research, Stockholm; Sweden

Abstract. Walldius G, Jungner I (Karolinska Institute, Stockholm; AstraZeneca, Södertälje; and CALAB Research, Stockholm; Sweden). The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy – a review of the evidence. *J Intern Med* 2006; **259**: 493–519.

During the last several years interest has focused

subjects and in patients with different clinical manifestations of atherosclerosis are reported. Risk of nonfatal and fatal myocardial infarction and stroke, and manifestations of atherosclerosis documented by angiographic, ultrasound and other techniques has been related to conventional lipids and apolipoproteins (apo). The cholesterol balance determined as the apoB/apoA-I

"The results indicate that the apoB/Apo A-1 ratio is a simple, accurate and new risk factor for CV disease-the lower the apoB/apoA1 ratio, the lower is the risk".

J Internal Medicine 2006; 259: 493-519

Introduction

Low-density lipoprotein cholesterol (LDL C) is recognized as the primary lipid risk factor. In order to make a proper evaluation of lipid-related risk, high-density lipoprotein cholesterol (HDL C), non-HDLC as well as triglyceride (TG) levels, and lipid ratios such as total cholesterol (TC)/HDL C and LDL C/HDL C, should also be considered as proposed in several major guidelines [1–3]. It is not easy for the treating doctor to properly remember and follow all recommended cut-values, and therefore most doctors concentrate on risk evaluation based on LDL C and HDL C values. Is it at all possible to simplify the risk evaluation and use apolipoproteins (apo) as markers of risk and as targets for lipid-lowering therapy? In fact, new data are accumulating which speak in favour of apo as more informative risk markers/factors than

Comparison of Apolipoprotein-B/Apolipoprotein-AI in Subjects With Versus Without the Metabolic Syndrome

Justo Sierra-Johnson, MD, MS[a], Virend Kristen Somers, MD, PhD[a], Fatima Helena Sert Kuniyoshi, MS[a], Carolina Ana Garza, MD[a], William Luther Isley, MD[b], Apoor Suresh Gami, MD[a], and Francisco Lopez-Jimenez, MD, MS[a,*]

Recent studies have suggested that the apolipoprotein-B (apo-B)/apolipoprotein-AI (apo-AI) ratio predicts cardiovascular risk better than any of the cholesterol indexes. The aim of the present study was to assess if the apo-B/apo-AI ratio is related to the metabolic syndrome and its components. Data were analyzed from 2,964 subjects (mean age 48 years; 1,516 men, 1,448 women) from the National Health and Nutrition Examination Survey III with apolipoprotein data who were evaluated for the metabolic syndrome and its components. The metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III and the International Diabetes Federation. The mean values of the apo-B/apo-AI ratio in subjects with and without the metabolic syndrome were compared. Overall, the median distribution of the apo-B/apo-AI ratio was significantly greater ($p < 0.0001$) in subjects with the Adult Treatment Panel III metabolic syndrome (0.90) than without (0.69). The apo-B/apo-AI ratio was associated significantly with each of the metabolic syndrome components, in descending order of magnitude: low high-density lipoprotein cholesterol (odds ratio [OR] 5.7), high triglycerides (OR 4.7), high waist circumference (OR 2.6), high fasting glucose (OR 1.9), and high blood pressure (OR 1.5). The apo-B/apo-AI ratio was also different between subjects with and without the metabolic syndrome. Mean values of apo-B/apo-AI increased significantly as the numbers of metabolic syndrome components increased in men ($p < 0.0001$) and women ($p < 0.0001$). After excluding high-density lipoprotein cholesterol and triglycerides as criteria for the metabolic syndrome, the association between means persisted (analysis of variance $p < 0.0001$) in men and women. Apo-B/apo-AI was significantly associated with the presence of the metabolic syndrome (OR 5.1, $p < 0.0001$). In conclusion, the apo-B/apo-AI ratio is strongly associated with the presence of individual metabolic syndrome components, with the metabolic syndrome itself, and with insulin resistance. An

"In conclusion, the apoB/apoA1 ratio is strongly associated with the presence of metabolic syndrome".

Am J Cardiol 2006; 98: 1369-73

apo-B/apo-AI and the metabolic syndrome and its individual components in a representative sample of the United States population.

provide an estimate of the health of the nation. Detailed methods used in NHANES III are available for public access on the World Wide Web at http://www.cdc.gov/nchs/nhanes.htm.

NHANES information was obtained from in-home interviews followed by medical evaluations and blood sample collections at a mobile examination center. We limited the present analysis of the 2 surveys to men and nonpregnant women aged ≥20 but <90 years (excluded n = 602) who attended the morning medical examination (excluded n = 3,979) and who had fasted for ≥8 hours (excluded n = 5,874). We excluded data for those judged by their interviewers to have provided unreliable data and those with missing data for apo-B, apo-AI, or the metabolic syndrome components (n = 10,409). This resulted in a final analytic sample of 2,964 subjects (1,516 men, 1,448 women). Height, weight, and body circumferences were

Divisions of [a]Cardiovascular Diseases and [b]Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota. Manuscript received February 3, 2006; revised manuscript received and accepted June 12, 2006.

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The HDL is a functional lipoprotein that reflects inflammatory status

Research article Related Commentary, page 595

Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL

Tomas Vaisar,[1] Subramaniam Pennathur,[1] Pattie S. Green,[1] Sina A. Gharib,[1] Andrew N. Hoofnagle,[2] Marian C. Cheung,[1] Jaeman Byun,[1] Simona Vuletic,[1] Sean Kassim,[1] Pragya Singh,[1] Helen Chea,[1] Robert H. Knopp,[1] John Brunzell,[1] Randolph Geary,[3] Alan Chait,[1] Xue-Qiao Zhao,[1] Keith Elkon,[1] Santica Marcovina,[1] Paul Ridker,[4] John F. Oram,[1] and Jay W. Heinecke[1]

[1]Department of Medicine and [2]Department of Laboratory Medicine, University of Washington School of Medicine, Seattle, Washington, USA. [3]Division of Surgical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA. [4]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.

HDL lowers the risk for atherosclerotic cardiovascular disease by promoting cholesterol efflux from macrophage foam cells. However, other antiatherosclerotic properties of HDL are poorly understood. To test the hypothesis that the lipoprotein carries proteins that might have novel cardioprotective activities, we used shotgun proteomics to investigate the composition of HDL isolated from healthy subjects and subjects with coronary artery disease (CAD). Unexpectedly, our analytical strategy identified multiple complement-regulatory proteins and a diverse array of distinct serpins with serine-type endopeptidase inhibitor activity. Many acute-phase response proteins were also detected, supporting the proposal that HDL is of central importance in inflammation. Mass spectrometry and biochemical analyses demonstrated that HDL_3 from subjects with CAD was selectively enriched in apoE, raising the possibility that HDL carries a unique cargo of proteins in humans with clinically significant cardiovascular disease. Collectively, our observations suggest that HDL plays previously unsuspected roles in regulating the complement system and protecting tissue from proteolysis and that the protein cargo of HDL contributes to its antiinflammatory and antiatherogenic properties.

Introduction

Mortality from cardiovascular disease has decreased significantly in the United States over the past 30 years (1, 2). Many factors have contributed to this improvement, including the identification of cardiovascular risk factors, development of interventions that reduce those risk factors, and new treatments for acute coronary syndromes. Despite these advances, however, cardiovascular disease remains the leading cause of mortality in the United States (1, 2).

One important risk factor for atherosclerosis is a low level of HDL, which directly protects against atherosclerosis by removing cholesterol from artery wall macrophages (3, 4). Thus, the risk of cardiovascular disease is inversely proportional to plasma levels of HDL and its major apolipoprotein, apoA-I (5). Also, low HDL levels are particularly common in men with premature atherosclerosis (6), whereas high HDL levels associate with longevity (7).

Antiinflammatory and antioxidant properties might also contribute to the cardioprotective effects of HDL (8). Moreover, both oxidative modifications and alterations in the protein cargo of HDL may alter its biological activity, creating potentially proatherogenic particles (8, 9). We and others recently showed that HDL isolated from plasma of patients with known coronary artery disease (CAD) is oxidatively modified and that oxidation impairs reverse cholesterol transport mediated by HDL (10–12). Circulating levels of serum amyloid A (SAA), an inflammatory protein in HDL, predict the risk of heart disease in humans (13), and HDL-associated SAA has been proposed to render the lipoprotein atherogenic (14). Furthermore, alterations in the balance between pro- and antioxidative enzymes in HDL appear to play a critical role in converting the lipoprotein to a proatherogenic form (8).

We hypothesized that quantifying the protein composition of HDL might provide insights into the antiatherogenic and antiinflammatory properties of the lipoprotein. We therefore used shotgun proteomics — direct analysis of a complex mixture of proteins (15) — to study the HDL proteome. After digesting the lipoprotein with trypsin, we analyzed the resulting peptide mixture with mass spectrometry (MS) and matched the tandem mass spectra of the peptides with spectra derived from protein sequences in protein database. We found that HDL carries protein families implicated in complement activation and regulation of proteolysis, raising the possibility that these proteins contribute to the innate immune system and the cardioprotective properties of HDL.

Results

Shotgun proteomics identifies distinct protein families in HDL. We first confirmed that liquid chromatography–electrospray ionization–tandem MS (LC-ESI-MS/MS) analysis reproducibly identifies the same HDL-associated proteins (Supplemental Figure 1; supplemental material available online with this article; doi:10.1172/JCI26206DS1). We then used this analytical strategy to investigate the protein composition of HDL isolated by ultracentrifugation in 2 independent groups of subjects (see Methods). The first used total HDL isolated from 20 apparently healthy control subjects (group 1), and the second used HDL_3 isolated from 13 subjects

Nonstandard abbreviations used: CAD, coronary artery disease; CETP, cholesteryl ester transfer protein; GO, Gene Ontology; LC-ESI-MS/MS, liquid chromatography–electrospray ionization–tandem MS; MS, mass spectrometry; PON1, paraoxonase-1; PRINCE study, Pravastatin Inflammation/CRP Evaluation study; SAA, serum amyloid A.

Conflict of interest: The authors have declared that no conflict of interest exists.

Citation for this article: *J. Clin. Invest.* **117**:746–756 (2007). doi:10.1172/JCI26206.

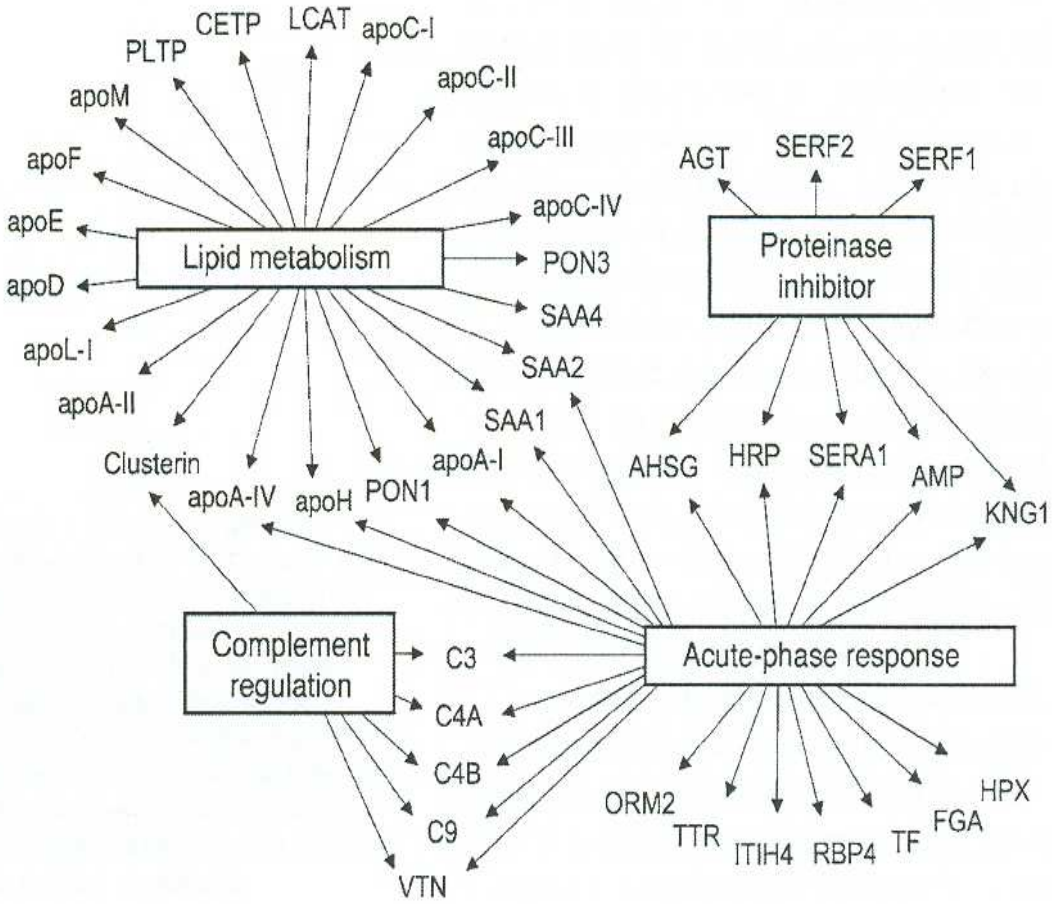
The HDL is different from all other lipoproteins in that it contains 42 proteins that reflect the immunoendocrine status of the person

These proteins vary in abundancy with changing inflammatory status

J Clin Invest 2007; 117: 746-52.

Functional Apo-proteins making up HDL

Figure 1
Global view of biological processes and molecular functions of HDL proteins. Proteins in total HDL and HDL_3 were identified using LC-ESI-MS/MS (Table 2). Proteins detected in HDL were associated with biological functions using GO process annotations. This approach demonstrated significant overrepresentation of proteins involved in several categories, including lipid metabolism ($P = 2 \times 10^{-27}$), the acute-phase response ($P = 1 \times 10^{-18}$), protease inhibitor activity ($P = 2 \times 10^{-6}$), and complement regulation ($P = 5 \times 10^{-5}$). apoH, β-2-glycoprotein I; AGT, angiotensinogen; AHSG, α-2-HS-glycoprotein; AMP, bikunin; FGA, fibrinogen; HRP, haptoglobin-related protein; HPX, hemopexin; ITIH4, inter-α-trypsin inhibitor heavy chain H4; KNG1, kininogen-1; LCAT, lecithin-cholesterol acyltransferase; ORM2, α-1-acid glycoprotein 2; PLTP, phospholipid transfer protein; RBP4, retinol binding protein; SERA1, α-1-antitrypsin; SERF1, serpin peptidase inhibitor (clade F, member 1); SERF2, α-2-antiplasmin; TF, transferrin; TTR, transthyretin; VTN, vitronectin.



Comparison of Representative Clinical Outcomes in Metabolic Syndrome

	TG	TG/HDL	Insulin	apoB/ apoA-1	LDL	HDL	BP S=systolic D=diastolic	Weight change (lbs)	Potential side effects
Medical food with SKRMs plus low glycemic load diet[#]	-35.2%	-42.7%	-26.8%	-15.4%	-17.3%	+7.0%	-4.9% (S) -5.7% (D)	-13	None reported
Mediterranean diet with low glycemic load diet[#]	-14.3%	-17.6%	-22.3%	-6.3%	-8.4%	+2.7%	-3.5% (S) -0.9% (D)	-12.6	None reported
Cholesterol Reduction									
Statins	-15-32%[aeil]		+8%[l] +1.3%[o*]	-22.7-45%[eim]	-30-47%[el]	+0-15%[aeil]	-2.9-0%[ai] (S) -2.6-3.5%[j] (D)	-0.5[l]	Muscle wasting, neuromuscular pain, liver toxicity, CoQ_{10} deficiency
Anti-Diabetic									
Metformin	-15%[a] +7-8.5%[fn]		-29%[o*]		+11.9%[n] -3.5%[o*]	+0.9-15%[afn]	-5-0%[af] (S) -2.2%[f] (D)	-3.0[n] -5.3[p]	Nausea, diarrhea, gas, bloating
TZD	-4-12%[ag] +3.8%[bf]	-13%[g]	-24.5%[bf] -16%[g]		+7%[g] 0%[b]	+9-14%[ag]	-5%[a] (S) -4.5%[n*] (D)	0[bg] +1.5-6.0[pr]	Nonalcoholic steatotic hepatitis, fluid retention, weight gain
Triglyceride Reduction									

[a]Wierzbicki, Int J Clin Pract 2006;60(12):1697-1706. [b]Samaha et al., Arterioscler Thromb Vasc Biol 2006;26:624-30. [d]Farragh et al., Br J Clin Pharmacol 2006;61(6):694-701. [e]McIntyne et al., Am J Cardiol 2003;91(suppl):25C-8C. [f]Nieuwdorp et al., Diabetes Obes Metab 2007;9:869-78. [g]Szapary et al., Arterioscler Thromb Vasc Biol 2004;24:2392-8. [i]Hunninghake et al., Clin Ther 2003;25(6):1670-86. [j]Davidson et al., Clin Ther 2005;27(6):715-27. [k]Goldberg et al., Am J Cardiol 2000;85:1100-5. [l]McKenney et al., Am J Med 1998;104:137-43. [m]Sirtori et al., Pharmacol Res 2007;55:499-508. [n]Einhorn et al., Circulation 2000;22(10):1404-1409. [o]Silva et al., Braz J Med Biol Res 2007;40:329-35. [p]Pavo et al., J Clin Endocrinol Metab 2003;88:1637-45. [q]Steinmetz et al., J Cardiovasc Pharmacol 1996;27(4):563-70. [r]Stadnyk et al., Diabetes Care 2003;26(11):3148-52.
*calculated from mean change divided by mean baseline value. †calculated from median change divided by median baseline value.
[#]Results obtained in a 12-wk, open-labeled, randomized, controlled clinical trial conducted with 44 subjects at the Functional Medicine Research Center. Published in Nutrition & Metabolism 2008, 5(1): 29 (PMID: 18983673)

Mediterranean Diet and Mild Cognitive Impairment

Nikolaos Scarmeas, MD; Yaakov Stern, PhD; Richard Mayeux, MD; Jennifer J. Manly, PhD; Nicole Schupf, PhD; Jose A. Luchsinger, MD

Background: Higher adherence to the Mediterranean diet (MeDi) may protect from Alzheimer disease (AD but its association with mild cognitive impairment (MC has not been explored.

Objective: To investigate the association between th MeDi and MCI.

Design, Setting, and Patients: In a multiethnic con munity study in New York, we used Cox proportional ha ards to investigate the association between adherence t the MeDi (0-9 scale; higher scores indicate higher adhe ence) and (1) the incidence of MCI and (2) the progre sion from MCI to AD. All of the models were adjusted fo cohort, age, sex, ethnicity, education, *APOE* genotype, ca loric intake, body mass index, and duration between bas line dietary assessment and baseline diagnosis.

Main Outcome Measures: Incidence of MCI and pro gression from MCI to AD.

Results: There were 1393 cognitively normal partic pants, 275 of whom developed MCI during a mean (SD follow-up of 4.5 (2.7) years (range, 0.9-16.4 years). Com-

THE CONC nitive im was deve subjects transitio normal aging and deme disease (AD). Because o sion rates, subjects with population suited for tia-AD risk factor epiden vestigation of possible b macological preventiv Among behavioral traits important role in the c tion of AD. However, epi on diet and AD have b Moreover, there is a pau the effect of dietary fact of development of MCI conversion to AD.

We recently demons adherence to the Me (MeDi) (a diet characte

Author Affiliations: Departments of Neurology (Drs Scarmeas, Stern, Mayeux, and Manly) and Medicine (Dr Luchsinger), the Gertrude H. Sergievsky Center (Drs Scarmeas, Stern, Mayeux, Manly, and Schupf), and the Taub Institute for Research in Alzheimer's Disease and the Aging Brain (Drs Scarmeas, Stern, Mayeux, Manly, Schupf, and Luchsinger), Columbia University Medical Center, New York, New York.

Table 3. Cox Proportional Hazard Ratios for Incidence of Mild Cognitive Impairment for Subjects Who Were Cognitively Normal at the First Evaluation by Mediterranean Diet Score

Predictor	HR (95% CI)	*P* Value
Unadjusted[a]		
MeDi continuous	0.93 (0.87-1.00)	.06
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.87 (0.66-1.14)	.33
High	0.73 (0.53-1.00)	.05
Trend	0.85 (0.73-1.00)	.05
Adjusted[b]		
MeDi continuous	0.92 (0.85-0.99)	.04
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.83 (0.62-1.12)	.24
High	0.72 (0.52-1.00)	.05
Trend	0.85 (0.72-1.00)	.05

Abbreviations: CI, confidence interval; HR, hazard ratio; MeDi, Mediterranean diet; NA, not applicable.

[a] A total of 1393 subjects were cognitively normal at the first evaluation; 275 subjects developed incident mild cognitive impairment.

[b] A total of 1199 subjects were cognitively normal at the first evaluation; 241 subjects developed incident mild cognitive impairment. Adjusted models include a slightly lower number of subjects because of missing data in some of the covariates; they simultaneously control for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment.

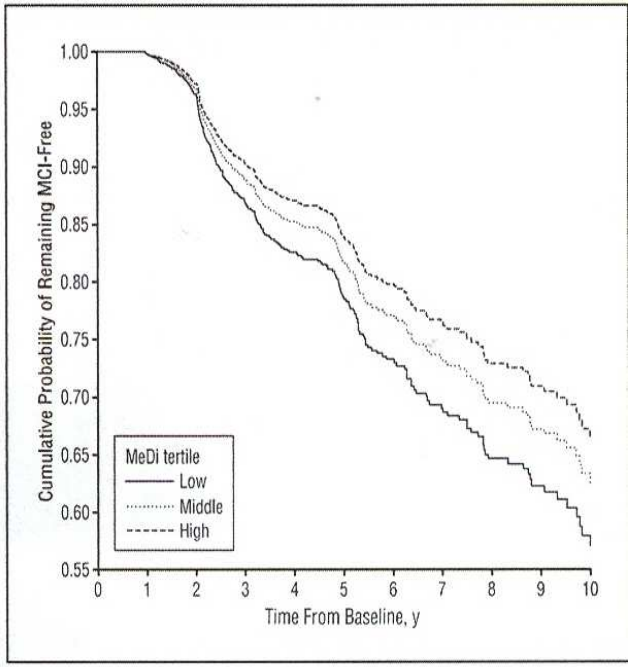


Figure 2. Survival curves based on Cox analysis comparing cumulative mild cognitive impairment (MCI) incidence in subjects who were cognitively normal at the first evaluation by each Mediterranean diet (MeDi) adherence tertile (*P* for trend = .05). The figure is derived from a model that is adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment. Duration of follow-up is truncated at 10 years. Results of log-rank tests for pairwise comparisons are as follows: middle vs low tertile, $\chi^2 = 0.91$, $P = .33$; low vs high tertile, $\chi^2 = 3.72$, $P = .05$; and middle vs high tertile, $\chi^2 = 1.22$, $P = .26$.

Mediterranean Diet and Risk for Alzheimer's Disease

Nikolaos Scarmeas, MD,[1–3] Yaakov Stern, PhD,[1–3] Ming-Xin Tang, PhD,[1,4] Richard Mayeux, MD,[1–3] and Jose A. Luchsinger, MD[1,5]

Objective: Previous research in Alzheimer's disease (AD) has focused on individual dietary components. There is converging evidence that composite dietary patterns such as the Mediterranean diet (MeDi) is related to lower risk for cardiovascular disease, several forms of cancer, and overall mortality. We sought to investigate the association between MeDi and risk for AD.

Methods: A total of 2,258 community-based nondemented individuals in New York were prospectively evaluated every 1.5 years. Adherence to the MeDi (zero- to nine-point scale with higher scores indica
in models that were adjusted for cohort, age, sex, ethnicity, education, apolip
medical comorbidity index, and body mass index.

Results: There were 262 incident AD cases during the course of 4 (±3.0; range, (
to the MeDi was associated with lower risk for AD (hazard ratio, 0.91; 95%
Compared with subjects in the lowest MeDi tertile, subjects in the middle M
confidence interval, 0.63–1.16) and those at the highest tertile had a hazard ratio
for AD (p for trend = 0.007).

Interpretation: We conclude that higher adherence to the MeDi is associated w

Diet may play an important role in the causation and prevention of AD.[1,2] Dietary restriction in animals extends their life span[3] and increases the resistance of neurons to degeneration.[3] However, epidemiological data on diet and AD have been conflicting. Higher intake of vitamin C,[4–6] vitamin E,[4–8] flavonoids,[9] unsaturated fatty acids,[10–12] fish[12,13]; higher levels of vitamin B12[14–16] and folate[15,16]; modest to moderate ethanol[17–21]; and lower total fats[22,23] have been related to a lower risk for AD or slower cognitive decline. At the same time, other studies have found that the risk for AD or cognitive decline is not associated to intake of antioxidants, such as vitamin C,[24] vitamin E,[24] and carotenes,[24] fats,[25] or levels of vitamin B12.[26]

There is paucity of data regarding the effect of composite dietary patterns (rather than individual foods or nutrients) on the risk for AD. Dietary pattern analysis in relation to many other diseases (ie, cirrhosis or various cancers) has recently received growing attention because individuals do not consume foods or nutrients in isolation, but rather as components of their daily diet. Defining diet by dietary patterns has the ability to capture its multidimensionality whereas reducing its apparent co
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Table 4. Cox Proportional Hazard Ratios for Incidence of Alzheimer Disease for Subjects With Mild Cognitive Impairment at the First Evaluation by Mediterranean Diet Score

Predictor	HR (95% CI)	*P* Value
Unadjusted[a]		
MeDi continuous	0.95 (0.85-1.07)	.48
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.62 (0.39-0.98)	.04
High	0.69 (0.41-1.14)	.15
Trend	0.82 (0.63-1.07)	.15
Adjusted[b]		
MeDi continuous	0.89 (0.78-1.02)	.09
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.55 (0.34-0.90)	.01
High	0.52 (0.30-0.91)	.02
Trend	0.71 (0.53-0.95)	.02

Abbreviations: CI, confidence interval; HR, hazard ratio; MeDi, Mediterranean diet; NA, not applicable.

[a] A total of 482 subjects had mild cognitive impairment at the first evaluation; 106 subjects developed incident Alzheimer disease.

[b] A total of 409 subjects had mild cognitive impairment at the first evaluation; 96 subjects developed incident Alzheimer disease. Adjusted models include a slightly lower number of subjects because of missing data in some of the covariates; they simultaneously control for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment.

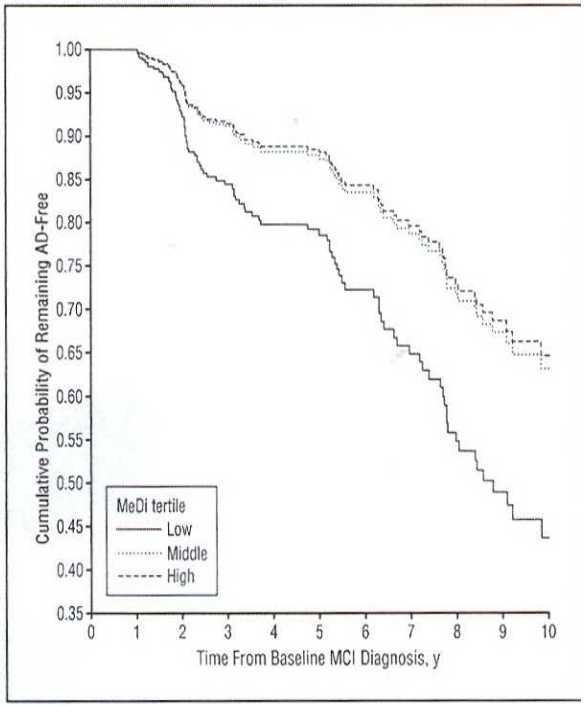

Figure 3. Survival curves based on Cox analysis comparing cumulative Alzheimer disease (AD) incidence in subjects with mild cognitive impairment (MCI) at the first evaluation by Mediterranean diet (MeDi) adherence tertile (P for trend = .02). The figure is derived from a model that is adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment. Duration of follow-up is truncated at 10 years. Results of log-rank tests for pairwise comparisons are as follows: middle vs low tertile, $\chi^2=4.26$, $P=.03$; low vs high tertile, $\chi^2=1.39$, $P=.23$; and middle vs high tertile, $\chi^2=0.12$, $P=.72$.

From the [1]Taub Institute for Research in Alzheimer's Disease and the Aging Brain; [2]Gertrude H. Sergievsky Center; [3]Department of Neurology; [4]Division of Biostatistics, Joseph P. Mailman School of Public Health; and [5]Department of Medicine, Columbia University, New York, NY.

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Stress/Mood/Sleep
Metabolic Syndrome

Therapeutic Approach for Cardiometabolic Syndrome

- Differentiation of Cardiac risk to metabolic syndrome seen as inflammation, elevated hsCRP and Lipoprotein-associated phospholipase A-2 (PLAX test)
- Clinical approach is to use the Mediterranean Food Plan
- Soy protein, phytosterol and phytochemical enriched medical food twice daily
- High EPA fish oil
  - 3-6grams per day

IV. Gut flora, Gut Barrier and inflammatory process

Leaky Gut | Auto-immunity | Probiotics

Nat Clin Pract Gastroenterol Hepatol. 2005 Sep;2(9):416-22. Related Articles,

nature

Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases.

Fasano A, Shea-Donohue T.

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. When the finely tuned trafficking of macromolecules is dysregulated, intestinal and extra intestinal autoimmune disorders can occur.

Leaky Gut | Auto-immunity | Probiotics

Nat Clin Pract Gastroenterol Hepatol. 2005 Sep;2(9):416-22. Related Articles,

nature

Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases.

Fasano A, Shea-Donohue T.

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

Ann Rheum Dis. 2001 Jan;60(1):65-6.
Intestinal permeability in Behcet's syndrome.
Fresko I, Hamuryudan V, Demir M, Hizli N, Sayman H, Melikoglu M, Tunc R, Yurdakul S, Yazici H.

The intestinal permeability in BS was significantly more than that seen among the healthy controls.

Diseases	Percentage (SD) rate of excretion chromium-51 EDTA
Behcet	4,6
AS	6
IBD	5,2
SLE	5,56
Health	2,3

Clin Exp Rheumatol. 2000 Nov-Dec;18(6):773-8. **Increased gut permeability in juvenile chronic arthritides. A multivariate analysis of the diagnostic parameters.**

Picco P, Gattorno M, Marchese N, Vignola S, Sormani MP, Barabino A, Buoncompagni A.

CONCLUSIONS: All of the subtypes of juvenile chronic arthritides that we studied displayed an increased Intestinal Permeability

Arch Dis Child. 2004 Mar;89(3):227-9.

Intestinal permeability is increased in bronchial asthma.

Hijazi Z, Molla AM, Al-Habashi H, Muawad WM, Molla AM, Sharma PN.

CONCLUSIONS: **Intestinal permeability** is **increased** in children with **asthma**, **suggesting that** the **whole mucosal system** may be **affected**.

Clin Exp Rheumatol. 2003 Sep-Oct;21(5):657-62.

Gastrointestinal symptoms and permeability in patients with juvenile idiopathic arthritis.

Weber P, Brune T, Ganser G, Zimmer KP.

CONCLUSION: We conclude that a high percentage of children and **adolescents** with **juvenile idiopathic arthritis** treated with **non-steroidal anti inflammatory drugs** show clinical or laboratory signs of **gastrointestinal involvement**.

Clin Exp Rheumatol. 1996 Sep-Oct;14(5):571-5.

Juvenile chronic arthritis and coeliac disease in The Netherlands.

George EK, Hertzberger-ten Cate R, van Suijlekom-Smit LW, von B lomberg BM, Stapel SO, van Elburg RM, Mearin ML

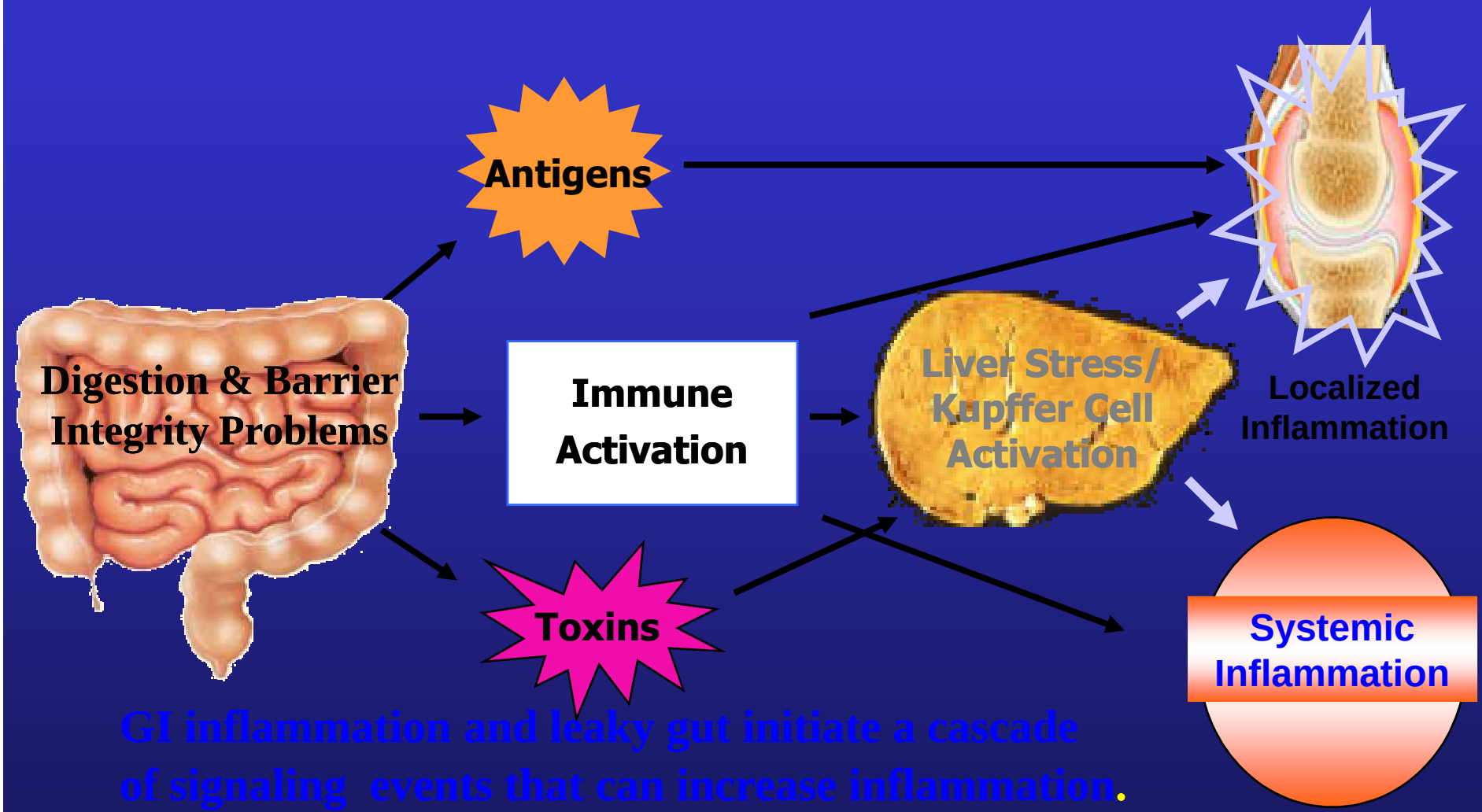
RESULTS: Of the **62 children** with **JCA** (juvenil chronic arthritis), **8** had an **abnormal screening** result and were **suspected** of having **coeliac disease**. In **four** of the **five** children in whom a small-bowel **biopsy** was performed, the intestinal mucosa was **normal** and in **one** child villous atrophy characteristic of **coeliac disease** was found. Therefore, the prevalence of coeliac disease in our study group was 1.5%, which is in agreement with the literature.

Rheumatology (Oxford). 2001 Oct;40(10):1175-9. **A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens.**

Hafstrom I, Ringertz B, Spangberg A, von Zweigbergk L, Brannemark S, Nylander I, Ronnelid J, Laasonen L, **Klareskog**

CONCLUSION: The data provide evidence that **dietary modification** may be of **clinical benefit** for **certain RA patients**, and that this benefit may be related to a **reduction in immunoreactivity** to **food antigens eliminated** (gliadin and lactobglobuline) by the change in diet.

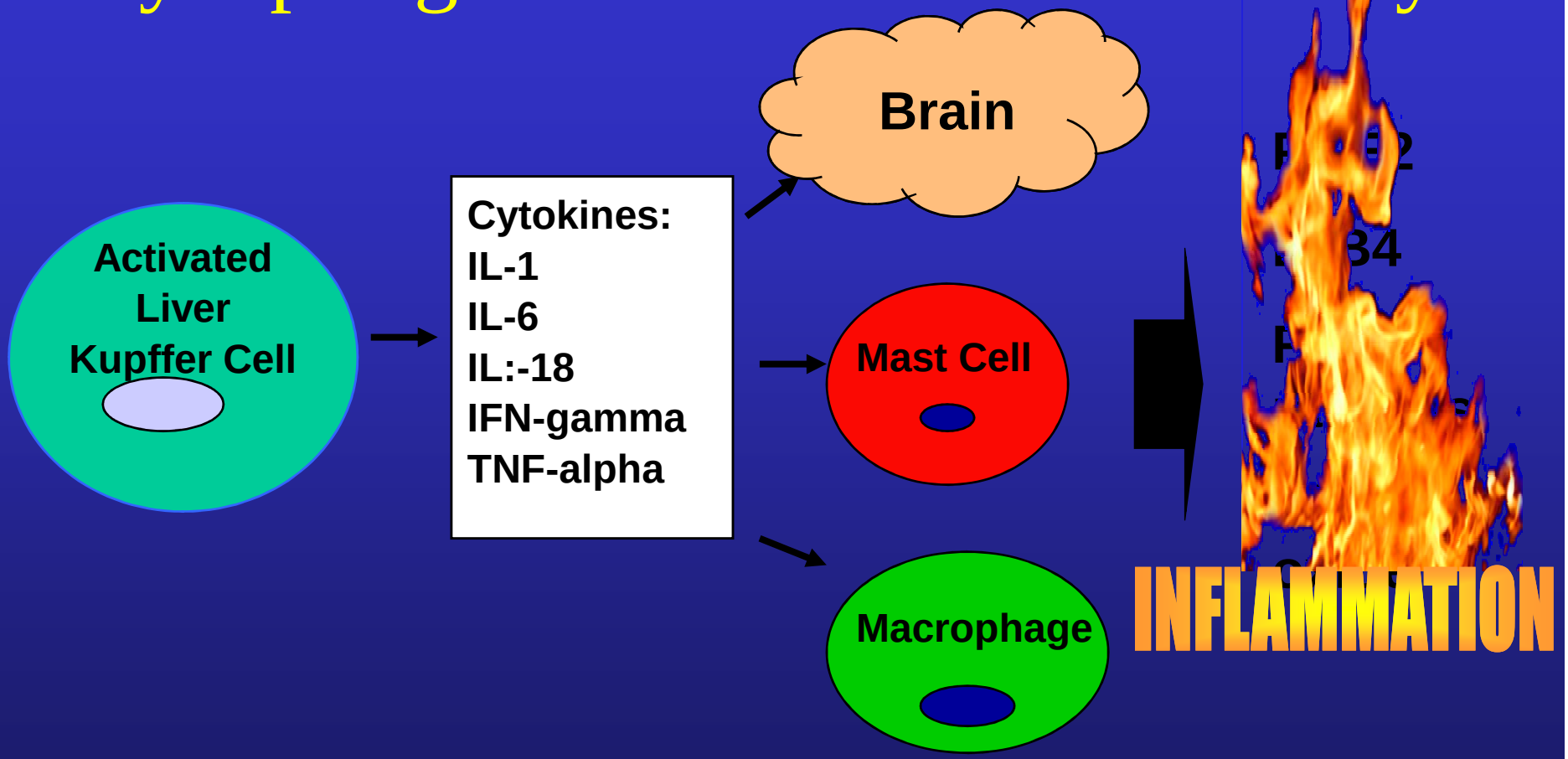
GI-Liver-Inflammation Connection



GI inflammation and leaky gut initiate a cascade of signaling events that can increase inflammation.

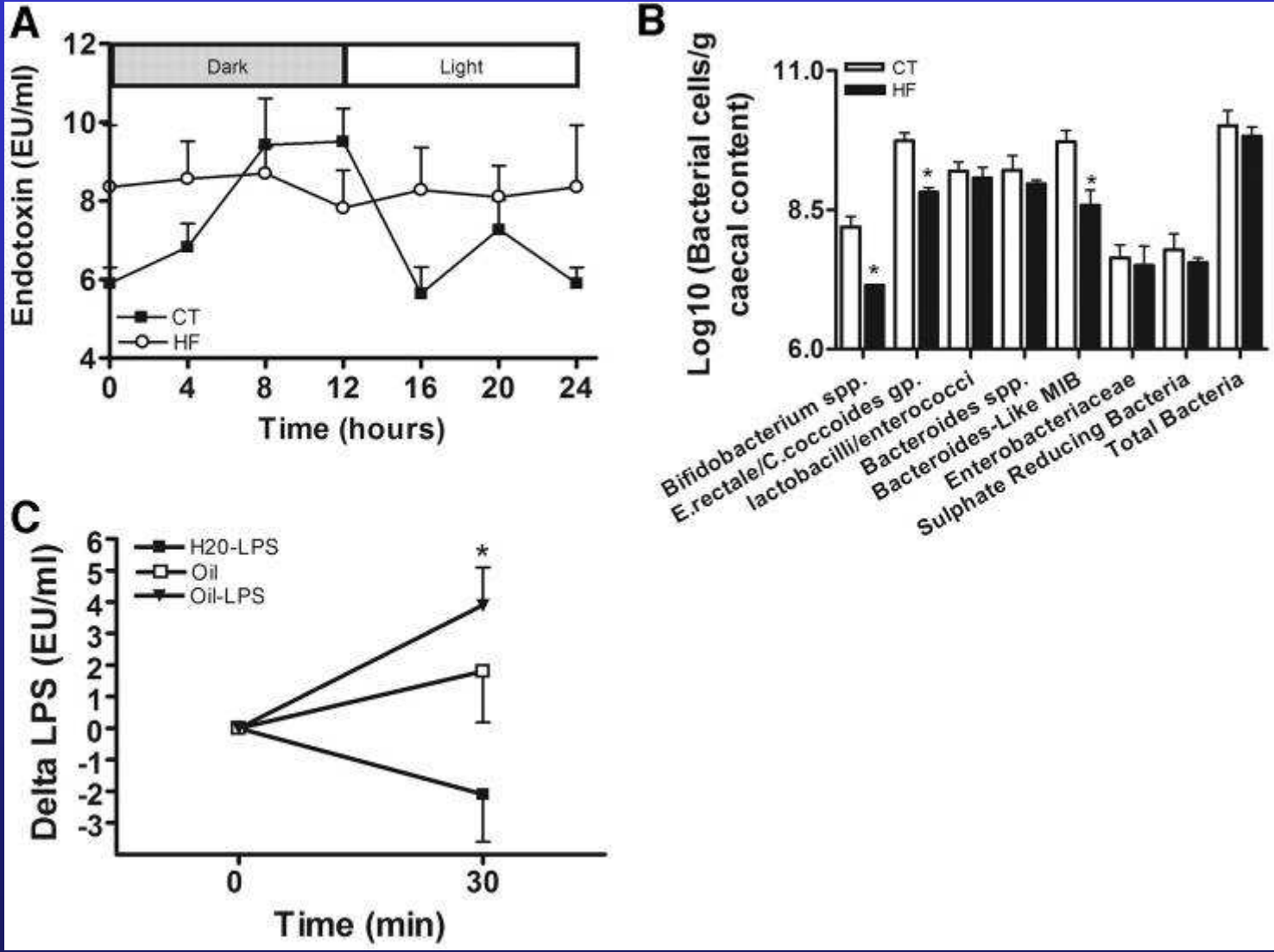
Scharz B, et al. Intestinal ischemic reperfusion syndrome: pathophysiology, clinical significance, therapy: *Wien Klin Wochenschr*1999;111(14):539-48.

Kupffer Cells Increase Inflammation By Up-regulation of Immune Activity



Blatties CM, Li S, Perlik V, Feleder C. Signaling the brain in systemic inflammation:the role of complement. *Front Biosci* 2004;9:915-31.

High fat intake increase LPS =endotoximia



Cani et al., Diabetes 2007

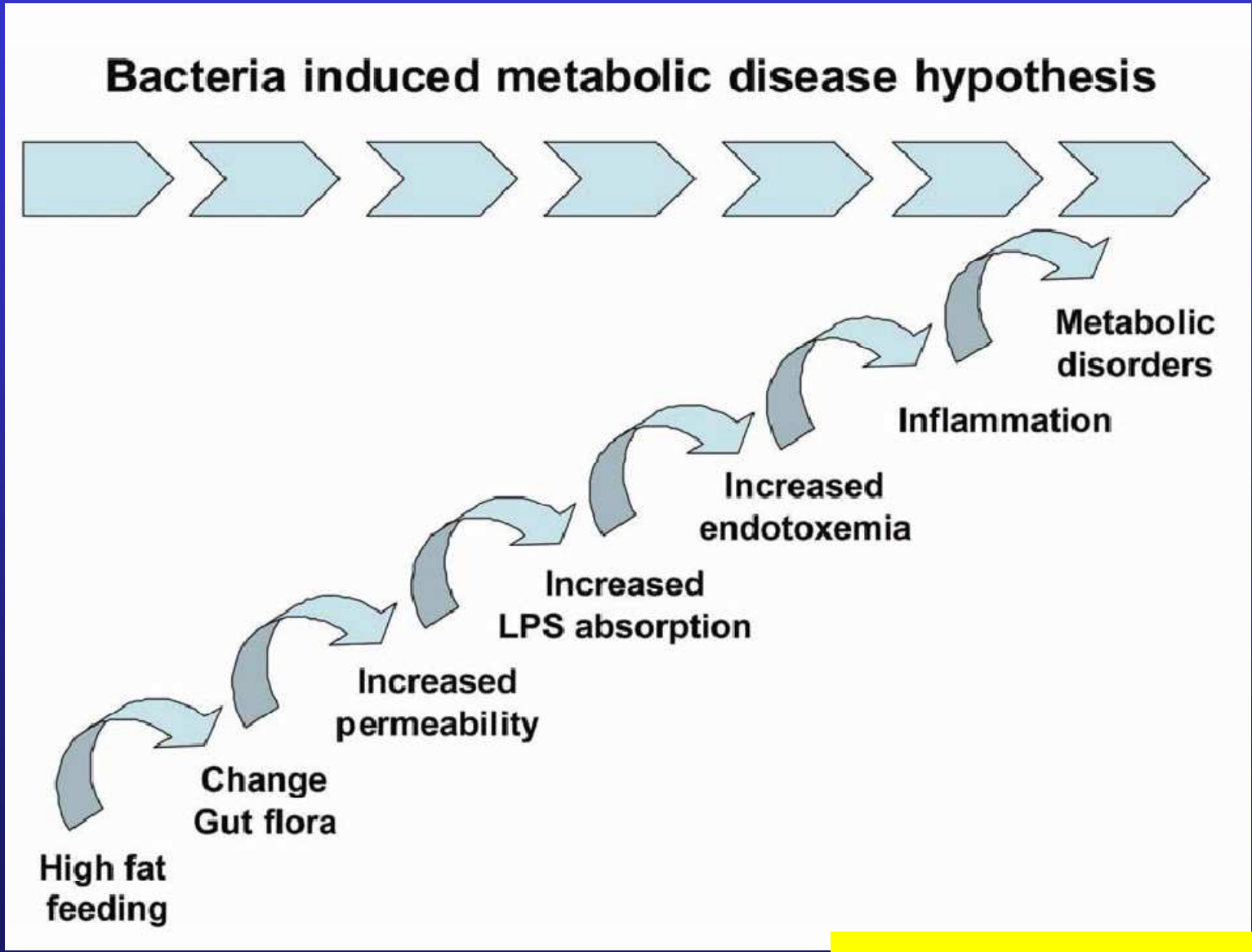
The HFD (High Fat Diet) induced endotoxemia

Increases	Body weight, Fat mass Liver fat
Leads to	Liver insulin resistance
Triggers	Inflammation

Oligofructose/Inulin improve the HFD induced metabolic dysregulation by altering the bacterial flora.

Cani et al., Diabetes 2007

The working model/hypothesis?

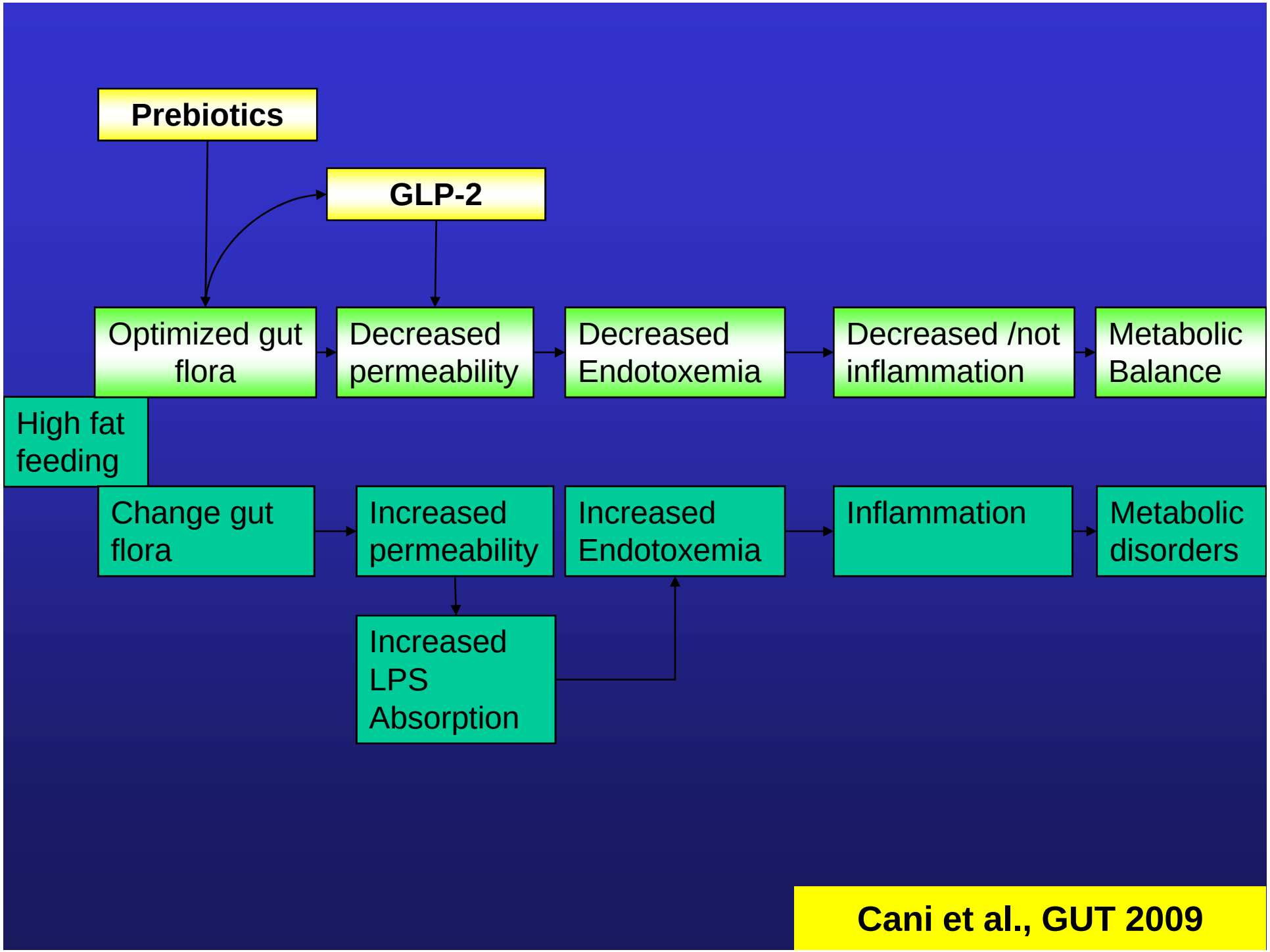


Cani et al., Diabetes 2008

Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability

Patrice D Cani, Sam Possemiers, Tom Van de Wiele, Yves Guiot, Amandine Everard, Olivier Rottier, Lucie Geurts, Damien Naslain, Audrey M Neyrinck, Didier M Lambert, Giulio G Muccioli and Nathalie M Delzenne

Gut published online 24 Feb 2009;
doi:10.1136/gut.2008.165886


Prebiotics
GLP-2
Optimized gut flora
Decreased permeability
Decreased Endotoxemia
Decreased /not inflammation
Metabolic Balance
High fat feeding
Change gut flora
Increased permeability
Increased Endotoxemia
Inflammation
Metabolic disorders
Increased LPS Absorption
Cani et al., GUT 2009

- **Prebiotic** treated mice exhibited
  - a lower plasma LPS and cytokines,
  - a decreased hepatic expression of inflammatory and oxidative stress markers.
- This decreased inflammatory tone was associated with
  - a lower intestinal permeability
  - an improved tight junction integrity via an increased endogenous intestinotrophic proglucagon derived-peptide (**GLP-2**) **production**.

Cani et al., GUT 2009

INTRODUCTION

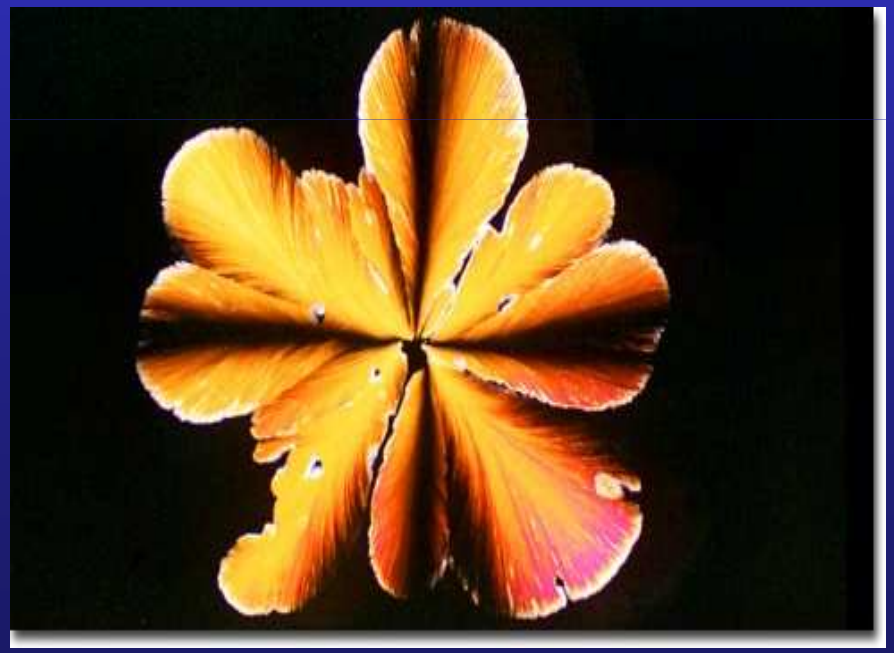
- At age 53, Pauling was awarded the Nobel Prize for Chemistry. The prize was given for ``research into the nature of the chemical bond . . .and its application to the elucidation of complex substances" –in other words, for the body of his work rather than for a specific discovery, a move unprecedented in the history of the Nobel Institute.
- The women in Pauling's life (daughter-in-law Anita, daughter Linda, and Ava Helen) look as joyful as the elated Pauling at the 1955 Nobel Prize Ceremonies. The prize, which many felt was long overdue, was cause for great celebration among his family and colleagues. Pauling's stature in the scientific community now seemed secure, though he was still target of Communist hunters at home. It took the intervention of the Secretary of State to renew Pauling's US passport so that Pauling could travel to the ceremony

THE HUMANITARIAN

-
- *We are the custodians of the human race. We have the duty of protecting the pool of human gene plasm against willfuldamage.*

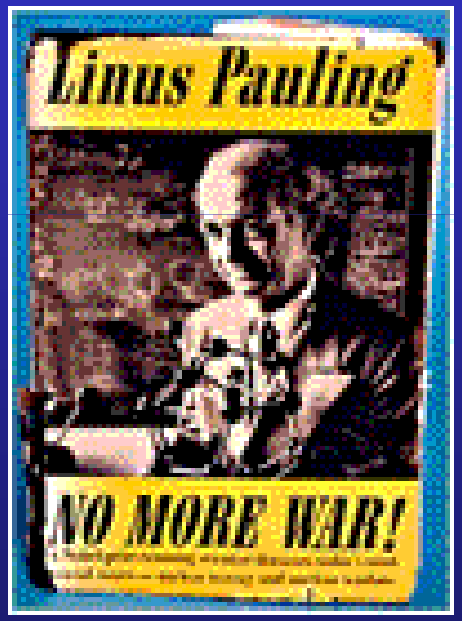
  I believe that the goal of general and complete world disarmament can be achieved, and that it is the duty of every human being to use his time and energy and money to assist in the fight to achieve this goal, rather than in a vain effort to alleviate the consequences of nuclear war, as by the construction of fallout shelters.

TRIBUTE TO LINUS PAULING



- From 1946 through the 1950s and 60s, Pauling spoke out vigorously on the perils of atomic fallout and made anti-war speeches all over the country. Eventually, while he continued to do brilliant scientific work, he dedicated nearly half of his time to anti-war activities. In the political climate of the time, with the Cold War with Russia in its early stages and Senator McCarthy and the House Un-American Activities committee hunting communists everywhere, Pauling's anti-war activities brought him floods of criticism. His public stand made Pauling the target of an internal investigation at Caltech, as well as governmental harassment and attacks in the press.(DNA single strand)

LINUS PAULING:
NO MORE WAR!!!



- In 1952, the State Department refused to renew Pauling's passport. the official reason was that his travels ``would not be in the best interest of the United States.'' The world scientific community was outraged.
- Pauling was unable to attend a meeting of the Royal Society in London which was called to honor him and to discuss his ideas about structures. Many felt that he missed the chance to be the first to unravel the structure of DNA because he wasn't able to confer with colleagues.
- Although issued a short term passport in the summer of 1952, Pauling's requests for passport renewals were routinely denied during the next two years.

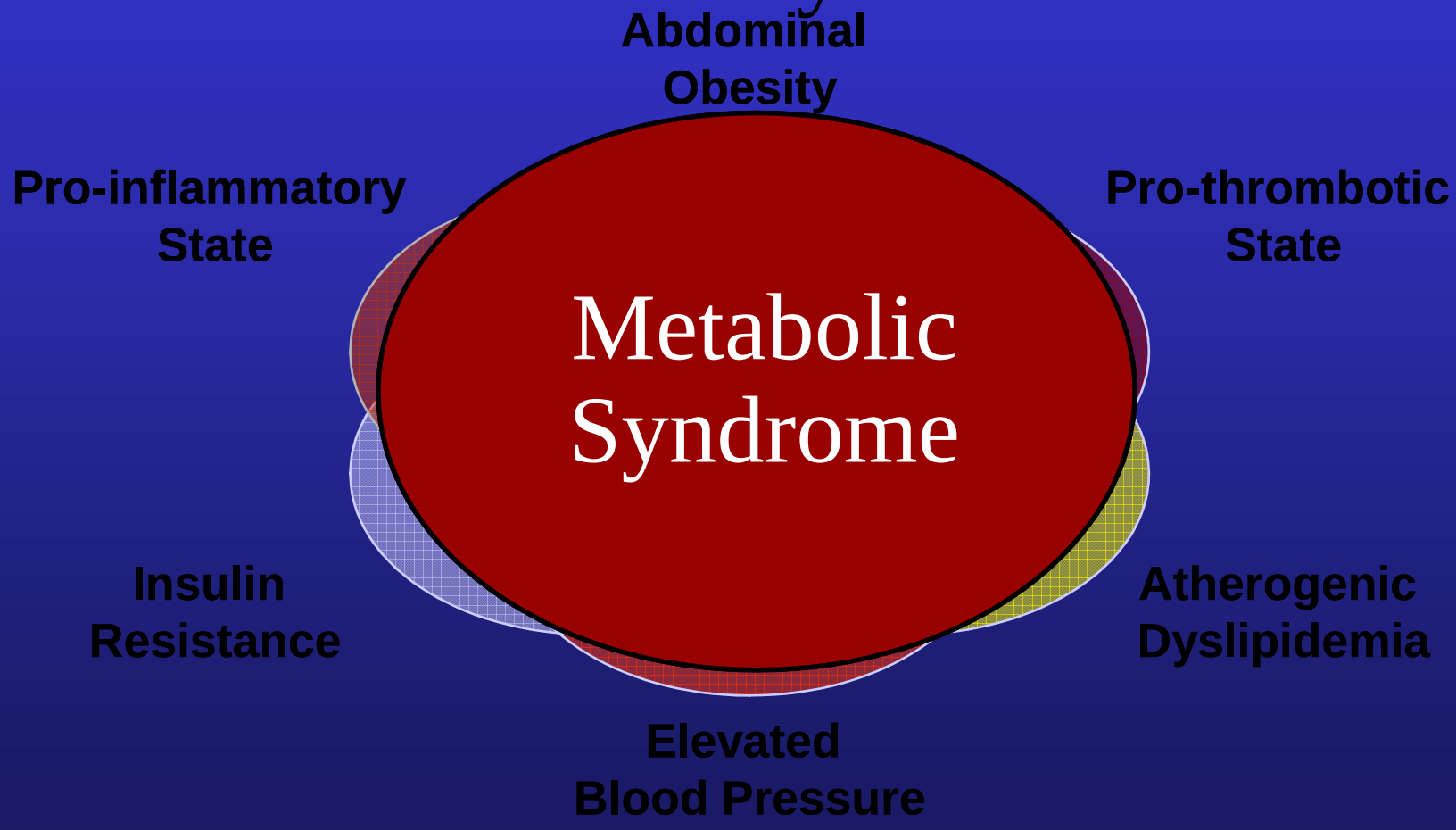
THE ATOMIC ERA

- ***I believe in morality, in justice, in humanitarianism. We must recognize now that the power to destroy the world by the use of nuclear weapons is a power that cannot be used – we cannot accept the idea of such monstrous immorality.***

TERRORISMO

Il "Ground Zero"
del World Trade Center

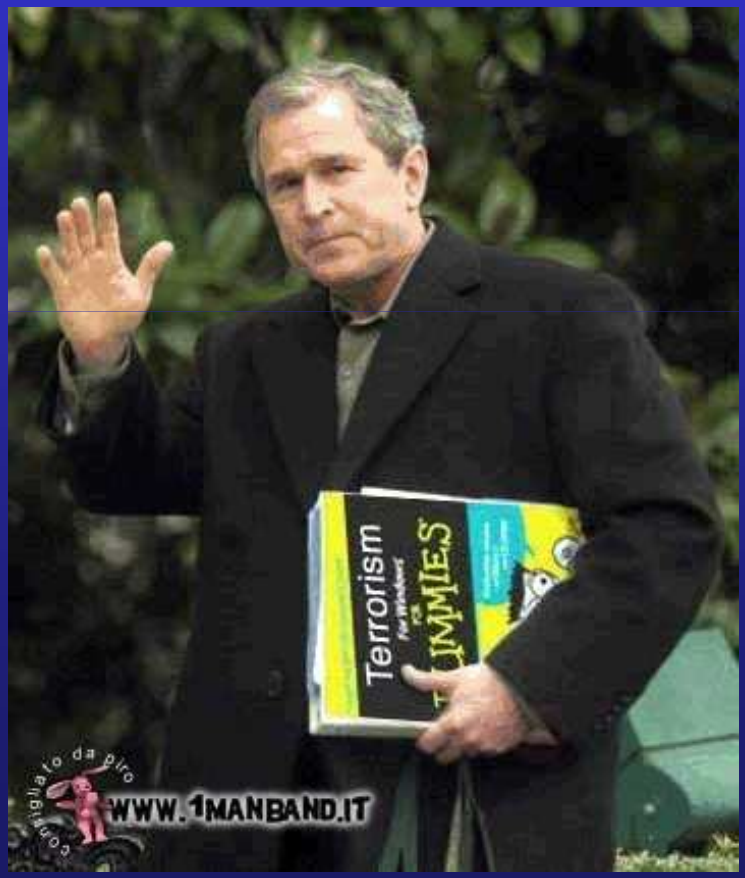
The Deathly Triad of Metabolic Syndrome



Grundy SM et al. *Arterioscler. Thromb. Vasc. Biol.* 2004;24;e13-e18.

TERRORISMO

- **Nuova guida anti-terrorismo per Bush (fornita dalla CIA)**
  "Terrorismo per deficienti"
- Con le figurine di chi è bravo e di chi è con Al Qaeda



Nel 2020 potremmo assistere a un aumento del 50% dei casi di cancro nel mondo. E per quella data, saranno in un anno 15 milioni le nuove diagnosi.

- Allarmante previsione e' il 'World Cancer Report', la piu' completa analisi sulla malattia, che viene condotta, per conto dell'OMS' dalla Iarc, l'International Agency for Research on Cancer. Ma se le previsioni sono tutt'altro che rosee, il documento lascia anche qualche spiraglio alla speranza: ''Stili di vita piu' sani, azioni mirate di sanita' pubblica messe in campo dai governi e medici possono arrestare questa escalation e prevenire almeno un terzo di tutti i casi di cancro del mondo''.
  Secondo lo Iarc il consistente aumento delle nuove diagnosi previsto per il 2020 ''e' dovuto principalmente a questi fattori: l'invecchiamento della popolazione, sia nei paesi occidentali che in via di sviluppo, ma anche alla diffusione del fumo e alla crescente adesione a stili di vita poco salutari''. Se nel 2000, secondo il rapporto dell'agenzia dell'Oms, i tumori maligni si sono resi responsabili del 12% dei circa 56 milioni di decessi registrati nel pianeta, in molti Paesi piu' di un quarto delle morti e' attribuibile ai tumori. ''Nel 2000 - prosegue il documento - 5,3 milioni di uomini e 4,7 milioni di donne hanno sviluppato forme maligne di cancro, e tra questi sono stati registrati 6,2 milioni di vittime. Senza contare - prosegue il rapporto - che i tumori sono destinati a diventare il maggiore problema sanitario anche nei Paesi in via di sviluppo, eguagliando gli effetti della malattia nelle nazioni occidentali''.
  Non tutto e' perduto pero' per gli esperti che hanno stilato il 'World Cancer Report'. ''Azioni mirate intraprese sin da ora - dice Paul Kleihues, direttore dello Iarc - potrebbero prevenire un terzo dei nuovi casi di cancro. Un altro terzo potrebbe essere messo all'angolo dalle terapie disponibili e per il restante terzo delle diagnosi potrebbero essere a disposizione cure palliative in grado di alleviare i malati''. Gli fa eco il direttore generale dell'Oms, Gro Harlem Brundtland: ''Il rapporto e' uno strumento importante per le future azioni di sanita' pubblica volte a ridurre morbidita' e mortalita' per cancro, ma anche per migliorare la qualita' di vita dei malati e delle loro famiglie''.

Uno studio Usa rivela l'esistenza di un legame tra la carenza di vitamina C e l'infezione di un batterio,Helicobacter Pilori.

- L'HP è un germe scoperto nel 1983 che colonizza la mucosa gastrica danneggiandola e che può essere trasmesso da un individuo ad un altro per via oro-orale attraverso la saliva oppure per via oro-fecale attraverso l'ingestione di alimenti contaminati dalle feci dei portatori.
  La pericolosità del batterio risiede non solo nel fatto che esso provoca gastrite e ulcera, ma anche per il fatto che si tratta di una delle cause del cancro allo stomaco. La scoperta americana ha come primo risvolto pratico quello di avvertire quanti sono già infettati da Helicobacter Pilori della necessita' di un maggior apporto di questa vitamina nella loro dieta per far fronte alla carenza.
  Lo studio, il piu' vasto nel suo genere, che ha permesso di scoprire questo legame è stato pubblicato sulla rivista Journal of the American College of Nutrition da Joel Simon del San Francisco VA Medical Center (SFVAMC).
  Anche se non e' ancora dimostrato in via definitiva un nesso di causa effetto tra carenza vitaminica ed infezione, alcuni studi su modelli animali hanno già evidenziato che un adeguato apporto di vitamina C riduce il rischio di infezione da H. pilori''.
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  Analizzando poi per la presenza di vitamina C e' emerso, che coloro che ne avevano un'elevata concentrazione avevano probabilita' di essere infettati da H. pilori ridotta di un quarto.
  Queste prime evidenze sperimentali devono esser lette come motivazione, una delle tante per stare in salute, per preferire una dieta ricca di vegetali, conclude Simon. Un corretto apporto di vitamina C potrebbe sia allontanare il rischio di infettarsi con H. pilori, sia mitigare gli effetti dell'infezione quando essa e' gia' in atto e, quindi, evitare le dolorose e pericolose

  ulcere.

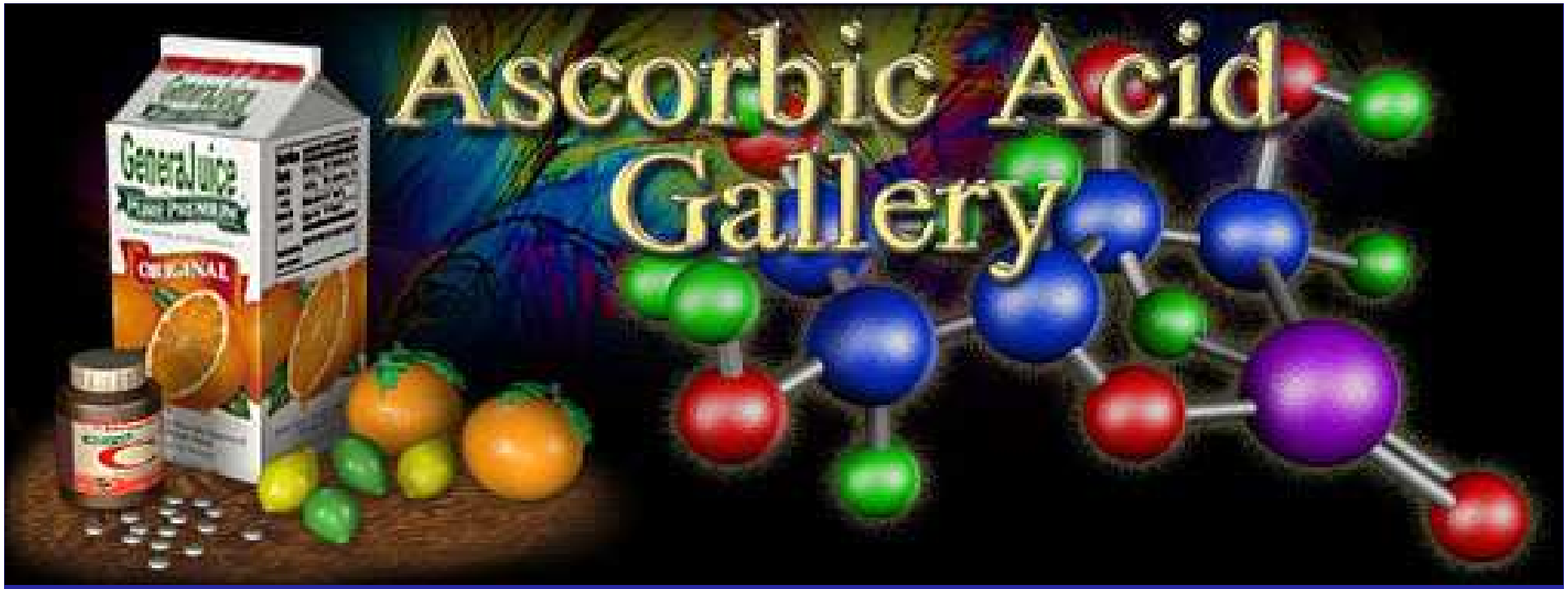
Dito puntato contro tabacco ''il piu' evitabile fattore di rischio per il cancro...

- Dito puntato contro tabacco ''il piu' evitabile fattore di rischio per il cancro, responsabile nel XX secolo di circa 100 milioni di morti. Ma colpa anche di stili di vita e diete sbagliati. Si dovrebbero mangiare molte piu' verdure e frutta - rivela il rapporto - e puntare su esami preventivi per scoprire 'in anticipo' la malattia''. Senza dimenticarsi delle infezioni che aprono le porte al tumore. ''Tabacco, dieta errata e infezioni, infatti - rivela Rafael Bengoa, direttore del programma dell'Oms sulle malattie non infettive - da sole sono responsabili del 43% di tutte le morti per cancro registrate nel 2000, pari a 2,7 milioni di decessi, e del 40% dei nuovi casi, cioe' 4 milioni di nuovi pazienti''. Nel concreto l'Oms ha messo in campo nuove strategie per intervenire su almeno due dei principali fattori di rischio, il tabacco e la dieta. Per questa ragione gli Stati membri dell'Oms hanno acconsentito a sottoscrivere, il prossimo maggio, la Convention on Tobacco control, oltre a partecipare alla Global Strategy on Diet, Phisical Activity and Health.

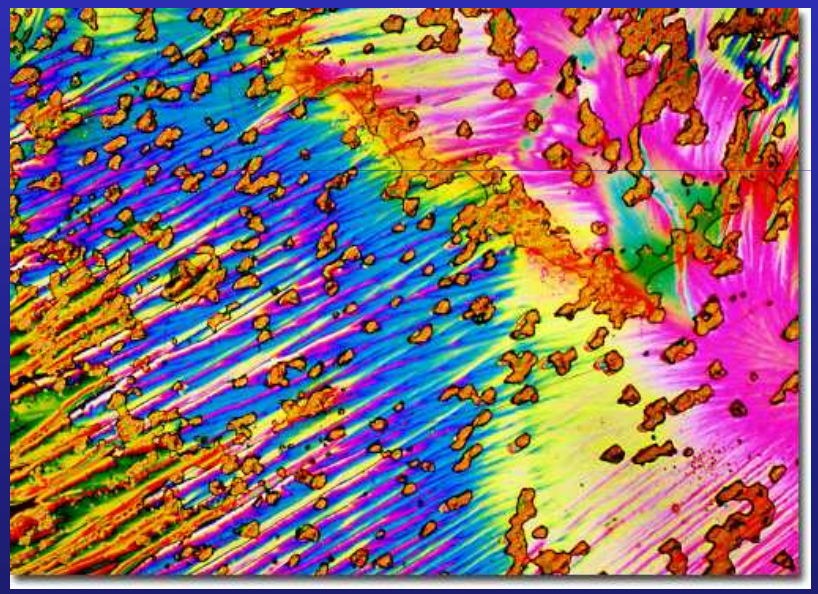
"OPEN MIND"

- *Minds are like parachutes… they only work when open !*

- *-Sir Thomas Dewar*


Ascorbic Acid
Gallery
ORIGINAL

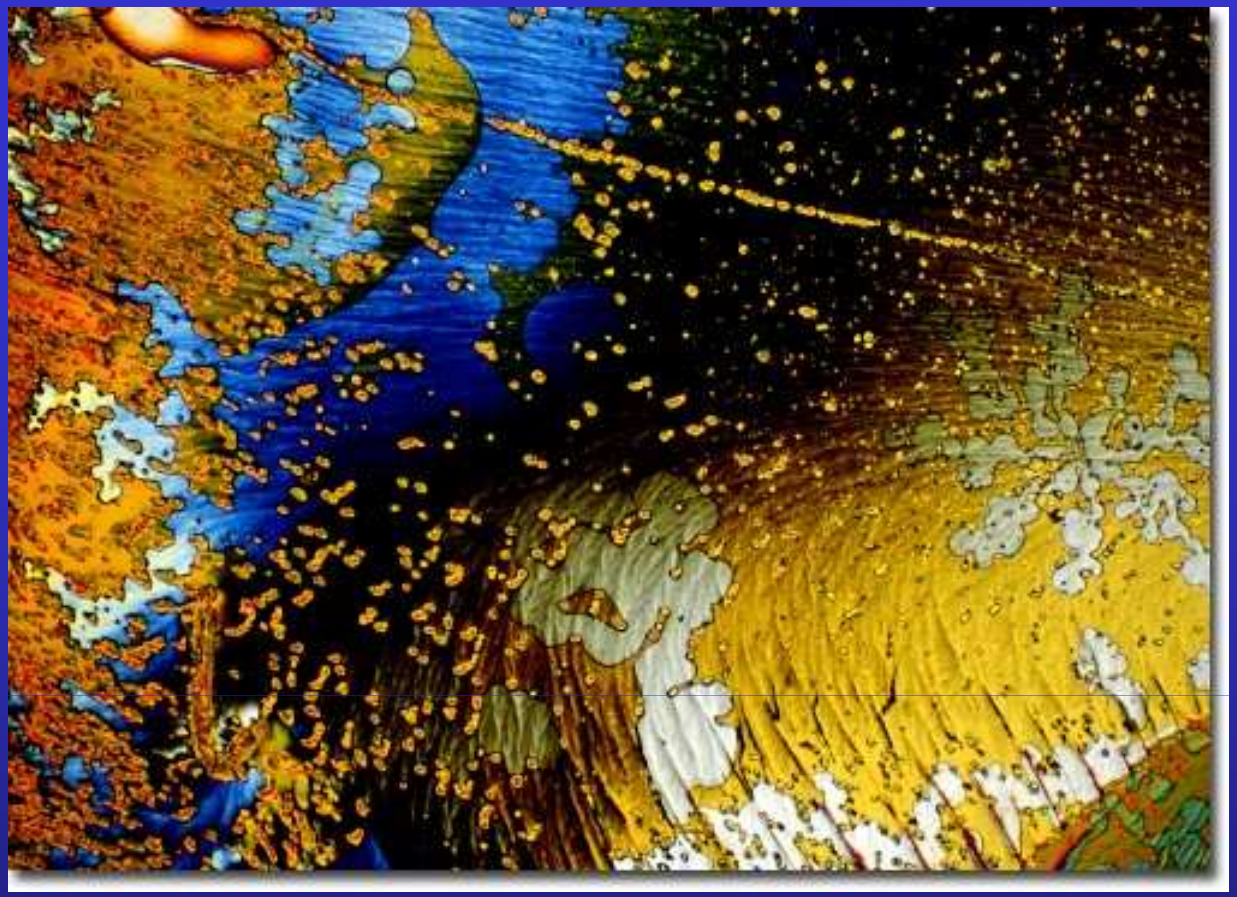
ASCORBIC ACID



Most popular vitamin among the common nutrients and biochemicals. Because the vitamin is water-soluble, it must be regularly replenished and is commonly found in fresh fruits, especially in the citrus family that is dominated by oranges, lemons, limes, and tangerines. Vitamin C (commonly referred to as ascorbic acid) is also abundant in green leafy vegetables.

One of the prime responsibilities of ascorbic acid is to assist in the production of collagen, the principal protein used to synthesize connective tissue that is essential to skin, bone, and cartilage formation. Vitamin C accomplishes this task by helping the body utilize such nutrients as carbohydrates, fats, and proteins. More Important, ascorbic acid is recognized as a potent anti-oxidant, helping to protect cells from damage by free radicals. The biochemical is also essential for wound healing and in strengthening blood vessel walls. Among the many sources of vitamin C are grapefruits, melons, papaya, cabbage, strawberries, broccoli, winter squash and raspberries

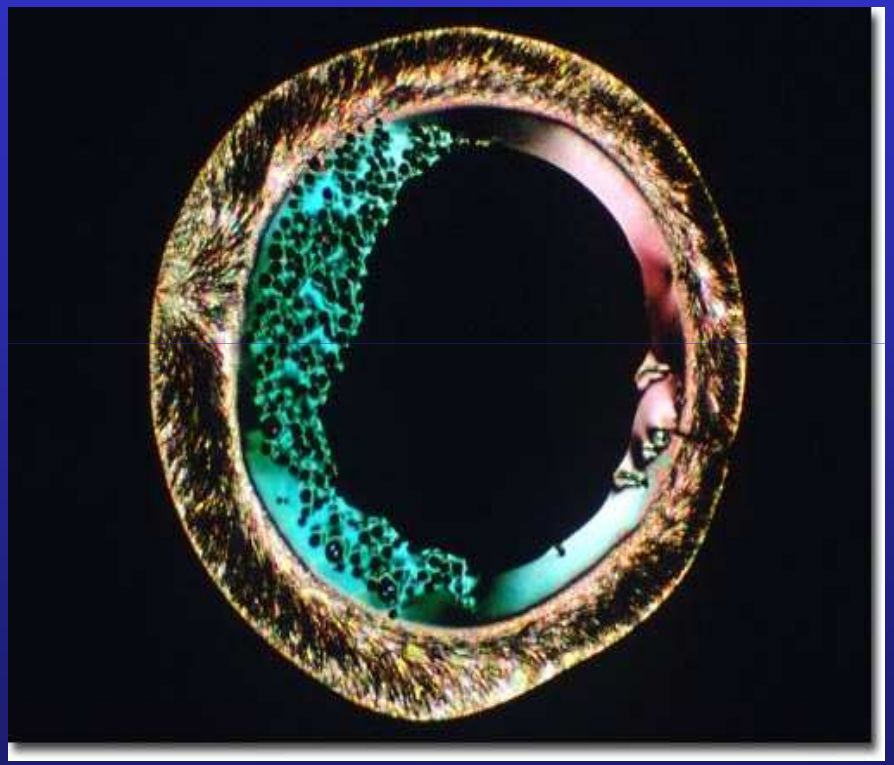
Ascorbic acid is a fragile molecule that is easily destroyed in neutral or alkaline solutions, at elevated temperatures, and upon exposure to oxygen. The vitamin C structure is freely soluble in water, less so in alcohol, and insoluble in certain chemicals such as chloroform, ether, and benzene. In its natural state, ascorbic acid appears in the form of a white to yellowish crystal or powder. The chemical name ascorbic acid refers to L-ascorbic acid, the levorotatory isomer, and has been widely synthesized as a supplement or food additive. Fruits and vegetables are rich natural sources, however the vitamin C content can be rapidly depleted as food becomes stale or when the labile biochemical leaches into water during cooking. The photomicrograph presented above was made with vitamin C recrystallized from the melt and has been titled: Vitamin C Horse



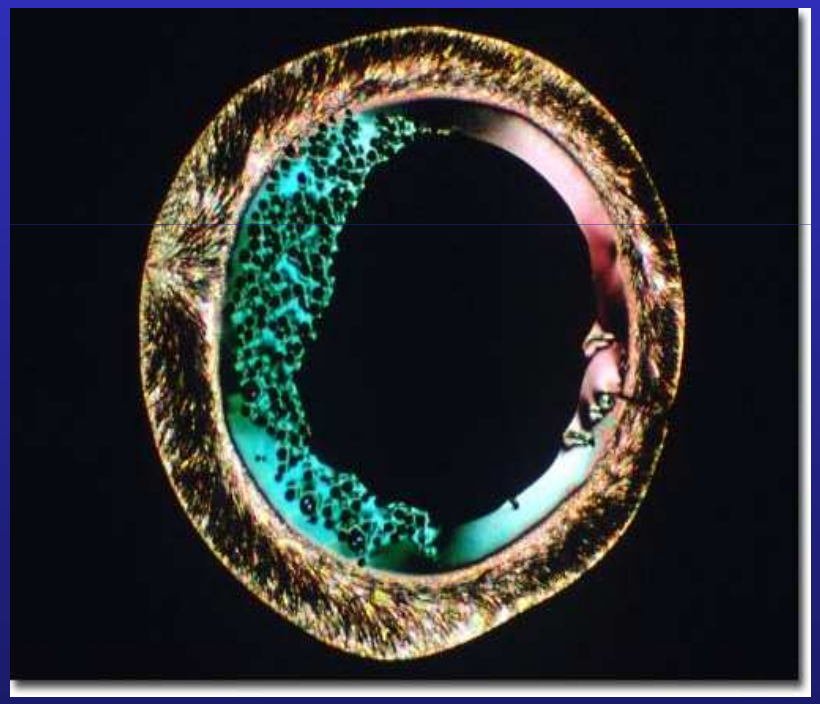
Ebers Papyrus of Ancient Egypt, describes symptoms associated with eating inadequate quantities of foods that are rich in vitamin C (ascorbic acid). The condition is called scurvy,symptoms include swollen gums, loose teeth, black-and-blue spots or open sores on the skin, and slow wound healing. The disease was especially prevalent in seamen on long sea voyages during the sixteenth and seventeenth centuries who primarily ate nonperishable foods that lacked this essential vitamin. Relief from scurvy finally came about when the curative properties of ascorbic acid-containing citruses were discovered in 1747 by the Scottish naval surgeon, James Lind. Naturally abundant in many fruits and vegetables, vitamin C is especially rich in citrus fruits such as oranges, lemons, tangerines, and limes. Although treatment with ascorbic acid usually achieves a quick recovery from the effects of scurvy, not all damage is reversible, especially that occurring in non-regenerative tissues such as eye cornea, nerve tissue, and calcified bone. Today, advanced techniques that help preserve freshness and the availablility of a large variety of vitamin C-rich foods have almost eradicated this disease.

VITAMIN C

- Vitamin C is so often found in sources of fresh fruits and vegetables that it is called ubiquitous, yet many details concerning how the vitamin precisely affects metabolism remain elusive. Described as a carbohydrate-like substance, vitamin C or ascorbic acid is essential to the synthesis of collagen, a protein important in the formation of healthy skin, teeth, and bones. Being a relatively strong reducing agent, this nutrient's reputation as a key *in vivo* antioxidant is well established. Although there is no question that the biochemical is essential to life, scientists are in considerable debate over the extent of vitamin C's influence in such arenas as lowering blood cholesterol, combating viruses and the common cold, and protecting against cancer-causing agents.



VITAMIN C



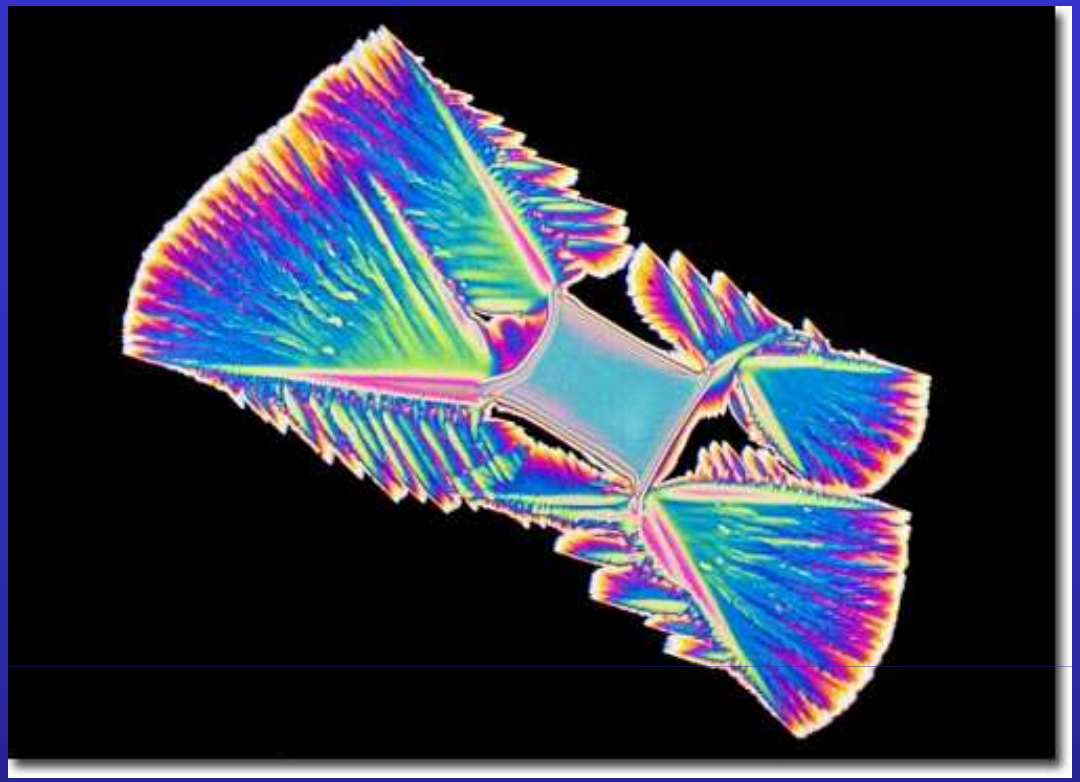
- Some of the scientific evidence seems to suggest that ascorbic acid helps prevent formation of carcinogenic compounds called nitrosamines that can be produced in the stomach when eating a meal of smoked, processed, or preserved meats such as bacon, sausage, ham, and hot dogs. Interestingly, many Old World European recipes have, for centuries, combined cured meats with such vitamin C rich fruits and vegetables as stewed apples, baked tomatoes, and/or onions.

Vitamin C has a simple chemical structure, yet this nutrient has an important role in intracellular formation of the body's most abundant protein, termed collagen. Collagen provides the foundation upon which tendons, ligaments, skin, and bones are formed. The water-soluble vitamin fulfills its role by hydroxylating proline and lysine, two amino acids that are indispensable to the body's production of healthy tissue, in a process called oxidation-reduction or redox. The vitamin C deficiency disease, scurvy, results when the body is unable to hydroxylate proline due to an inadequate supply of vitamin C. The affliction, which results from weakened collagen fibers, is manifested in rotting teeth, slow healing, and open sores on the skin. Many scurvy symptoms can be corrected by proper intake of ascorbic acid. As a relatively strong reducing agent, this water-soluble vitamin also serves as an anti-oxidant to protect cells from damage by free radicals. Some plants and animals are able to produce their own ascorbic acid because they have a cascade of enzymes that can transform glucose into ascorbic acid when needed.

Interestingly, somewhere in the chain of evolution, humans either lost or never developed the enzymes that that can manufacture vitamin C, and therefore are dependent on dietary intake of ascorbic acid

Vitamin C is found in a wide spectrum of popular foods, but occurs most commonly in citrus fruits such as lemons, limes, and grapefruits, as well as tomatoes. The sugar-like vitamin easily oxidizes in air and is sensitive to both light and heat. Ascorbic acid is a relatively fragile molecule and may be lost from foods during preparation, cooking, and/or storage. In spite of the fact that vitamin C is easily destroyed, it has the ability to preserve foods by virtue of its role as a reducing agent. Leafy greens such as collards, spinach, and turnip greens are good sources of needed vitamin C in either raw or cooked forms. Most foods, however, yield maximum amounts of ascorbic acid when eaten raw or minimally cooked. Other good food sources of vitamin C include rosehips, strawberries, watercress, papaya, and mangos. Potatoes and green vegetables such as broccoli, brussel sprouts, and cabbage also provide this essential nutrient. In addition to natural sources, vitamin C may be obtained in synthetic derivatives of glucose. Supplemental forms include tablets, capsules, powdered crystalline, and liquid forms.

Many plants and most animals, including reptiles, do not need to consume ascorbic acid rich foods and are instead genetically programmed to produce enzymes that convert glucose into vitamin C. Mammals, in particular, possess the L-gulonolactone oxidase enzyme, enabling them to manufacture ascorbic acid from blood glucose in a metabolic cascade of enzymatic action. Curiously, however, the only way that humans, guinea pigs, and several primate species can satisfy their ascorbic acid requirements is to obtain the vitamin in their diets. As it happens, although humans have three essential enzymes required to convert glucose into ascorbic acid, they lack the fourth and final enzyme needed to complete the biochemical pathway.



RDA is a benchmark for nutritionally well-balanced diets, originally developed to ensure that World War II soldiers received proper food for maintaining good health. Designed to protect people against possible nutrient deficiencies, the RDA sets minimum dietary requirements of nutrient intake for average, healthy individuals. Different levels, however, may be recommended for children, the elderly, and people whose health is comprised by disease or stressed by activities such as physical exertion, smoking, and exposure to extreme environmental conditions. The Food and Nutrition Board of the National Research Council (a division of the National Academy of Sciences) is currently supplementing the RDA baseline by issuing nutrient recommendations that are based on optimizing health in individuals and certain groups. An additional indictor, **Adequate Intake,** has been assigned to nutrients that do not have sufficient scientific evidence to establish average requirements. Increasing interest in nutritional supplements and fortified foods has led to maximum intake indicators, which provide general guidance about possible toxic levels to healthy people in specific groupings of gender and age, called the **Tolerable Upper Intake Level** or **ULs**. Labels on packaged foods, termed the **Nutrition Facts Panel**, are mandatory on all processed foodstuffs and must quantitatively indicate the product's content of ascorbic acid and other vitamins.

Some scientists believe that naturally occurring bioflavinoids increase the influence of ascorbic acid on good health. Flavinoids are, in essence, plant pigments largely responsible for the colors of many fruits and vegetables that often contain large quantities of vitamin C. Over 4,000 flavinoid-type compounds have been identified and classified according to chemical structure. Some of the better-established citrus flavinoids include rutin, hesperidin, and quercitin, which function to increase capillary permeability. The scientist who discovered both vitamin C and the first flavinoids, Dr. Albert Szent-Gyorgyi, received a Nobel Prize for his research relating to these substances

THE TERM "VITAMIN" IS DERIVED FROM THE LATIN WORD VITA MEANING LIFE, AND DESCRIBES A CLASS OF NUTRIENTS THAT REGULATE IMPORTANT METABOLIC REACTIONS.

- Collectively, vitamins assist in the formation of a wide spectrum of biochemicals including hormones, enzymes, proteins, neurotransmitters, and the genetic materials RNA and DNA.
- Although these organic nutrients are generally not structurally related to each other, they all promote metabolic balance within cells, ensuring that important biochemical reactions proceed as required.
- Many vitamins combine with proteins to create enzymes (termed ***co-enzymes***) that mediate chemical reactions occurring within the body. Vitamins are divided into two categories, one of which is commonly known as ***fat soluble*** and includes vitamins A, D, E, and K.
- The other, ***water soluble***, vitamin category includes the B-vitamin complex and vitamin C. Both of these vitamins must frequently be replenished because they are not stored in body tissue, and are usually rapidly excreted with urine. Vitamin C, or ***ascorbic acid***, is necessary for a wide range of biochemical reactions and its antioxidant properties are vital to several key metabolic pathways.

Uno studio Usa rivela l'esistenza di un legame tra la carenza di vitamina C e l'infezione di un batterio,Helicobacter Pilori.

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  ulcere.

VITAMIN C PREVENTS OSTEOPOROSIS

- The need for such treatment is growing as trials continue to show that hormone replacement therapy, previously the mainstay of osteoporosis prevention, may have serious side effects.
- Osteoporosis was recently classified by the World Health Organisation as the second leading health care problem after cardiovascular disease. The disease means that bone is lost more rapidly than it is replaced which can lead to a predisposition to fractures.
- Professor Tim Chambers and his team from St George's Hospital Medical School at the University of London found that when there is a deficiency in

VITAMIN C PREVENTS OSTEOPOROSIS

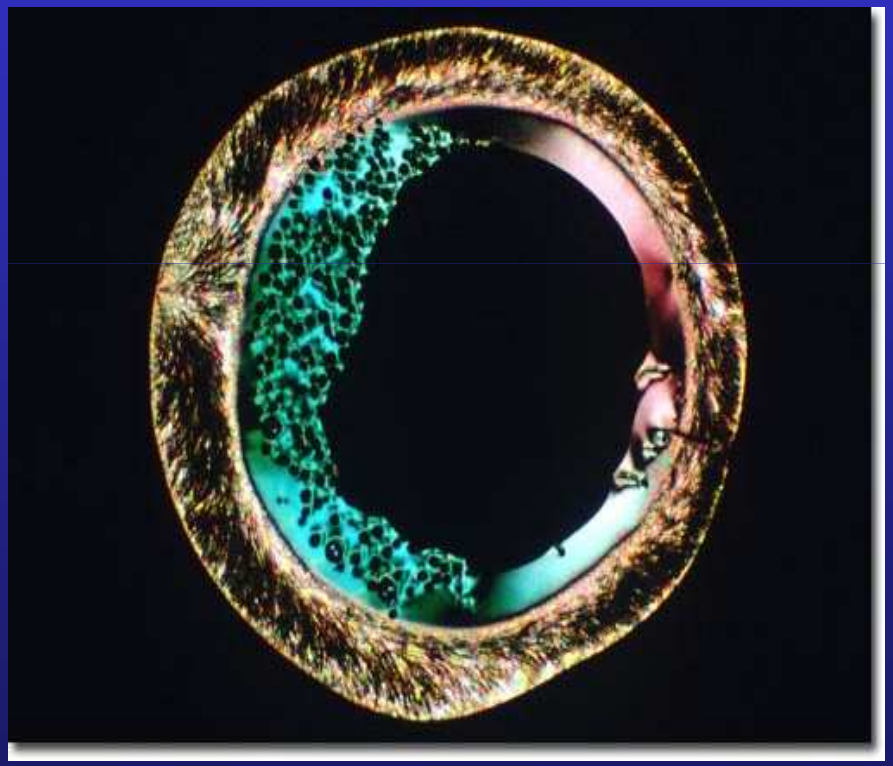
- For the study, published in the recent issue of the *Journal of Clinical Investigation*, experiments on mice showed that antioxidants, and the enzymes responsible for maintaining them in a reduced state, fell substantially in rodent bone marrow after ovariectomy. Bone loss was however entirely preventable by giving the mice 20mg of vitamin C per day.
- The researchers cautioned however that women should not increase RDA intake of the vitamin until further investigation confirms the findings.
- While prevention of osteoporosis has mainly focused on vitamin D and calcium intake, researchers are also investigating the effect of consuming isoflavones on bone density and metabolism in postmenopausal women.
- **Source: Journal of Clinical Investigation 112:915-923 (2003)**

The very first medicine is made in the kitchen.....(Ippocrate di Coo)

- Although many patients did well on strictly vegetarian diet and low fat diets, a certain number of clients did not improve in health or even became worse. He rationalised that since blood is the fundamental source of nourishment for the body, perhaps some aspect of the blood could help identify these difference outcome

VITAMIN C

- Vitamin C is so often found in sources of fresh fruits and vegetables that it is called ubiquitous, yet many details concerning how the vitamin precisely affects metabolism remain elusive. Described as a carbohydrate-like substance, vitamin C or ascorbic acid is essential to the synthesis of collagen, a protein important in the formation of healthy skin, teeth, and bones. Being a relatively strong reducing agent, this nutrient's reputation as a key ***in vivo*** antioxidant is well established. Although there is no question that the biochemical is essential to life, scientists are in considerable debate over the extent of vitamin C's influence in such arenas as lowering blood cholesterol, combating viruses and the common cold, and protecting against cancer-causing agents. Some of the scientific evidence seems to suggest that ascorbic acid helps prevent formation of carcinogenic compounds called **nitrosamines** that can be produced in the stomach when eating a meal of smoked, processed, or preserved meats such as bacon, sausage, ham, and hot dogs. Interestingly, many Old World European recipes have, for centuries, combined cured meats with such vitamin C rich fruits and vegetables as stewed apples, baked tomatoes, and/or onions.



YOU CAN LAUGH WITH RDA

- **Vitamin A** - (beta carotene is a precursor to vitamin A) Night blindness, itching, dry skin, loss of sense of taste. Powerful anti-oxidant. Natural sources: fruits & vegetables, eggs & diary products, liver, fish oils. Fat soluble. RDA 5000iu (1 mcg= 3.3 iu di retinolo)
  25000 iu= 8000 mcg RE/die
- **Vitamin B1** - (thiamin or thiamin chloride) Fatigue, poor appetite, tingling in legs, depression. Natural sources: yeast, vegetables, whole wheat, peanuts, oatmeal, milk, rice husks. Water Soluble. RDA 1.5mg
  (50-200 mg/die -500 mg)
- Vitamin B2 - (riboflavin or vitamin G) Cracks at corners of mouth, sore tongue, eyes sensitive to light. Low riboflavin (B2) levels have been reported in 81% of patients with cataracts. It is not known if this is a cause or result of the cataract disorder. Natural sources: milk, cheese, yeast, liver, kidney. Water Soluble. RDA 1.7mg(25-200 mg /die)
- **Vitamin B3, Niacin** - (nicotinic acid/niacin, niacinamide/*nicotinamide*) Weakness, skin rash, memory loss, irritability, insomnia. Natural sources: whole wheat, yeast, green vegetables, beans, lean meats & liver. Water Soluble. RDA 18mg
  (30-100 mg)

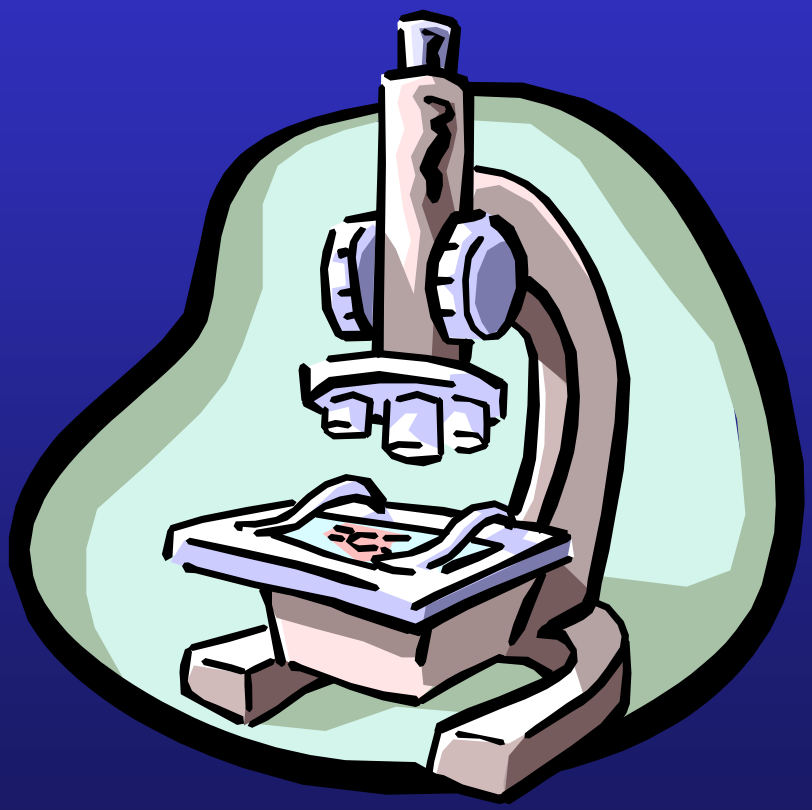
YOU CAN LAUGH WITH RDA II

- **Vitamin B5** – Calcium Pantothenate. Natural Sources: Yeast.
- **Vitamin B6** (Pyridoxine) - Fatigue, anemia, nerve dysfunction, irritability. Controversy concerning potential toxic side effects from large doses during pregnancy. Water Soluble. RDA 2mg (10-50 mg/die)
- **Vitamin B9, Folic Acid** - Pteroylglutamic Acid, - Anemia, intestinal problems, pale & shiny tongue. Water Soluble. Natural Sources: Yeast. RDA 400mcg (800-4800 mcgr/die)
- **Vitamin B12** (Cobalamin)- Anemia, weakness, fatigue, red sore tongue, nerve degeneration.Water Soluble. Natural Sources:Liver,yeast,RDA 3mcg (8-mcg/die) many MD are orthomolecular becasuse they prescribe 1000 mcg/die…1000 times more than the RDA)
- **Vitamin B13** – Calcium Orotate, Orotic Acid
- **Vitamin B15** – Calcium Pangamate
- **Vitamin B17** – Laetrile. Natural Sources: Appicot, peach or plum pits.

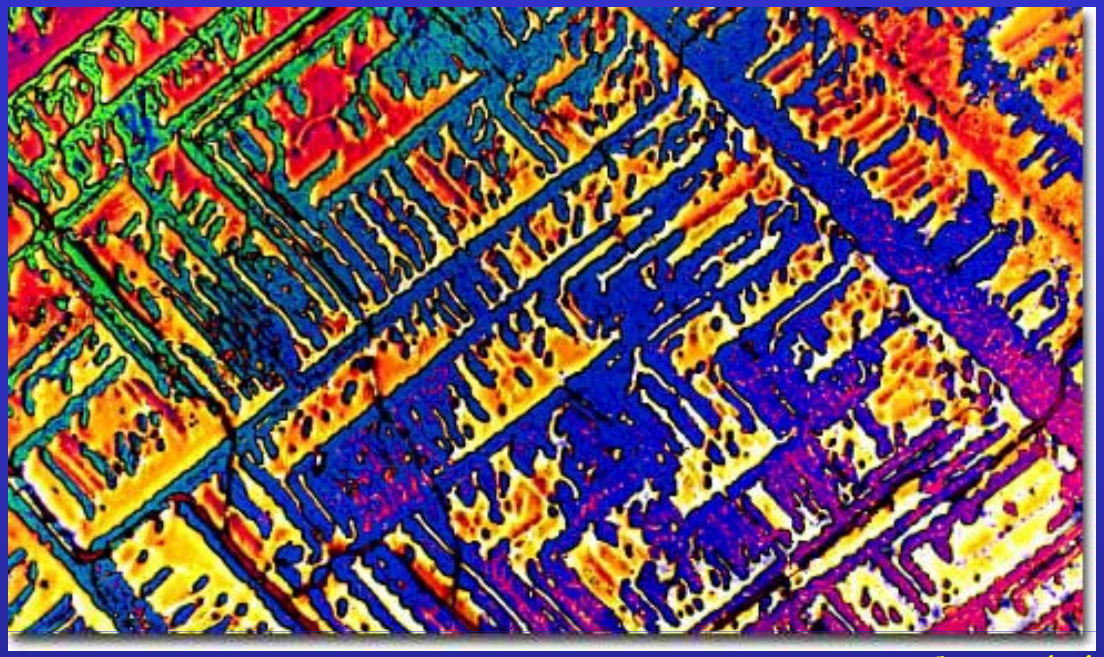
- **Vitamin C** - Bruise easily, slow wound healing, tooth/gum defects, aching joints, scurvy. Water Soluble. Natural Sources: Fruits. RDA 60mg (4-16 gr/die)
- **Vitamin D** - Soft bones/teeth, spontaneous fractures, bone curvature. May affect hearing. Fat Soluble. Natural Sources: Fish oils(RDA 400iu-1 mcg=40iu) (10 mcg/die)
- **Vitamin E** - Poor muscle/circulatory performance. Hemolytic Anemia & degenerative changes in muscle. Protects cell membranes against lipid peroxidation & destruction. Natural Sources: Vegetable oils, dark green leafy vegetables. Fat Soluble. RDA 30iu
- (1iu di a.tocoferil acetato=1 mg of alfaTE:alfatocopherol equivalent)
- **Vitamin F** - Acne, allergies, dry skin, brittle hair & nails, eczema. Natural Sources: vegetable oils & sunflower seeds. RDA none
- **Vitamin H**, Biotin - Lassitude, anorexia, depression, muscle pains, dermatitis & hyperesthesia of the skin. Water Soluble. Natural Sources: yeast, milk, egg yolks, liver & kidney. RDA 200mcg

YOU CAN LAUGH WITH RDA

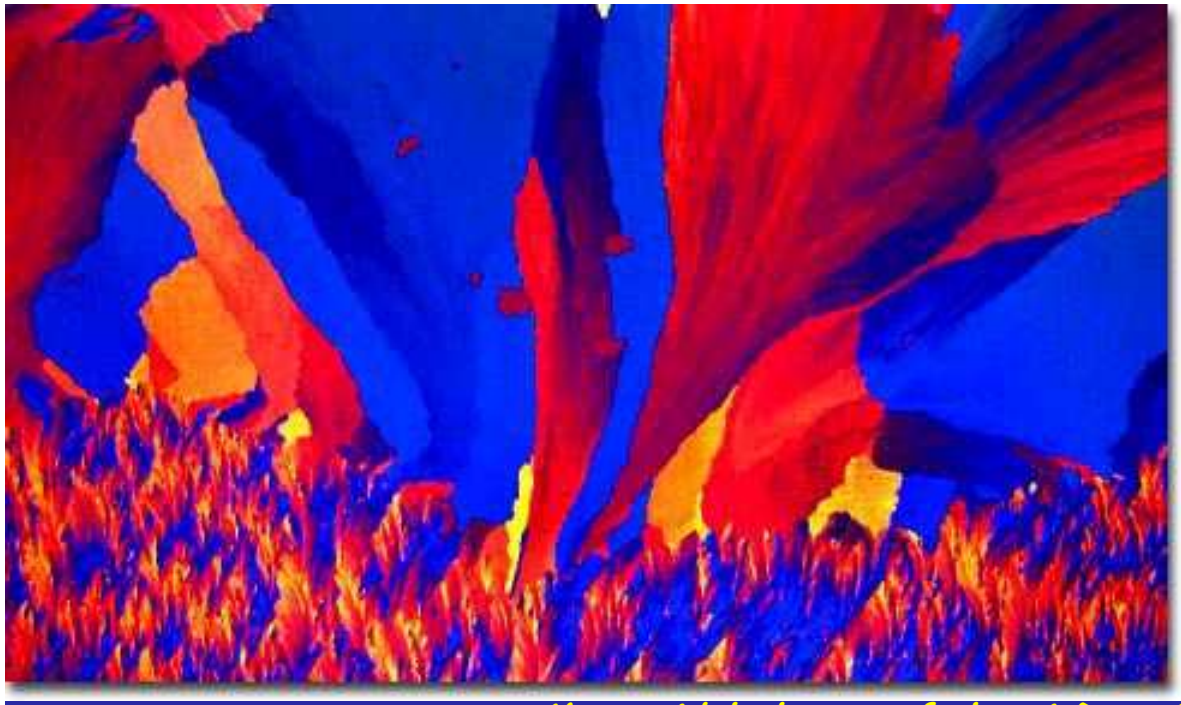
- Vitamin K (Phyllochinon is a basic step for protrombine synthesis) DO NOT USE Menadione, it could be toxic - Diarrhea, increased tendency to hemorrhage. Fat Soluble. Natural Sources: Alfalfa.
  (RDA none just few years ago, but now 80 mcg/die)
-
- Vitamin P - Bleeding gums, colds, eczema. Natural Sources: skin & pulp of fruits. RDA none
- Vitamin T - Natural Source: Sesame seed.
- Vitamin U - Natural Source: Cabbage extract.



CYANOCOBALAMIN (VITAMIN B-12)



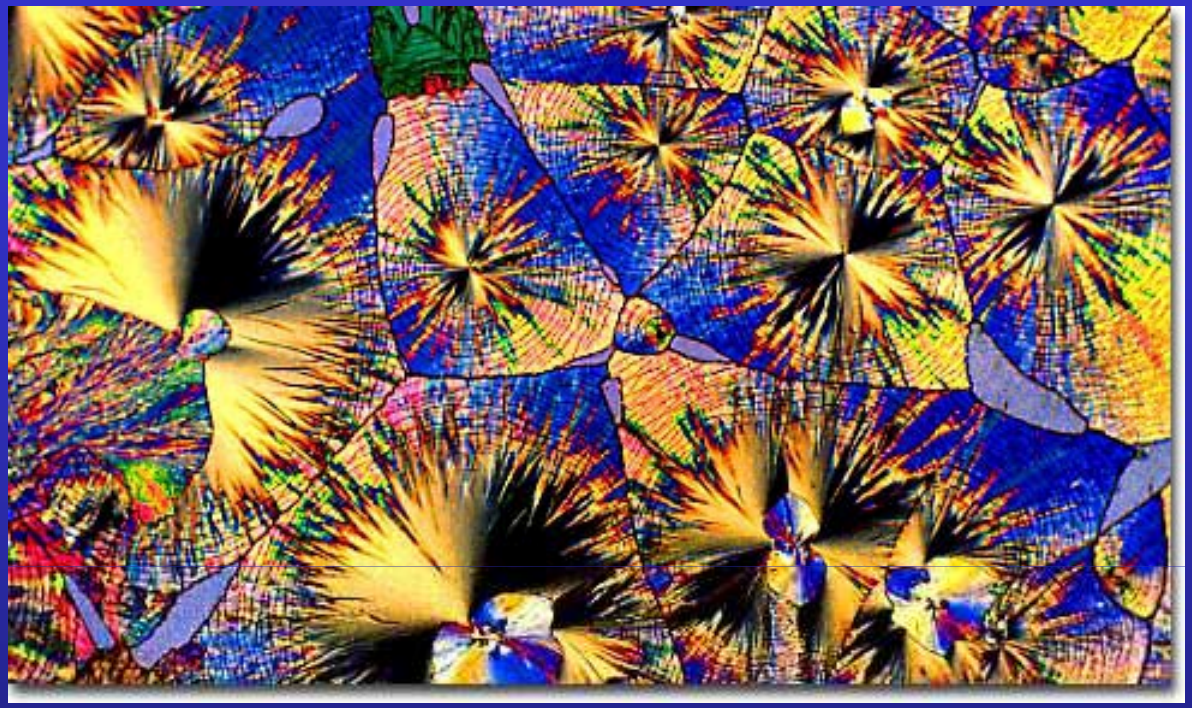
Cyanocobalamin is considered the most potent vitamin and is one of the last true vitamins that has been classified. The vitamin was discovered through studies of pernicious anemia, a condition that begins with a megaloblastic anemia and leads to an irreversible degeneration of the central nervous system. Scientists found that this condition could be reversed by feeding afflicted patients large amounts of raw liver. The active material in the liver was later found to be vitamin B-12, but it is present only in very small concentrations, so many years passed before enough was isolated for serious investigations. Cyanocobalamin is a very unusual biochemical that contains a tetrapyrrole ring system, called a **corrin** ring, that is chemically very similar to the porphyrin ring system of the heme compounds. Contained within the corrin ring, at the coordination point, is a cobalt ion that is associated with a cyanide ion and a dimethylbenzimidazole nucleotide. Vitamin B-12 functions to provide a methyl group that is used in the synthesis of a number of products during biochemical reactions. Clinically, cyanocobalamin works to promote normal growth and development, helps with certain types of nerve damage, and treats pernicious anemia. This vitamin is not available from plant sources (vegetarians beware!), but animal sources include beef, liver, blue cheese, eggs, fish, milk, and milk products. Symptoms associated with a deficiency of vitamin B-12 are primarily those of pernicious anemia



CHOLECALCIFEROL (VITAMIN D)

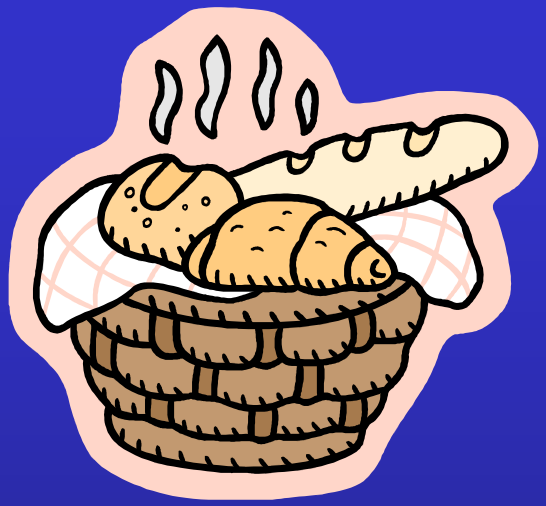
Most widely known of the vitD series and is a fat soluble vit that is stored to some degree in the body. Many people know that sunlight is a source of vit D, but this is true only in the fact that uvlight from the sun acts as a catalyst on a vit D precursor in the skin. Vit D formed in this manner is termed "natural vitamin D" or vit D_3. Vit D precursors obtained from milk and other products as well as sunlight-produced vit D must be metabolized in the liver to form the active coenzyme. The primary functions of vit D are stimulation of calcium and magnesium absorption, two minerals that are essential for strong bones. Sources of vit D include fish liver oil, butter, and milk.

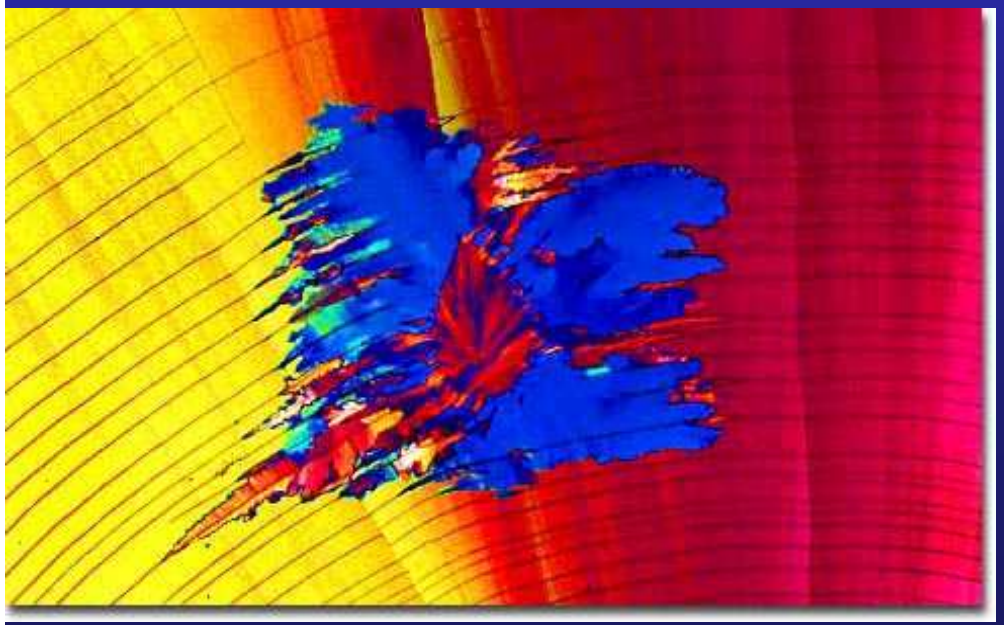
NIACIN (NICOTINAMIDE, VITAMIN B-3)



For metabolic purposes, niacin is interchangeable with its amide, niacinamide, also known as nicotinamide. Important in the biochemistry of humans and other organisms, both substances are components of the coenzymes nicotinamide adenine dinucleotide (**NAD**) and nicotinamide adenine dinucleotide phosphate (**NADP**), which function in a number of oxidation and reduction reactions catalyzed by enzymes. A niacin deficiency in humans often leads to a chronic illness called pellagra, characterized by gastrointestinal problems, lesions of the skin, and dementia. In dogs, a similar condition is known as black tongue disease. Both illnesses can generally be avoided by regularly including sources of niacin in the diet, including legumes, lean meats, and whole-grain or enriched breads and cereals. Some protein-rich food items that are poor sources of niacin, such as eggs and milk, can also help reduce the risk of niacin deficiency because they contain tryptophan, an amino acid that can be converted into niacin through bacterial action in the body.

RETINOL (VITAMIN A)

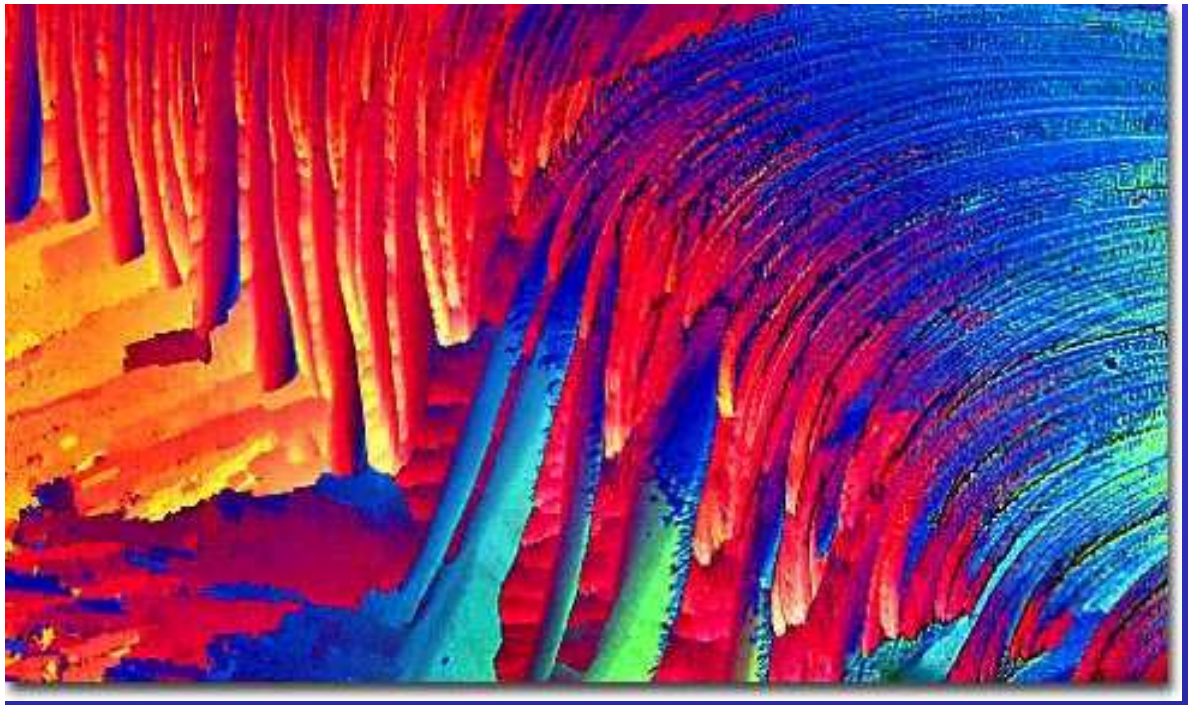




The first nutritional deficiency disease to be identified and studied was night blindness. Ancient cultures recognized this and utilized cooked liver as both a topical and systemic cure for this malady. Retinol was first identified in 1920 and, being the first vitamin, was named vitamin A under the alphabetical nomenclature system. Its high concentration in the liver is due to the fat-soluble nature of this polyene biochemical, although because of the storage mechanism, excessive doses of vitamin A can be very toxic. The most critical biochemical to vision is retinal, an aldehyde that can be synthesized ***in vivo*** from retinol by NAD oxidation. Retinal exists in several isomeric states that are modulated by photon irridation and are very important in the conversion of light waves into vision. The most common source of vitamin A is liver, but many plants contain ***beta***-carotene, which is metabolically converted to vitamin A. Symptoms associated with a deficiency of vitamin A are night blindness, changes in the eyes, poor bone growth, weak tooth enamel, slow growth, and dry skin.

FOLIC ACID (FOLATE, VITAMIN B-9)

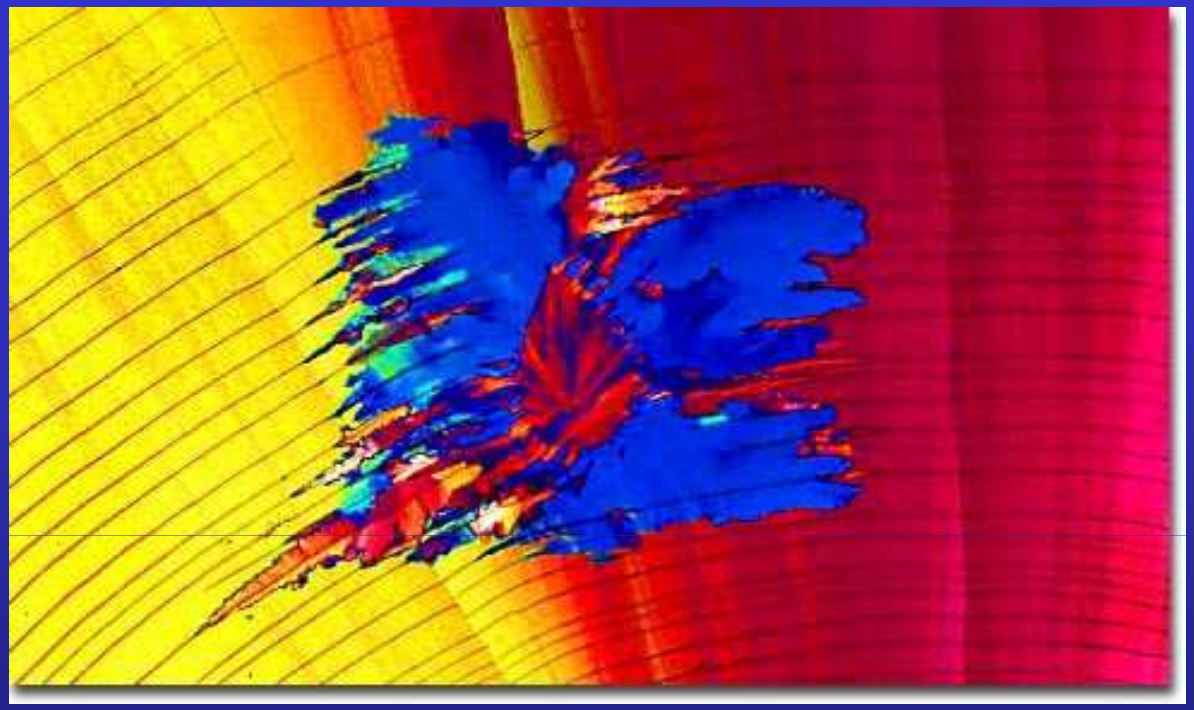
Folic acid is a water-soluble B vitamin that takes its name from the Latin word for leaf, *folium*, because it was first isolated from spinach leaves. Biochemically, folic acid (or folate) functions as a methyl donor after being enzymatically reduced to tetrahydrofolate by the enzyme dihydrofolate reductase. This biochemical reaction is the target of a number of chemotherapeutic antimetabolites such as methotrexate that bind to the enzyme and prevent the reduction. Folic acid is found in brewer's yeast, liver, fruits, leafy vegetables, oranges, rice, soybeans, and wheat. Clinically, folic acid promotes normal red blood cell formation, helps to maintain the central nervous system, and promotes normal growth and development. Deficiencies in folic acid cause conditions such as anemia, weakness, lack of energy, paleness, mental confusion, and headaches



PYRIDOXINE (VITAMIN B-6)

Discovered in 1930s as the result of a series of nutritional investigations of rats fed vitamin-free diets. The original compound that was isolated is pyridoxine, named due to its structural similarity with pyridine, but possessing an additional hydroxymethyl group in the para position. In the body, however, the parahydroxymethyl moiety is oxidized to an aldehyde and the similar group in the meta position is phosphorylated, resulting in the biologically active pyridoxal phosphate. This coenzyme is remarkably versatile, being involved in transaminations, decarboxylations, racemizations, and numerous modifications of amino acid side chains. Clinically, pyridoxine helps normal function of the brain, promotes blood cell formation, maintains the chemical balance among body fluids, and assists in carbohydrate, protein, and fat metabolism. Common sources of pyridoxine include bananas, carrots, nuts, rice, fish, soybeans, and wheat germ. Symptoms of pyridoxine deficiency are very non-specific and hard to reproduce.

RETINOL (VITAMIN A)



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CREATINA PER MIGLIORARE LE PRESTAZIONI DEL CERVELLO

- *Aggiungere alla dieta un supplemento a base di creatina aumenterebbe la memoria di lavoro e, più in generale, l'intelligenza. "Benzina speciale" per il cervello, stando ai risultati di un recente studio australiano.*
  LO STUDIO :
- Caroline Rae e i suoi collaboratori dell'università di Sidney, in Australia, hanno voluto verificare l'effetto di un supplemento a base di creatina su 45 giovani adulti attraverso un trial placebo-controllato in doppio cieco. I partecipanti sono stati divisi in due gruppi: il primo ha assunto ogni giorno per sei settimane 5 grammi di creatina, il secondo un placebo.

Trascorso tale periodo, i soggetti non hanno assunto alcun supplemento per altre 6 sett; poi i gruppi sono stati invertiti e per 6 sett. hanno ripreso creatina o placebo. La dose scelta è quella in grado di incrementare i livelli cerebrali di creatina ed è anche quella impiegata comunemente dagli sportivi per migliorare la forma atletica. All'inizio della sperimentazione, al termine delle prime sei settimane e all'inizio e alla fine del secondo periodo di sei settimane ai partecipanti sono state valutate memoria e intelligenza attraverso due test. Per la valutazione della memoria di lavoro, i soggetti dovevano ripetere una sequenza sempre più lunga di numeri al contrario; per l'intelligenza è stato impiegato il test delle matrici di Raven, esame in grado di valutare il quoziente intellettivo senza tener conto di fattori culturali.

CREATINA PER MIGLIORARE LE PRESTAZIONI DEL CERVELLO

- **I RISULTATI**
  La supplementazione con creatina ha aumentato in maniera significativa la "potenza" e le funzioni del cervello, proprio come migliora le prestazioni di cuore e muscoli.

  IL COMMENTO
  "La scelta di includere soltanto partecipanti vegetariani potrebbe far pensare a una stima scorretta dei risultati: in realtà, per arrivare alle quantità di creatina contenuta nel supplemento impiegato dai ricercatori si dovrebbe consumare una quantità di carne enorme (circa due chili al giorno)", spiega il professor Domenico Pellegrini, docente di farmacologia del corso di laurea di Scienze Motorie presso l'università di Firenze, "i risultati, inoltre, sono in linea con studi precedenti che avevano indicato un effetto della creatina su altre funzioni cerebrali: si è già dimostrato, infatti, che la sostanza è in grado di aumentare la memoria di riconoscimento e ridurre la fatica mentale. Anche per questo esiste una corrente di pensiero che intende impiegare la creatina per il trattamento di varie malattie neurodegenerative".


EXCALIBUR

The "Holy Grail"

- All the traditional systems such as Ayurveda, Traditional Chinese Medicine and Tibetan Medicine have their ways. Modern nutritional therapy is moving steadily away from subjective methods towards measurements based on knowledge of medical science.
- The "Holy Grail" is a simple, accurate, reproducible test that will deliver, at low cost, a complete read-out of a patient's unique biochemical andphysiological profile.

GENERAL CRITERIA FOR A HEALTHY BIOLOGICAL TERRAIN

- **Relative Hydrogen (rH) scale. The neutral point is at 28. Below this point, each increment (27 through 0) grows by the power of ten (that is, the number of electrons in a cubic centimeter is ten times that of the previous increment). The scale identifies mainly the Hydrogen ions (H-), essentially revealing the number of free electrons available in the fluid tested. For example, a glass of freshly squeezed organic orange juice was tested for electron content.**

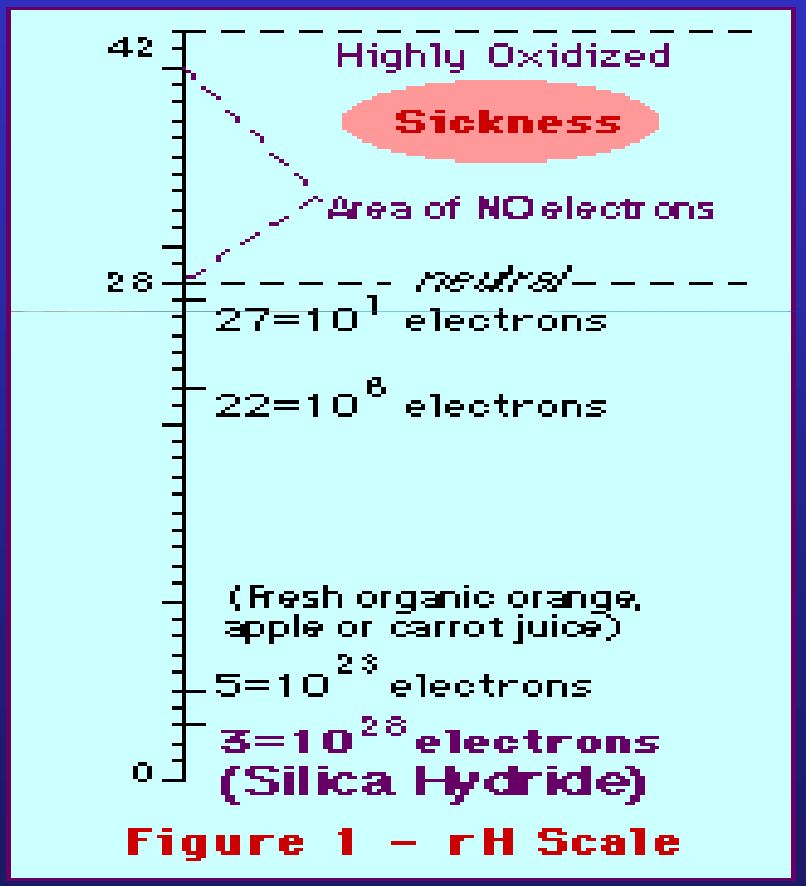
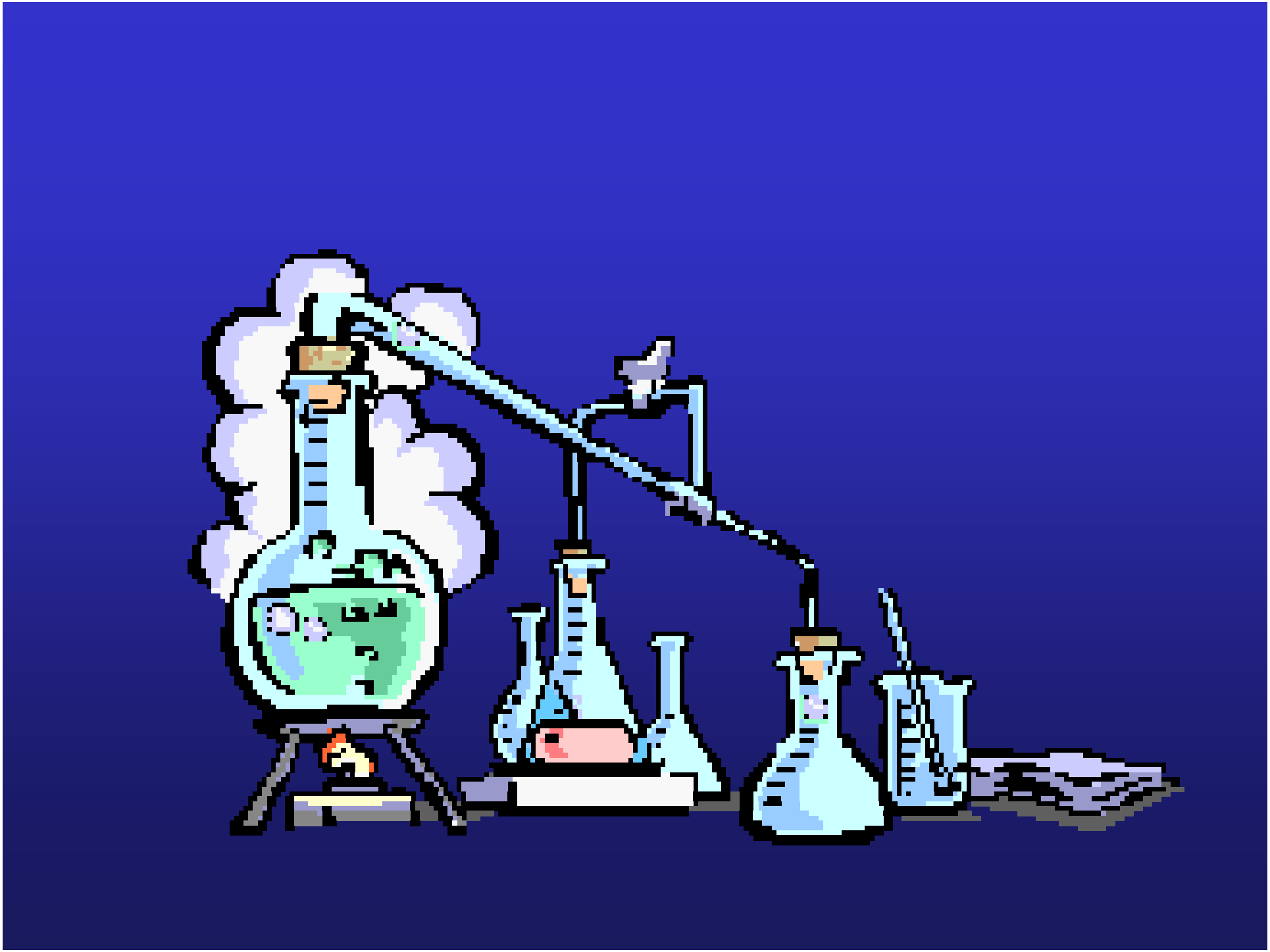


Figure 1 – rH Scale

- Valencia’s Holy Grail



THE END

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