Health in the 21st century

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Education material for

"Young Doctors Club"

University Hospital, Ljubliana, April 2008

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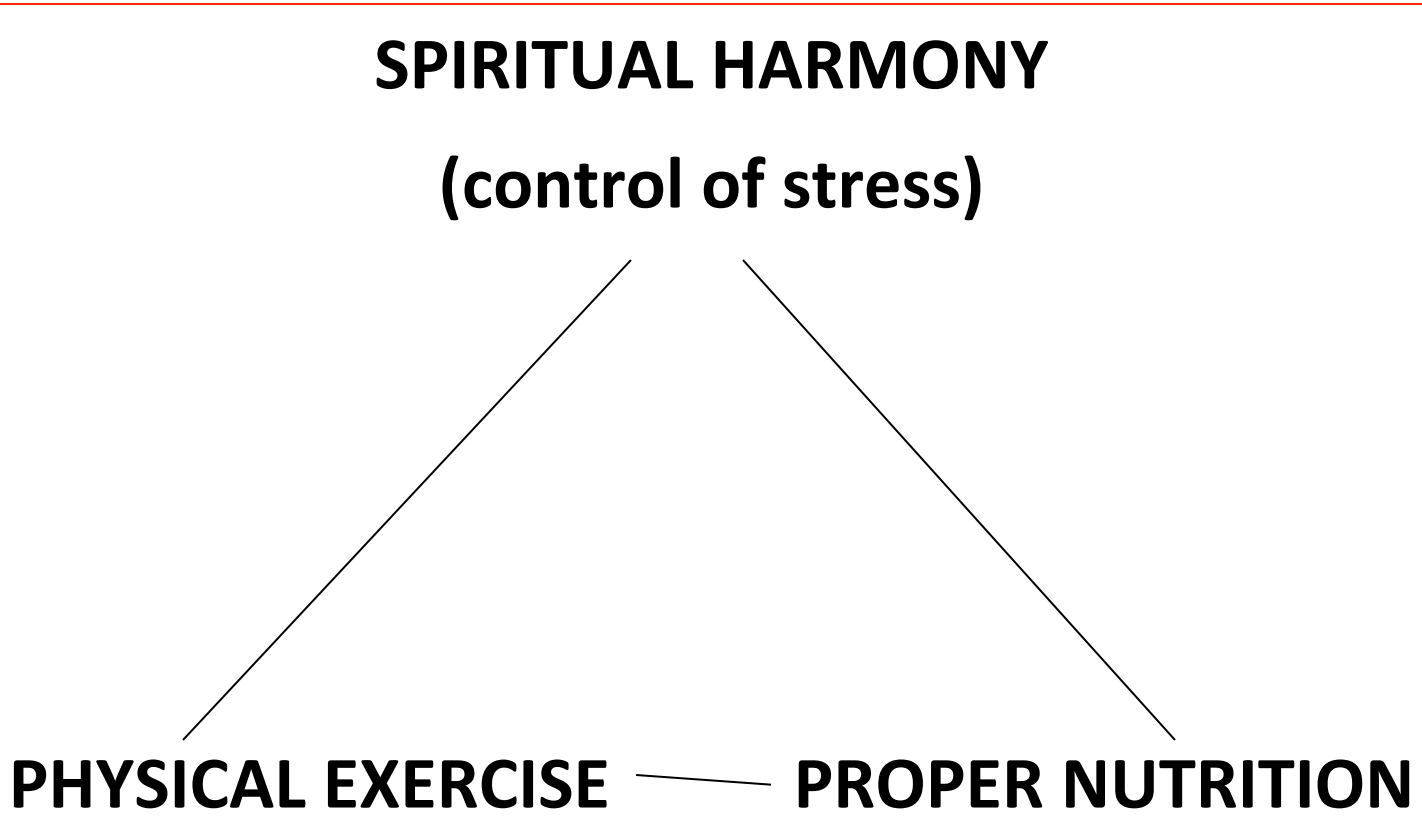
"HEALTH IS MORE THAN MERELY ABSENCE OF DISEASE" M. Twain



A WORLD-WIDE EPIDEMIC

TSUNAMI OF CHRONIC DISEASES (ChDs)

World Health Organisation. Process for a global strategy on diet, physical activity and health. WHO Geneva 2003

- **46 % of global disease burden**
- **59 % of global mortality**
- **35 million die each year on earth in chronic diseases**
- **and it increases every year**

KATRINA OF SEPSIS (USA)

- 751000 each year treated for severe sepsis
- 215 000 deaths
- Increases by 15 % per decade
- 10th commonest cause of death in USA
- *Angus DC, Wax RS (2001) Crit Care Med 2001;29:109*

"Conventional Medicine has been unable to stem the tide of these conditions"

James Gordon, MD, Washington

PROSPECT FOR 3RD MILLENIUM

- Pharmaceutical medicine “unable” to control acute and chronic diseases
- A series of pharma-associated disease entities have been induced
- Urgent need of new treatment concepts

THE DILEMMA OF MEDICINE

Example USA:

- 2 % adverse drug reactions
- 5-6 % nosocomial infections
- > 4 % iatrogenic injuries
- **App 1 milj deaths /year**
  e.g. > 10 jumbo crashes each day
  compare: cardiovascular 700 000, cancer 550 000, accidents 100 000

THE HOSPITAL PATIENT - MALNUTRITION

- **34 % of general ward patients are malnourished (P = 0.05)**
- Only half (54%) identified by staff
- **Have in average 2 chronic diseases**
- Little information to general practitioner (GP) in discharge letters. 3 months after discharge, most GPs are not aware of any nutritional problems
  van Bokhorst-de van der Schueren MA et al. Eur J Clin Nutr 2005;59:1129-1135

THE MALNOURISHED PATIENT (USA)

- **App 50 % increase in length of stay – also in ICUs**
- **App 50 % higher hospital costs**
- **Higher complication rates**
- **Use app 3 times as much of home care facilities**

Chima CS et al J Am Diet Assoc. 1997 Sep;97(9):975-8

PROTEIN MALNUTRITION IN BURNS (USA – Harvard)

Present in 61%

- **Increased infection rate,**
- **Decreased rate of healing**

Mortality:

with PEM: 17%

without PEM: 9%

Demling RH. J Burn Care Rehabil 2005;26:94-100 ;

PREDICTION OF POSTOPERATIVE OUTCOME IN MAJOR SURGERY

The odds ratio for morbidity between well nourished and malnourished patients is:

2.30 (CI: 1.43-3.71) - Maastricht Index

2.81 (CI: 0.79-9.95) - Mini Nutritional Assessment

3.09 (CI: 1.96-4.88) - Subjective Global Assessment

3.47 (CI: 2.12-5.68) - Nutritional Risk Index

Kuzu MA et al. World J Surg 2006;30:378-390

IMMUNE DEFICIENCIES –

ELDERLY PATIENTS WITH COLORECTAL CANCER

- **Immuno-reactivity impaired in under-nourished**
- **Preoperatively:** high age, low BMI, high levels of IL-1 receptor antagonist (IL-1Ra)
- **Postoperatively: E**xaggerated IL-6 increase & increased postoperative loss of body weight
  Miki C et al Crit Care Med 2005;33:177-80

EXAGERRATED INFLAMMATION – THE CAUSE!

APR & CPR – NUTRITIONAL CONTROL

Bengmark S Nutrition 2001;17:489-495

Nutritional Modulation of Acute- and "Chronic"-Phase Responses

Stig Bengmark, MD, PhD

From the Departments of Hepatology and Surgery, University College of London, London, United Kingdom

AN EPIDEMIC OF CHRONIC AND DRUG-INDUCED DISEASES

Fifty years have passed since I decided to dedicate my life to surgery. At that time, there was enormous enthusiasm for pharmaceutical medicine, with some investigators forecasting that almost all diseases soon would be treated medically, thus drastically reducing the need for surgery and surgeons. However, developments in the last 50 y of the 20th century went in quite the opposite direction. As we enter a new millennium, the main treatment for almost all endemic diseases—arteriosclerosis; diabetes; cancer; failures of organs such as the heart, lung, liver, kidney, and intestine; and even obesity—is surgery.

Although it is not often said, it is clear that pharmaceutical medicine has not fulfilled the high expectations of the past. Although we have reduced suffering, we have not reduced disease. Instead, we are witnessing an epidemic of chronic and drug-induced diseases (Table I). In addition to the diseases listed in Table I, the incidence of asthma and other allergies, chronic fatigue, coronary artery disease, congenital malformations, diabetes, immune deficiency, human immunodeficiency virus, and overwhelming infections has increased dramatically. The medical profession seems unable to stem the tide of these diseases, and some physicians and biologists, and also consumers, have begun to

TABLE I.

THE INCREASING INCIDENCE OF CHRONIC AND DRUG-INDUCED DISEASES IN THE WESTERN WORLD*

Disease	Incidence (*n* persons)
Chronic disease	
Hypertension	60 million
Arthritis	40 million
Migraine	23 million
Cancer	40% of Americans in their lifetimes (1 million/y)
Drug-induced disease	
Adverse effects	1 million
Drug-induced parkinsonism	61 000
Automobile accidents due to prescription drugs	16 000
Drug-induced memory problems	163 000
Hip fractures caused by drug-induced falls	32 000
Prescription drug abuse	6 million
Medical accidents	97 000

APR & Immunoparesis

The height of acute phase response in the early nervous phase is strongly associated with the depth of immunoparesis in the subsequent so called immune phase.

ACUTE PHASE RESPONSE

- Rise in cytokines and coagulation factors within seconds
- Rise in acute phase reactants with hours
- Disappearance of ”protective” flora 6-8 hrs
- Overgrowth with PPMs after 10-12 hrs and
- TRANSLOCATION

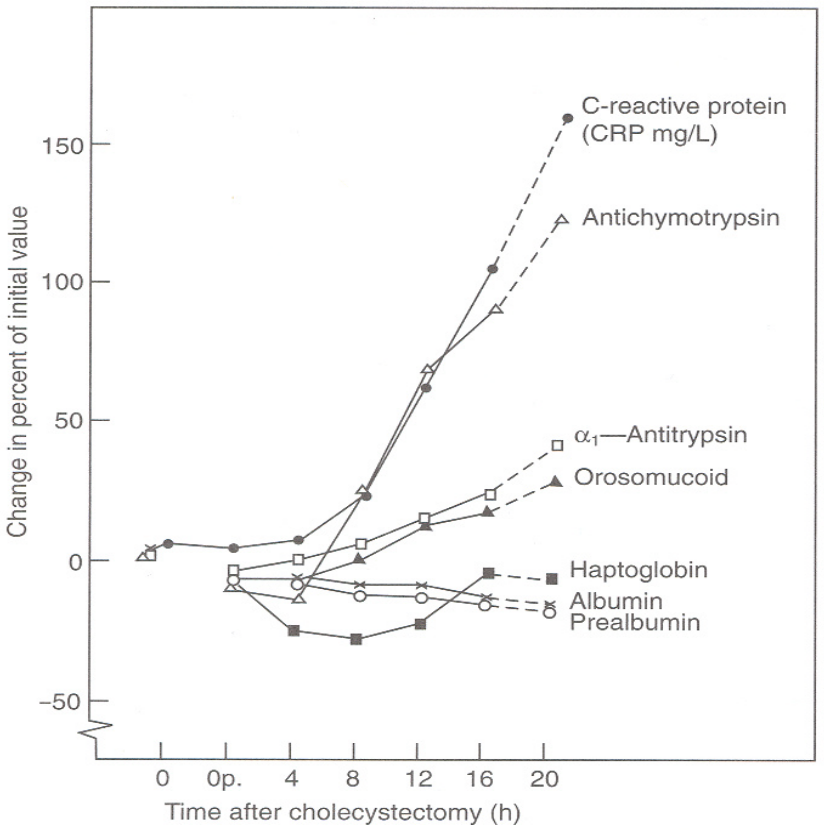


Figure 33.2

Fast Quantitative Changes in Acute Phase Reactants During the First 20 Hours After Cholecystectomy

Reprinted with permission Aronsen KF, Ekelund G, Kindmark CO, et al. Sequential changes of plasma proteins after surgical trauma. *Scandinavian Journal of Clinical & Laboratory Investigation*. 1972;29,(Suppl)124:127–136l.

NARROW THERAPEUTIC WINDOW

if to prevent:

- **Reduced intestinal motility**
- **Deficient epithelial integrity**
- **Reduced preventive flora**
- **Overgrowth and increased virulence of PPMs**
- **Deranged metabolism**
- **Intestinal translocation**
- **REDUCED RESISTANCE TO MORBIDITY**

CYTOKINE REACTION IN LIVER TRANSPLANTATION

- **Sixfold and more increase in TNF-alpha and IL-6 observed in patients**
- **at the end of the unhepatic phase**
- **after 10 minutes of reperfusion**
- **at the end of the operation**

who subsequently developed infections

Sautner T et al Eur J Surg 1995;161:97-101

APR & PRESSURE SORES

Cordeiro MBC et al Nutrition 2005; 21:901–907

Table 2

Clinical indicators of the acute-phase response in patients in the PS, IC, and C groups*

Parameter	Patient groups		
	PS (n = 11)	IC (n = 12)	C (n = 12)
Total proteins (g/dL)	5.2 ± 0.7†	5.8 ± 0.8	7.8 ± 0.8
Albumin (mg/dL)	2.1 ± 0.6‡	3.1 ± 1.0	3.9 ± 0.4
C-reactive protein (mg/dL)	14.8 (6.1–23.4)§	9.3 (0.4–22.0)	0.8 (0.1–5.6)
α_1-acid glycoprotein (g/L)	1.9 ± 0.3§	1.3 ± 0.5	0.9 ± 0.2
Leukocytes (cell/mm^3)	13 100 (5900–22 400)‡	7700 (4400–11 400)	7700 (4600–9200)
Lymphocytes (cell/mm^3)	2180 ± 1300	1680 ± 0.8	2460 ± 0.7

C, patients who did not develop pressure sores or any type of infection (control); IC, patients who had infectious pneumonia; PS, patients who had pressure sores.

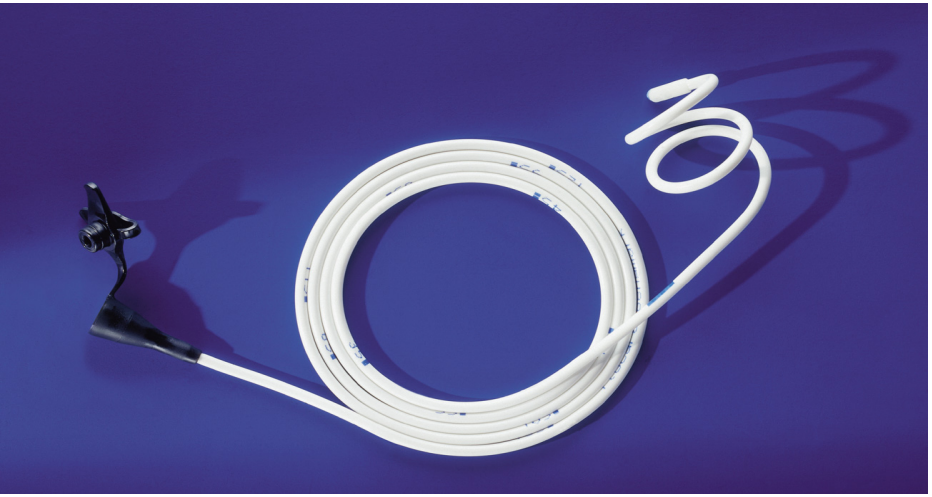
* Values are presented as mean ± standard deviation or median (range).

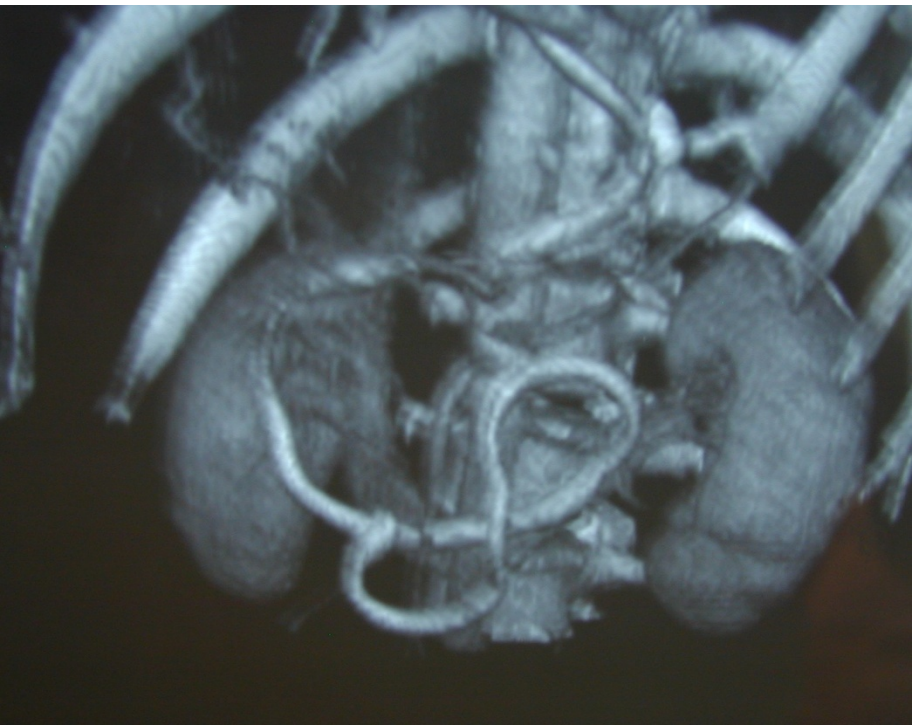
† $P < 0.05$, PS versus C.

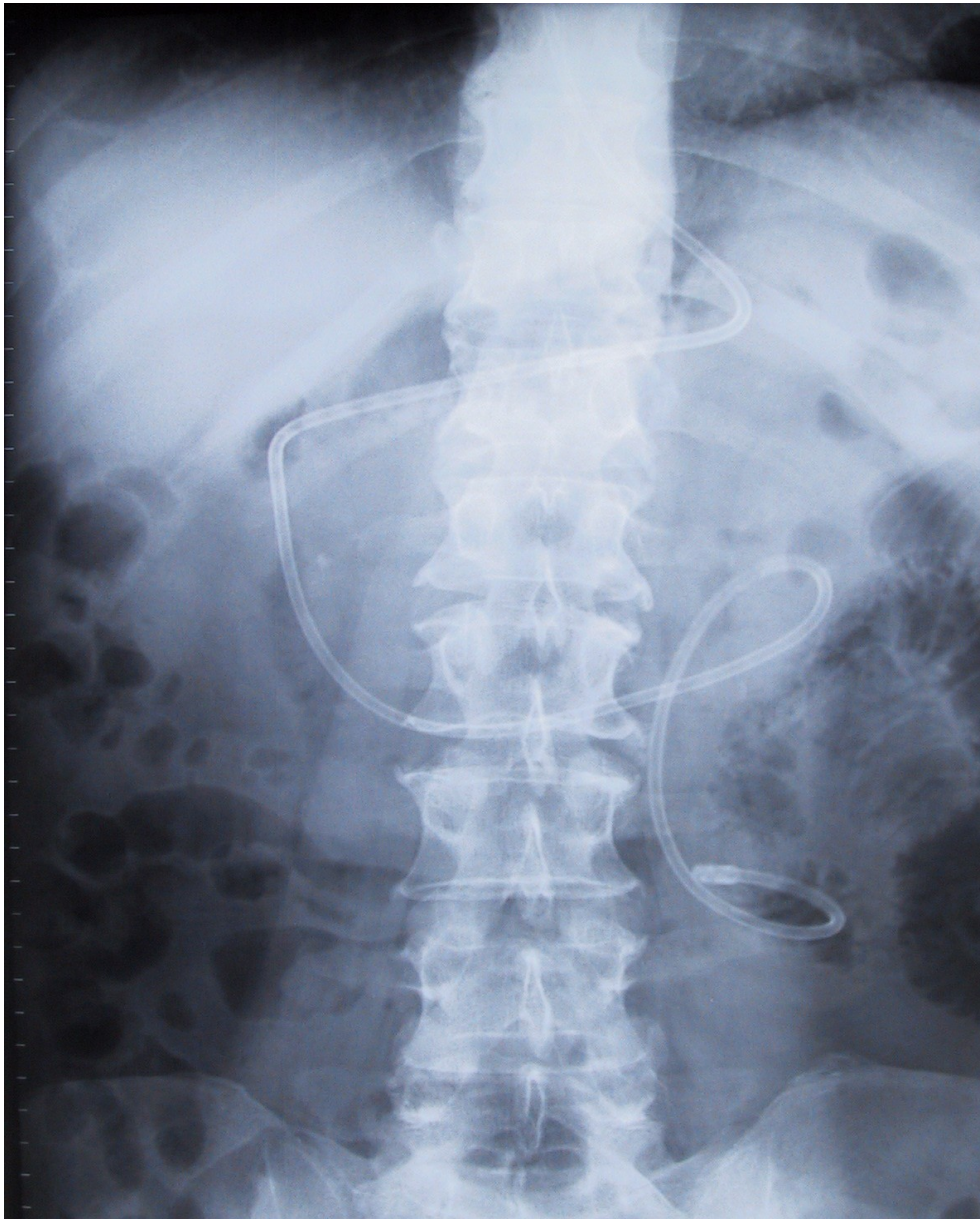
‡ $P < 0.05$, PS versus IC and C.

§ $P < 0.05$, PS and IC versus C.

The BENGMARK Flocare feeding tube







INFLAMMATION AND AGING

AGING – A HORMONAL CHAOS

Senescence - "*a multiple hormone deficiency syndrome*", accompanied by:

Excessive free radical formation

Glycation & cross-linking of proteins

Imbalanced apoptosis system

Accumulation of waste products

Poor cell proliferation & failure of repair

Deficient immune system

Hertoghe T Ann NY Acad Scien 2005;1017:448-465

AGING CHARACTERISTICS

Poor gene polymorphisms

Premature telomere shortening

Poor chaperone expression &

Activation of various genetic factors

Accelerated by lifestyle factors: behavioural, dietary & environmental conditions**, which aggravate aging & enhancing development of acute and chronic diseases**

PHYSICAL AGING

Seven "deadly" factors in physical aging:

- **Cell loss/atrophy**
- **Death-resistant cells**
- **Nuclear mutations and epimutations**
- **mtDNA (mitochondrial DNA) mutations**
- **Protein cross links**
- **Junk inside cells**
- **Junk outside cells**

Cambridge geneticist Aubrey de Grey 2007

AGING & ORGAN FUNCTION

After Hertoghe T Ann NY Acad Scien 2005;1017:448-465

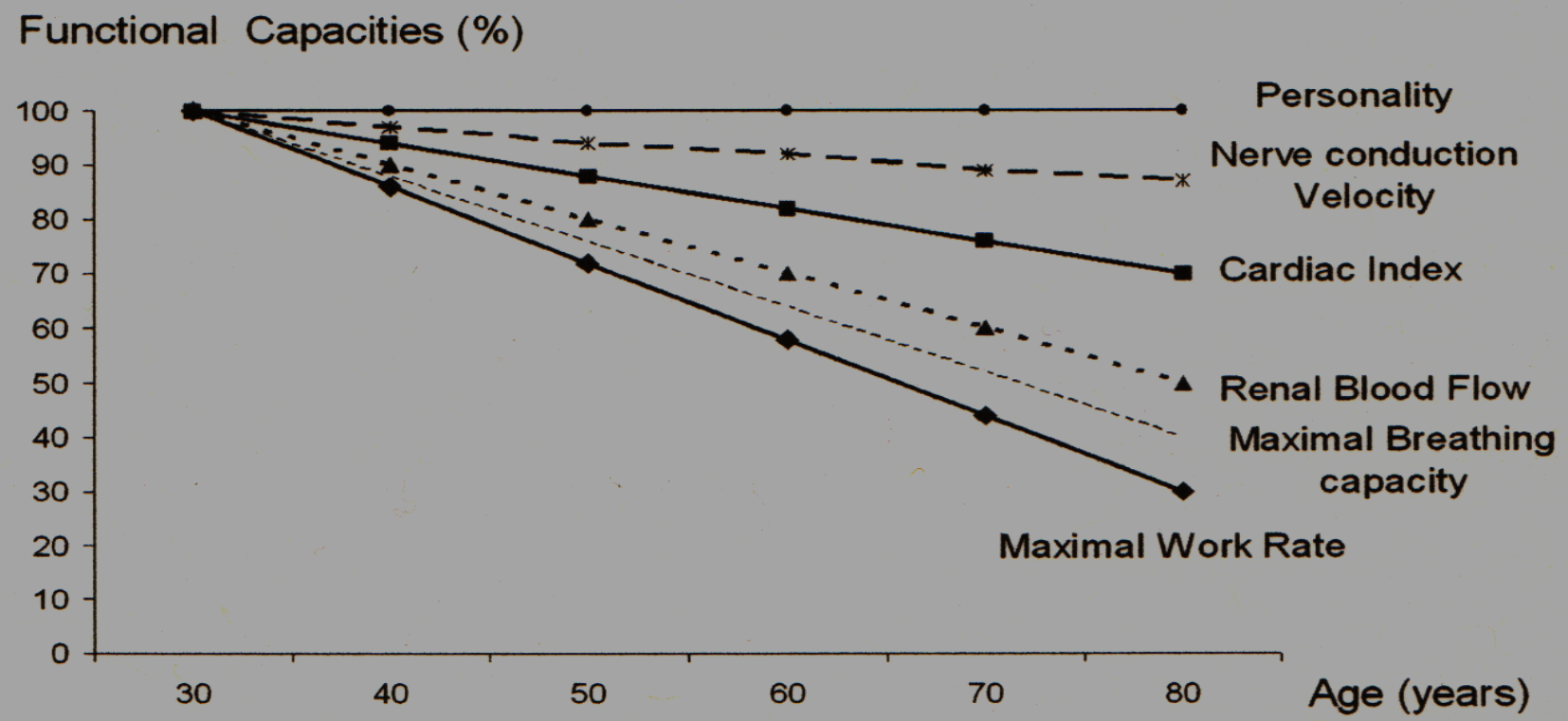


FIGURE 2. Representation of the progressive decline of the functional capacities with aging, a decline that bewgins for most around age 30. Cross-sectional data for male partic-ipan ts from the Baltimore Longitudinal Study. (G.T. Baker III & G.R. Martin, in *Geriatric Medicine* 1(1): 4, Fig. 1.1, as adapted from Refs. 248–250.)

SINGLE ORGAN FAILURE

Example: severe acute pancreatitis

Lungs 81 - 91 %

Kidneys 4.5 - 5 %

Coagulation 4.5 - 14%

McKay CJ, Buter A 2003;3:111-114

Johnson CD, Abu-Hilal M Gut 2004;53:1340 -1344

DELAY OF AGING

Hipkiss AR Mech Ageing Dev 2007 E-pub

Decreasing mRNA translation &

Phenotypic upregulation of homeostatic, proteolytic & chaperone activities will reduce misfolded/ aberrant polypeptides, **contribute to increased stress resistance, delay ageing and extend lifespan**

THE ROLE OF CHAPERONES

The number, size and complexity of chaperones has during evolution increased from the small to larger chaperones: Hsp40/ DnaJ, Hsp60, Hsp70, Hsp90, and Hsp110

The cellular expression of chaperones correlate with cellular and species longevity

Particular importance of the DNA/RNA chaperones suggested in longevity

ATHEROSCLEROSIS & TELEMERIC AGING

The telomere length of somatic cells inversely correlated with age & with chronic diseases (ChD)

Leukocyte telomere length (LTL) inversely associated to diabetes, fasting glucose, insulin, diastolic blood pressure, carotid intima-media thickness, and interleukin-6

Each shortened kilobase pair of TRF correspond in younger (but not older) subjects, to a threefold increased risk of myocardial infarction (hazard ratio = 3.08) and stroke (hazard ratio = 3.22)

Fitzpatrick AL et al Am J Epidemiol. 2007;165:14-21

HOMOCYSTEINE & TELEMERIC AGING

Leukocyte telomere length (LTL) negatively correlated to plasma homocysteine levels &

cumulative oxidative stress and inflammation

The difference in LTL between the highest and lowest tertile of homocysteine levels was
111 base pairs (*p* = 0.004*)*

equivalent to 6.0 years of telomeric aging &

further accentuated by

- **decreased conc serum folate &**
- **increased levels of C-reactive protein**

Richards JB et al Atherosclerosis. 2008 Feb 15

PHYSICAL ACTIVITY & TELEMERIC AGING

Physical inactivity - an important risk factor for shortening of LTL & many aging-related diseases

LTLs positively associated with increased physical activity level (P< .001)

LTLs of the most active subjects were 200 nucleotides longer than those of the least active subjects (P= .006) (app 10 yrs)

LTLs of active twins was 88 nucleotides longer than that of less active twins (P= .03)

Cherkas LF et al Arch Intern Med. 2008;168:154-158

PHYSICAL EXERCISE & AGING

Mortality is significantly lower in people expending >2000 kcal a week during exercise

Paffenbarger RS Jr, N Engl J Med 1986;314:605–613

Moderate exercise benefits health

Acute vigorous &

High-intensity exercise induces increase in

- **pro-inflammatory mediators**
- **prolonged dysfunction of mitochondria**
- **dysfunctioning innate immunity**

SOCIOECONOMIC STATUS & TELEMERIC AGING

Low socio-economic status (SES) associated with harmful effects of smoking, obesity and lack of exercise & shorter life expectancy

The mean difference in LTL between non-manual and manual groups was 163.2 base pairs (bp) (app 8 yrs)

of which app 14 % (22.9 bp) was accounted for by higher BMI, smoking & lack of exercise

Cherkas LF et al Aging Cell. 2006:5:361-365

SOCIOECONOMIC STATUS & HEALTH

Analyses of 308 female twin pairs

The working class twin fared worse & showed compared to her professional twin significantly higher :

- **Systolic blood pressure**
- **Diastolic blood pressure**
- **Low-density lipoprotein cholesterol**

Krieger N et al PLoS Med. 2005 Jul;2(7):e162

VITAMIN D & TELEMERIC AGING

Vitamin D - a potent inhibitor of the pro-inflammatory response

Serum vitamin D conc. are positively associated with LTL (P = 0.001)

The difference in LTL between the highest and lowest tertiles of vitamin D was 107 base pairs (P = 0.0009),

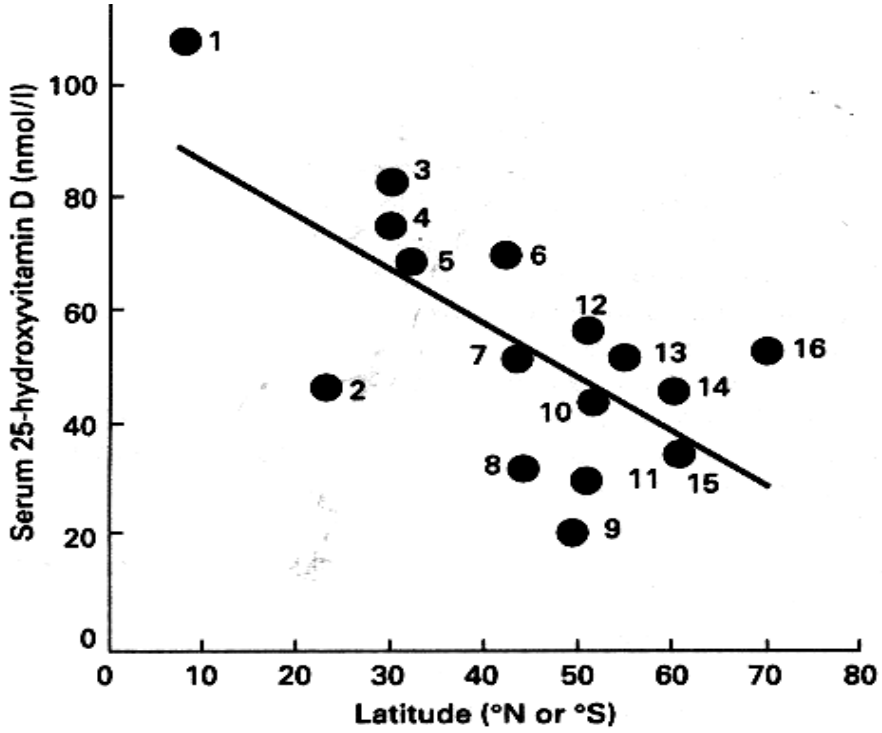
equivalent to 5.0 years of telomeric aging

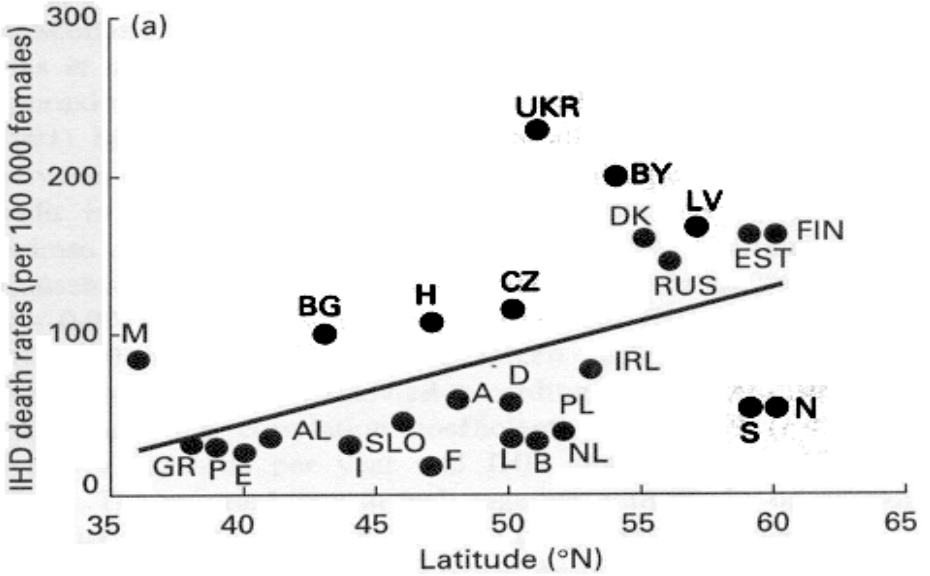
Richards JB et al Am J Clin Nutr 2007;86:1420-1425

VITAMIN D/s, LATITUDE & incidence of CHD

Zittermann A et al.

Br J Nutr 2005;94:483-492





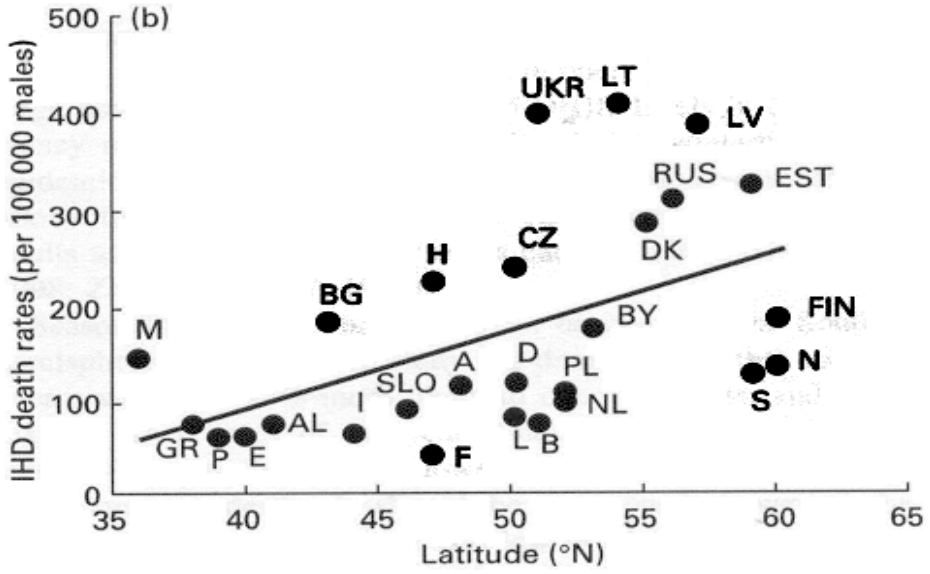


Fig. 2. Associations between geographic latitude and IHD death rates in (a) females (r 0·49; $P<0·01$) and (b) males (r 51; $P<0·01$) of different European countries. A, Austria; AL, Albania; B, Belgium; BG, Bulgaria; BY, Belarus; CZ, Czech; D, Germany; DK, Denmark; E, Spain; EST, Estonia; F, France; FIN, Finland; GR, Greece; H, Hungary; I, Italy; L, Luxembourg; LT, Luthuania; LV, Latvia; M, Malta; N, Norway; NL, Netherlands; P, Portugal; PL, Poland; S, Sweden; SLO, Slovenia; RUS, Russia; UKR, Ukraine.

VITAMIN INTAKE – COGNITIVE DECLINE (CD)

CD associated with high conc/s homocysteine **& low conc/s of vitamin B6, B12 & folate**

Cortical volume studied with MRI scans:

Persons with larger B6 intake had greater gray matter volume in several locations:
along the medial wall, anterior cingulate cortex, medial parietal cortex, middle temporal gyrus &superior frontal gyrus

Persons with larger B12 intake had greater volume in the left and right superior parietal sulcus

Folate had no effect on brain volume

Erickson KI et al Brain Res. 2008 Jan 26

ZINC & IMMUNOSCENESCENCE 1

Older persons have significantly:

- **lower plasma zinc**
- **higher inflammatory cytokines & IL-10,**
- **higher levels of oxidative stress markers & and of endothelial cell adhesion molecules**

The incidence of infections & levels of oxidative stress markers/plasma are significantly lower in zinc-supplemented

Prasad AS et al Am J Clin Nutr. 2007;85:837-844

ZINC & IMMUNOSCENESCENCE 1

Similarities between aging & zinc deficiency:

- Reduction in activity of thymic hormones
- Decreased response to vaccination
- **Shift of the T helper cell balance towards TH2**
- **Impaired functions of innate immune cells**

Marginal zinc deficiency may contribute to premature immunosenescence:

- **Cell-mediated immune dysfunction**
- **Susceptibility to infections &**
- **Increased oxidative stress**

ZINC IN FOODS mg/100 g

- **Wheat germ 18**
- **Dry yeast 14**
- **Sesami seed 10.2**
- **Flaxseed, dry 7.8**
- **Pumpkin seed 7.5**
- **Squash seed 7.5**
- **Cacao 7.0**
- **Pecan nuts 5.5**
- **Sunflower seeds 5.1**
- Liver 4-7
- Beef 4-6
- Soy protein 4.4
- Brazil nuts 4.2
- Peas 3.8
- Lentils 3.1
- Peanuts 3.1
- Bacon 3.0
- Walnuts 3.0
- **Flour 3.0**
- **Cheese 2-3**
- **French fries** 0.4
- **Milk** 0.4
- **Cream** 0.3

A MOTHER OF DISEASE

Bengmark S. J Clin Nutr 2004;23:1256-1266

Clinical Nutrition (2004) 23, 1256–1266

ELSEVIER

Clinical Nutrition

www.elsevier.com/locate/clnu

REVIEW

Acute and ''chronic'' phase reaction—a mother of disease

Stig Bengmark

Department of Surgery and Liver Institute, UCL, London, UK

Received 23 July 2004

KEYWORDS
Acute phase response;
Chronic phase response;
Metabolic syndrome;
Cellular membranes;

Summary The world is increasingly threatened by a global epidemy of chronic diseases. Almost half of the global morbidity and almost two thirds of global mortality is due to these diseases—approximately 35 million die each year from chronic diseases. And they continue to increase. Increasing evidence suggest that these diseases are associated with lifestyle, stress, lack of physical exercise, over-consumption of calorie-condensed foods rich in saturated fat, sugar and starch, but also under-consumption of antioxidant-rich fruits and vegetables. As a result the

INFLAMMATION – A MOTHER OF DISEASE

INFLAMMATION & INFECTION

- **Superinflammation precedes and paves the way for the subsequent disease incl infections**
- *"the challenge in critical illness is less the infection than the exuberant inflammatory response"*

Tanaja et al Crit Care Med 2004; 32: 1460–1469

SYSTEMIC INFLAMMATION IN ELDERLY

Many elderly with yet no obvious disease demonstrate:

higher levels of serum inflammatory proteins:

C-reactive protein, fibrinogen, factor VIII activity, interleukin-6 and TNF-α &

are candidates to develop chronic diseases & complications to disease

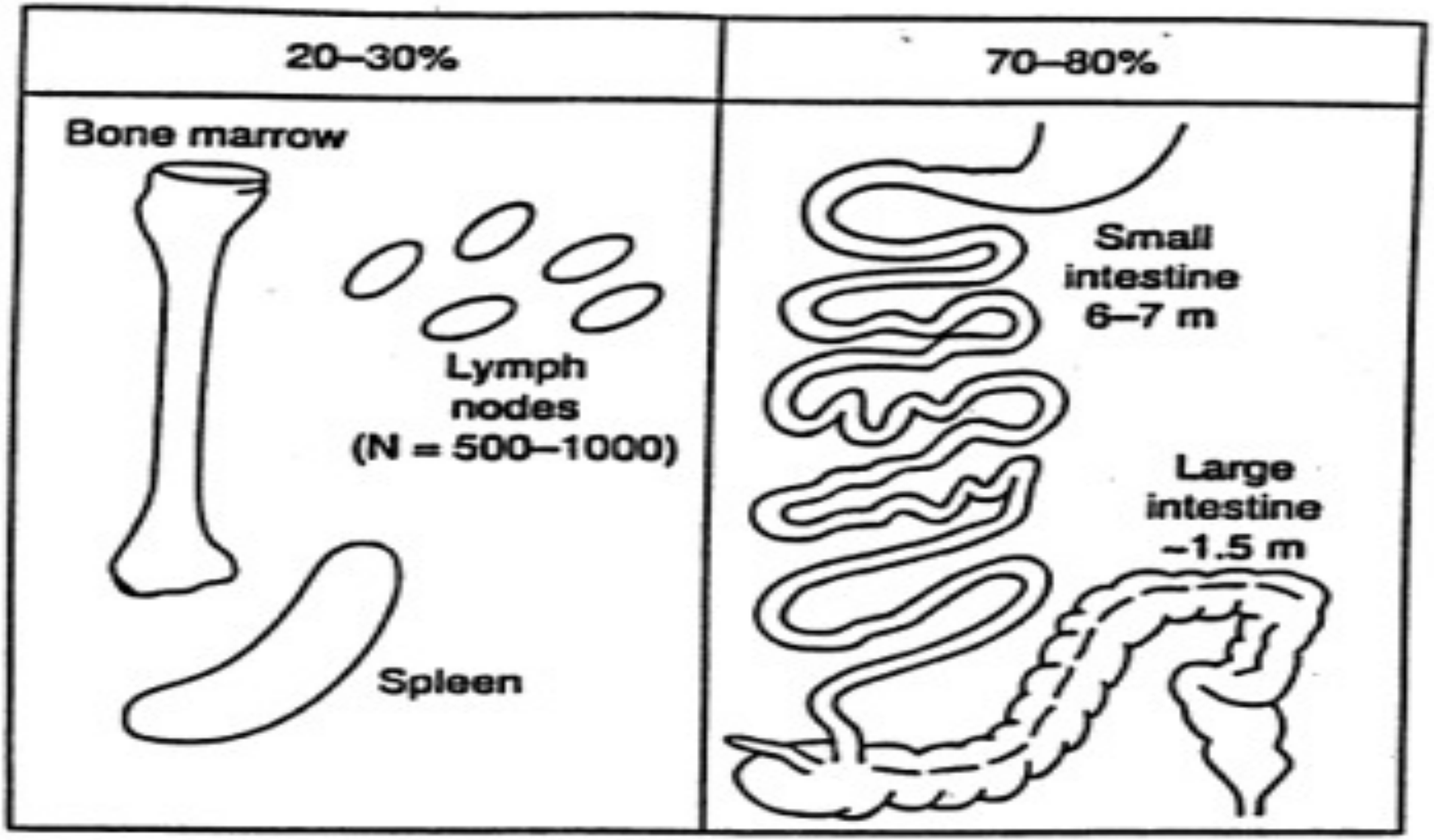
Finch CE, Crimmins EM. Science 2004; 305:1736–1739

INFLAMMATION & PHYSICAL PERFORMANCE

- **Chronic inflammation** – key to physical decline in elderly people
- **Physical performance (PP) is significantly correlated to markers of inflammation: CRP, IL-6, and IL1RA**
- **Bad PP strongly associated with high levels of IL-6 and IL-1RA (p < .001 and p=0.004 resp)**
- **Hand-grip strength correlate with CRP and IL-6**
  Cesari M et al J Gerontol 2004;59A:242–248

THE IMMUNE SYSTEM

Brandtzaeg, P et al Gastroenterlogy 1989;97:1562-1584

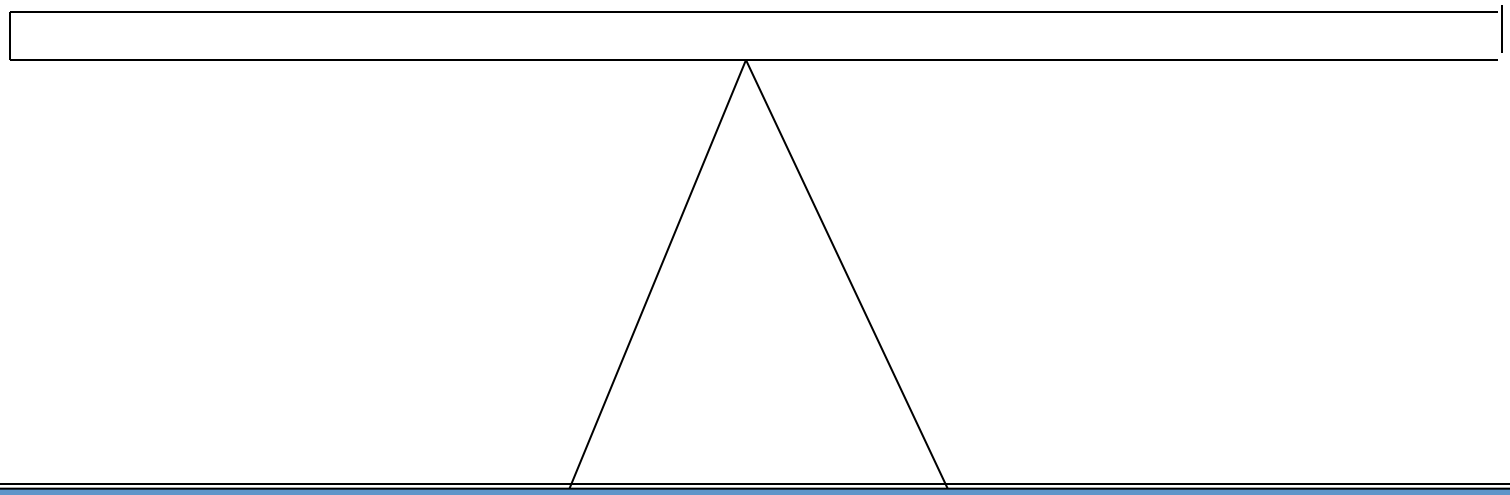


THE INFLAMMATION BALANCE

> 2 mill different molecules in absolute balance

homeostasis

+ -



Cannon WB The autonomic nervous system: an interpretention Lancet 1930;1: 1109

DESTABILIZING FACTORS

Mental and physical stress

Excess of refined foods: fats, sugars, dysfunctioning peptides - AGEs & ALEs, hormones, chemicals (pharma)

increases prooxidant actions, stimulate overexpression of NF-κB, COX-2, LOX &INOS, destabilizes the immune system, reduces flora & decreases resistance to disease

HORMESIS

Chemical substances, depending on dose, can have both stimulatory and inhibitory functions

- a phenomenon given the name of **chemical hormesis** and referred to as the **Arndt–Schultz law**

INFLAMMATION AND NUTRITION

PROTEOME HOMEOSTASIS

Bach WE Science 2008;319:916-919

Protein homeostasis

– proteostasis –

protects against aging and disease by reducing protein damage and increasing protein repair

Especially protective are the heat shock response (HSR) and the so called the unfolded protein response (UPR)

SEMEN QUALITY – AN INDICATOR

"Frequent intake of lipophilic foods like meat products or milk affects negatively semen quality in humans,
whereas some fruits or vegetables may maintain or improve semen quality.“

Mendiola J et al Fertility and Sterility 2008

WESTERN FOOD – the problem?

- Nature provides about 195 000 plants
- Paleolithic forefathers ate from > 500 plants – and fresh!
- 90 % of our daily intake today from 17 plants
- And > 50 % of calories from 8 cereals
- **Processing, heating and drying etc of food eliminates numerous important food ingredients**
- **And kills important microorganisms in food**

CHANGING EATING HABITS (USA)

	1973	2008 (estim)
Corn syrup	0.5 kg (1448 cal)	20 kg (62205 cal)
Sugar	32 kg (122873 cal)	21 kg (80747 cal)
Cheese	4.5 kg (18276 cal)	14.5 kg (58435 cal)
Total	142577 calories	201387 calories *

Increase: 58790 calories **

* the calories needed for 70 marathon runs

** the calories needed for 20 marathon runs

CALORIC RESTRICTION & AGING

Fontana L, Klein S. JAMA. 2007;297:986-994

"**Calorie restriction in adult men and women causes beneficial metabolic, hormonal, and functional changes,**

but the precise amount of calorie intake or body fat mass associated with optimal health and maximum longevity in humans is not known."

AGING & HORMESIS MECHANISMS

Dietary energy restriction (DER), controlled caloric restriction or intermittent fasting, increases the resistance of cells to various types of stress

Certain food ingredients such as polyphenols (and thiols) in animal models protect the cells from diseases such as cataract formation, pulmonary toxicity, multiple sclerosis and Alzheimer's disease

primarily through cytoprotective proteins, antioxidant enzymes, protein chaperones,

growth factors and mitochondrial proteins.

OXIDATIVE STRESS – INTELLECTUAL DISTURBANCIES

Oxidative stress (OS) key to severe motor and intellectual disabilities (SMID) &

Respiratory disturbances

SMID patients show significantly higher levels of OS markers:

8-OHdG (8-hydroxy-2'-deoxyguanosine) 18.8±9.0 vs 10.5±2.9ng/mg ($p<0.01$).

ACR (acrolein-lysine adduct) 220.5±118.6 vs 144.9±62.0 nmol/mg ($p<0.05$).

Tanuma N et al Brain Dev. 2008 Feb 13

AGING & INSULIN RESISTANCE

Barbieri M et al Exp Gerontol 2003;38:137–143

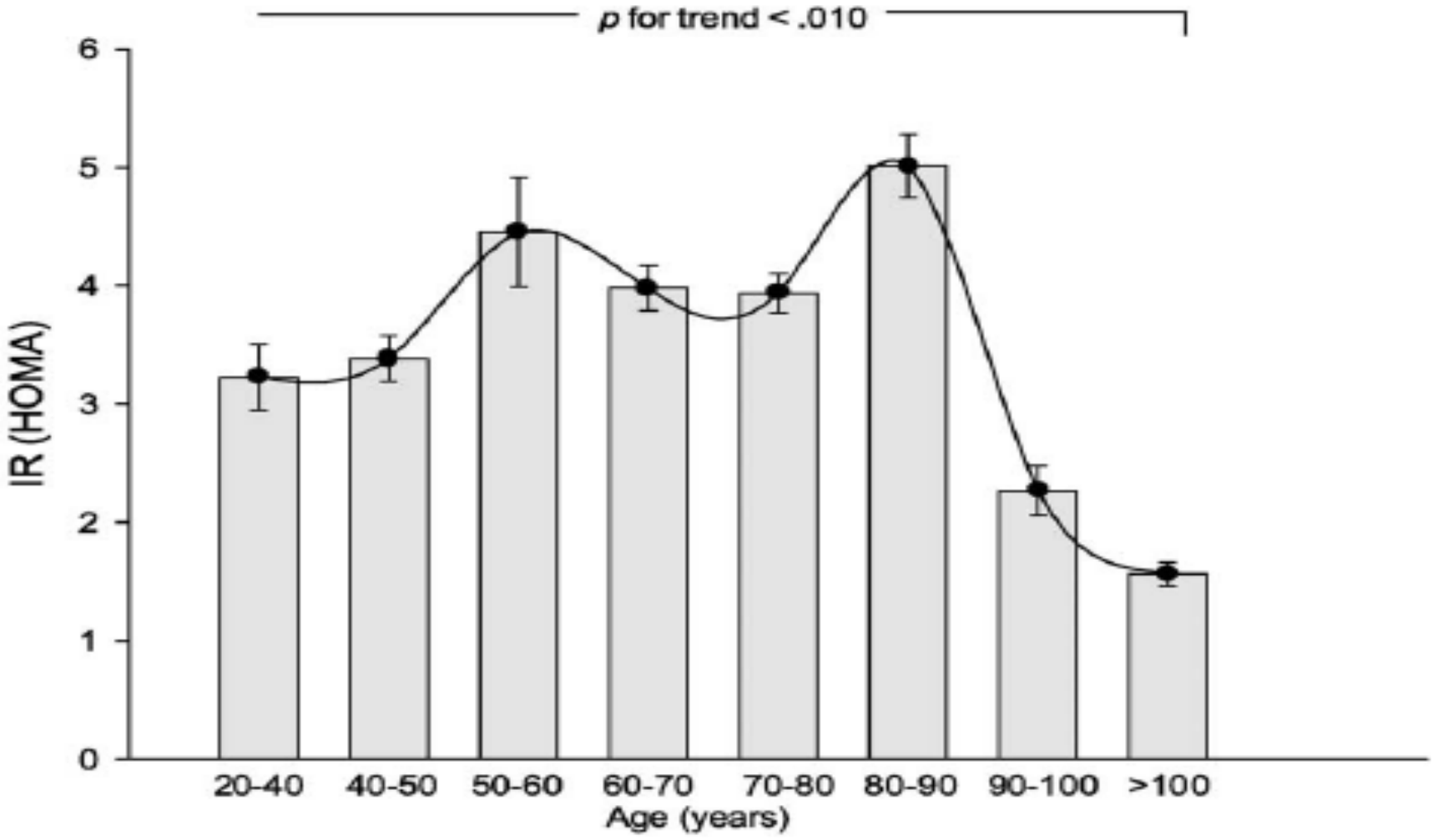


Fig. 1. Age-related difference in insulin resistance in 466 healthy subject.

OXIDATIVE STRESS, ANTIOXIDANTS & AGING

Barbieri M et al Exp Gerontol 2003;38:137–143

Table 1
Plasma oxidative stress and vitamin E levels in aged subjects (AS) and in centenarians (C)

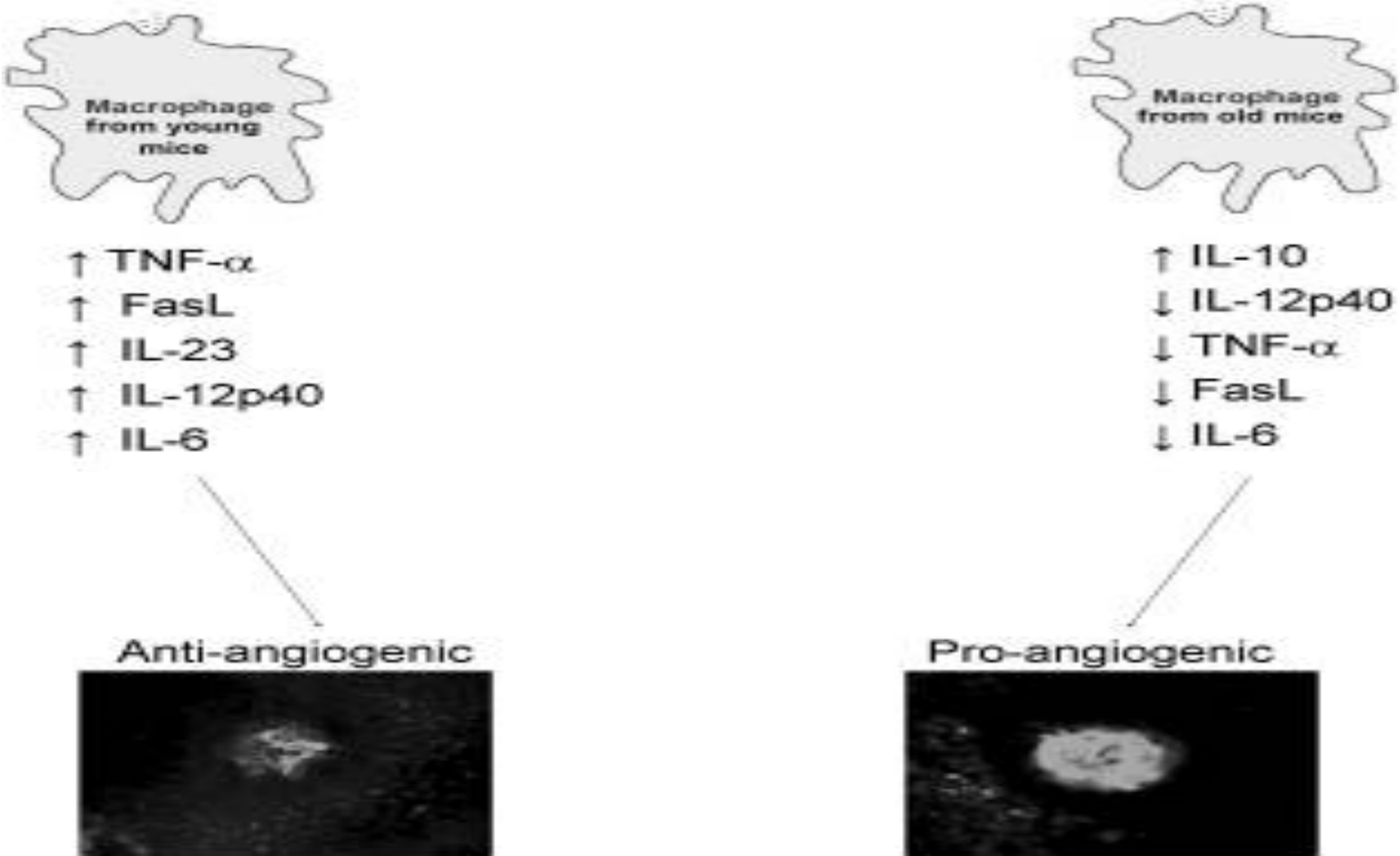
	AS ($n = 30$)	C ($n = 22$)
TBARS (mmol MDA/ml plasma)	0.51 ± 0.07	0.39 ± 0.04*
LPO (pmol/l)	0.39 ± 0.05	0.31 ± 0.03*
Vitamin E (pmol/l)	25 ± 3	29 ± 4*

All results are mean ± SD; statistically significant differences were *$p < 0.03$; TBARS, Thiobarbituric acid reactive substance, LPO, Lipid hydroperoxides.

THE MACROPHAGE – A KEY CONTRIBUTOR

Dace DS, Apte RS Rejuvenation Res. 2008;11:177-185

macrophages & angiogenesis – key to diseases of aging, ex. neoplasias, arthritis, macular degeneration.



MACROPHAGE – A KEY CONTRIBUTOR

Macrophages from old mice demonstrate:

- Reduced production of nitric oxide
- Reduced phosphorylation of mitogen-activated protein kinase (MAPK) & signal transducer and activator of transcription-1 (STAT-1)
- Higher secretion of immunosuppressive substances such as prostaglandins (PGE), especially PGE2
- **Impaired antigen presentation and phagocytosis**
- **Lower levels of T cell proliferation**
- **Decreased expression of MHC class II**

PROINFLAMMATORY NUTRITION

AGEs/ALEs – AMPLIFIERS OF INFLAMMATION

Bengmark S JPEN 2007;31:430-440

0148-6071/07/3105-0430$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
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Review

Advanced Glycation and Lipoxidation End Products–Amplifiers of Inflammation: The Role of Food

Stig Bengmark, MD, PhD, FRACS (hon), FRCPS (hon)

From UCL Institute of Hepatology, University College, London Medical School, London, United Kingdom

ABSTRACT. *Background:* High levels of glycated and lipoxidated proteins and peptides in the body are repeatedly associated with chronic diseases. These molecules are strongly associated with activation of a specific receptor called RAGE and a long-lasting exaggerated level of inflammation in the body. *Methods:* PubMed reports over 5000 papers plus >13,500 articles about the related HbA_{1c}, most of them published in the past 5 years. Most of the available abstracts have been read and approximately 800 full papers have been studied. *Results:* RAGE, a member of the immunoglobulin superfamily of cell surface molecules and receptor for advanced glycation end products, known since 1992, functions as a master switch, induces sustained activation of nuclear factor κB (NFκB), suppresses a series of endogenous autoregulatory functions, and converts long-lasting proinflammatory signals into sustained cellular dysfunction and disease. Its activation is associated with high levels of dysfunctioning proteins in body fluids and tissues, and is strongly associated with a series of diseases from allergy and Alzheimers to rheumatoid arthritis and urogenital disorders. Heat treatment, irradiation, and ionization of foods increase the content of dysfunctioning molecules. *Conclusions:* More than half of the studies are performed in diabetes and chronic renal diseases; there are few studies in other diseases. Most of our knowledge is based on animal studies and *in vitro* studies. These effects are worth further exploration both experimentally and clinically. An avoidance of foods rich in deranged proteins and peptides, and the consumption of antioxidants, especially polyphenols, seem to counteract such a development. (*Journal of Parenteral and Enteral Nutrition* 31:430–440, 2007)

AGEs/ALEs IN TISSUES

- **Glycated proteins produce about 50 X more free radicals than non-glycated proteins**

  AGEs and ALEs accumulate in tissues (amyloid) & make the body autofluorencing

  - induce inflammation & infection
  - reduce antioxidant defense
  - weaken immune system
  - impair DNA repair mechanisms
  - induce tissue accumulation of toxins **&**

  accelerate the development of various diseases

  Thorpe SR, Baynes JW Amino Acids 2003;25:275-281

SOURCES OF AGEs

Vlassera H Ann N Y Acad Sci 2005;1043:452-460

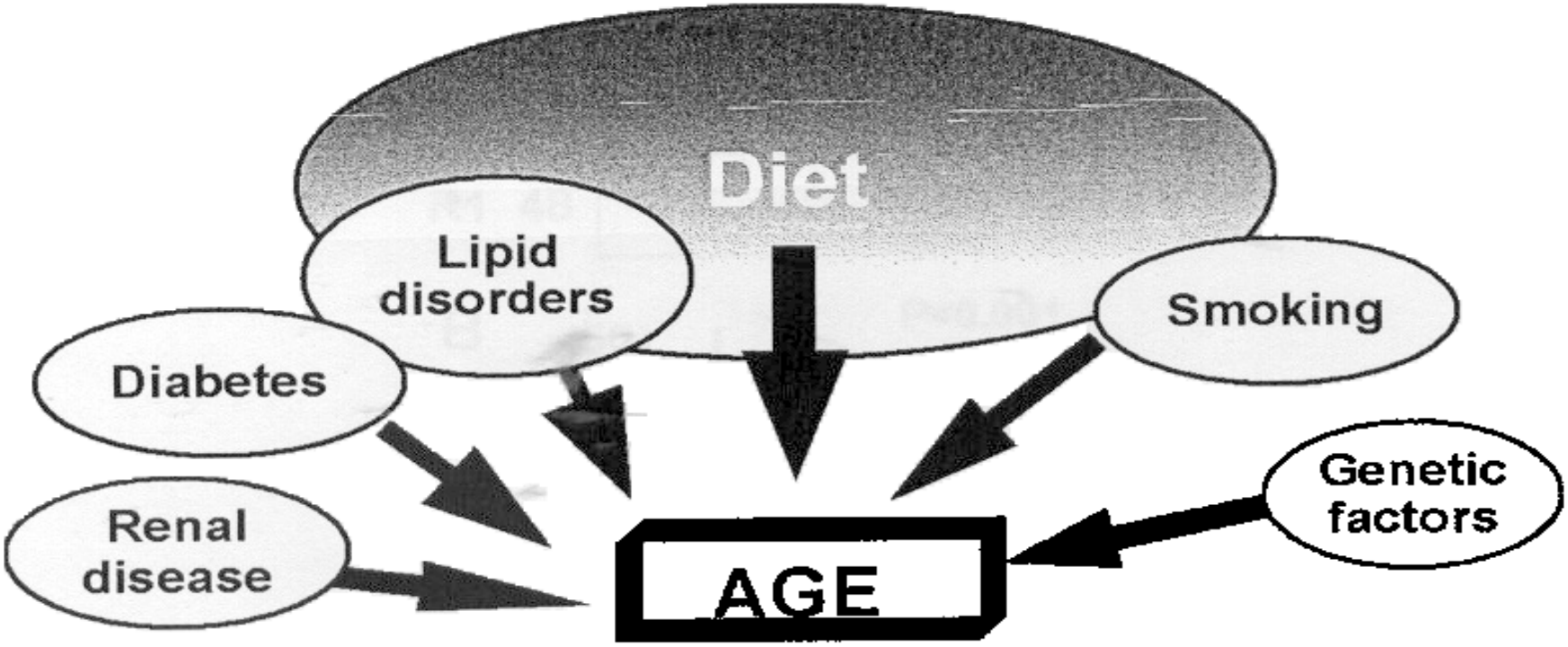


FIGURE 3. Schematic depiction of the multiple sources of AGEs. Beyond the known conditions associated with elevated circulating and tissue AGEs, exogenous sources—namely, diet and tobacco—constitute significant contributors.

AGEs/ALEs IN FOODS

HEATED DAIRY: powdered milk (ice cream, baby & clinical nutrition formulas) **cheese, espec when heated**: rich in pizza, tacos, nachos, salads, fast-food sandwiches and sauces & brown cheeses

HEATED GRAIN PRODUCTS: Bread esp. toasted bread, bread crusts & crisp breads

HEATED MEAT, POULTRY, FISH: content increases as one goes from boiling to oven frying: boiling (**1000** kU/serving) < roasting (**4300** kU)< broiling (**5250** kU) < deep frying (**6700** kU) < oven frying (**9000** kU/serving).
Goldberg T et al. J Am Diet Assoc 2004;104:1287-1291

Egg yolk powder, lecithin powder, **coffee**, espec dark roasted, **hard-cured teas**, **roasted and salted peanuts**, **dark and sugar-rich alcoholic beverages**, broth, Chinese soy, balsamic vinegar, **Cola drinks** etc

AGEs & INFLAMMATION

Bohlender JM Am J Physiol Renal Physiol 2005;289:F645-659

Table 2. *Cytokines and cellular events associated with AGE or RAGE activation*

VCAM-1 ↑	Endothelial cells
ICAM-1 ↑	Endothelial cells
E-selectin ↑	Endothelial cells
PDGF ↑	Pancreatic cancer cells
eNOS ↓	Endothelial cells
Tissue factor ↑	Endothelial cells
TGF-β ↑	Mesangial cells, proximal tubular cells, vascular smooth muscle cells, macrophages
TNF-α ↑	Endothelial cells, mesangial cells, mononuclear macrophages
IGF-1 ↑	Mesangial cells
MCP-1 ↑	Mesangial cells, endothelial cells
CTGF ↑	Fibroblasts, mesangial cells
IL-6 ↑	Endothelial cells
PAI-1 ↑	Endothelial cells
RAGE ↑	Mesangial cells, endothelial cells, podocytes
VEGF ↑	Podocytes, endothelial cells, mesangial cells
ANG II-dependent cell activation ↑	Vascular smooth muscle cells
Type IV collagen expression ↑	Mesangial cells
Fibronectin ↑	Mesangial cells
Cell cycle progression ↓	Fibroblasts, mesangial cells

eNOS, endothelial nitric oxide synthase; TGF-β, transforming growth factor-β; MCP-1, monocyte chemotactic protein-1; CTGF, connective tissue growth factor; PAI-1, plasminogen activator inhibitor-1.

DISEASES ASSOCIATED WITH ELEVATED AGEs/ALEs

- **Aging**
- **Allergy**
- **Autoimmune diseases**
- **Alzheimer´s disease**
- **Parkinson´s disease**
- **Amyotrophic lateral sclerosis**
- **Huntington´s disease**
- **Stroke**
- **Familial amyloidotic polyneuropathy**
- **Creutsfeldt-Jakob disease**
- **Down´s syndrome**
- **Atherosclerosis**
- **Cardiovacular disease**
- **Cataract**
- **Glaucoma**
- **Macula degeneration**
- **Diabetes**
- **Hormone deficiencies**
- **Polycystic Ovary Syndrome**
- **Liver cirrhosis**
- **Chronic pulmonary disorders**
- **Rheumatoid diseases**
- **Fibromyalogia**
- **Ruptured Achilles tendon**
- **Osteoporosis**
- **Nephropathies**
- **Paradontosis**

”SMOKING WITH THE STOMACH”

COPD doubled in the last 30 years

Cured meats: (bacon, sausage, luncheon meats, and cured hams) **induce inflammation**

FEV1 when eating cured meats

3 to 4 times/mo – 11.5 ml

5 to 13 times/mo – 42.0 ml

14 or more times/mo – 110 ml

Jiang R et al Am J Respir Crit Care Med 2007;175:798–804

COPD & ANTIOXIDANT INTAKE

Tabak C et al Am J Respir Crit Care Med 2001; 164:61–64

Study of 13,651 adults from three Dutch cities

16 % reported COPD

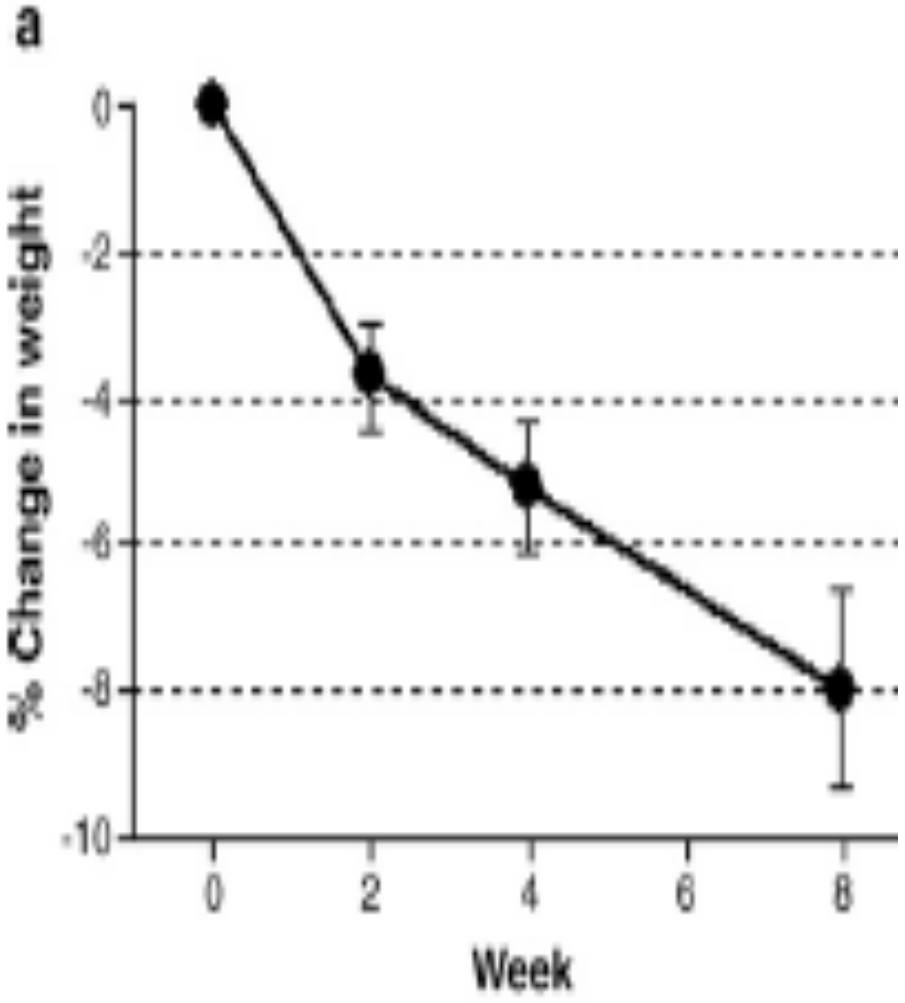
Intake of solid fruits & esp. catechin (tea & apple is assoociated with an increase in

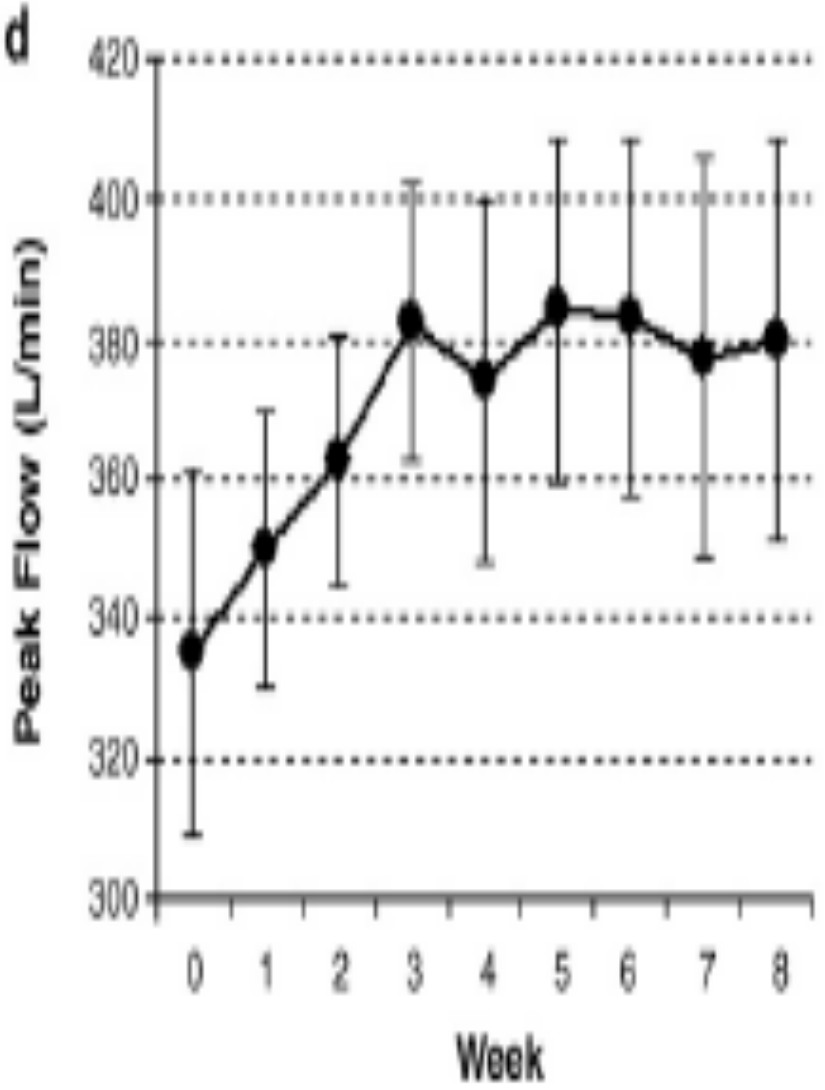
FEV1 of + 130 ml & reduction of four main COPD symptoms: chronic cough, phlegm, breathlessness $p < 0.001$

Flavonol and flavone (vegetables)intake was independently associated with chronic cough only.

DIETARY ENERGY RESTRICTION & ASTHMA

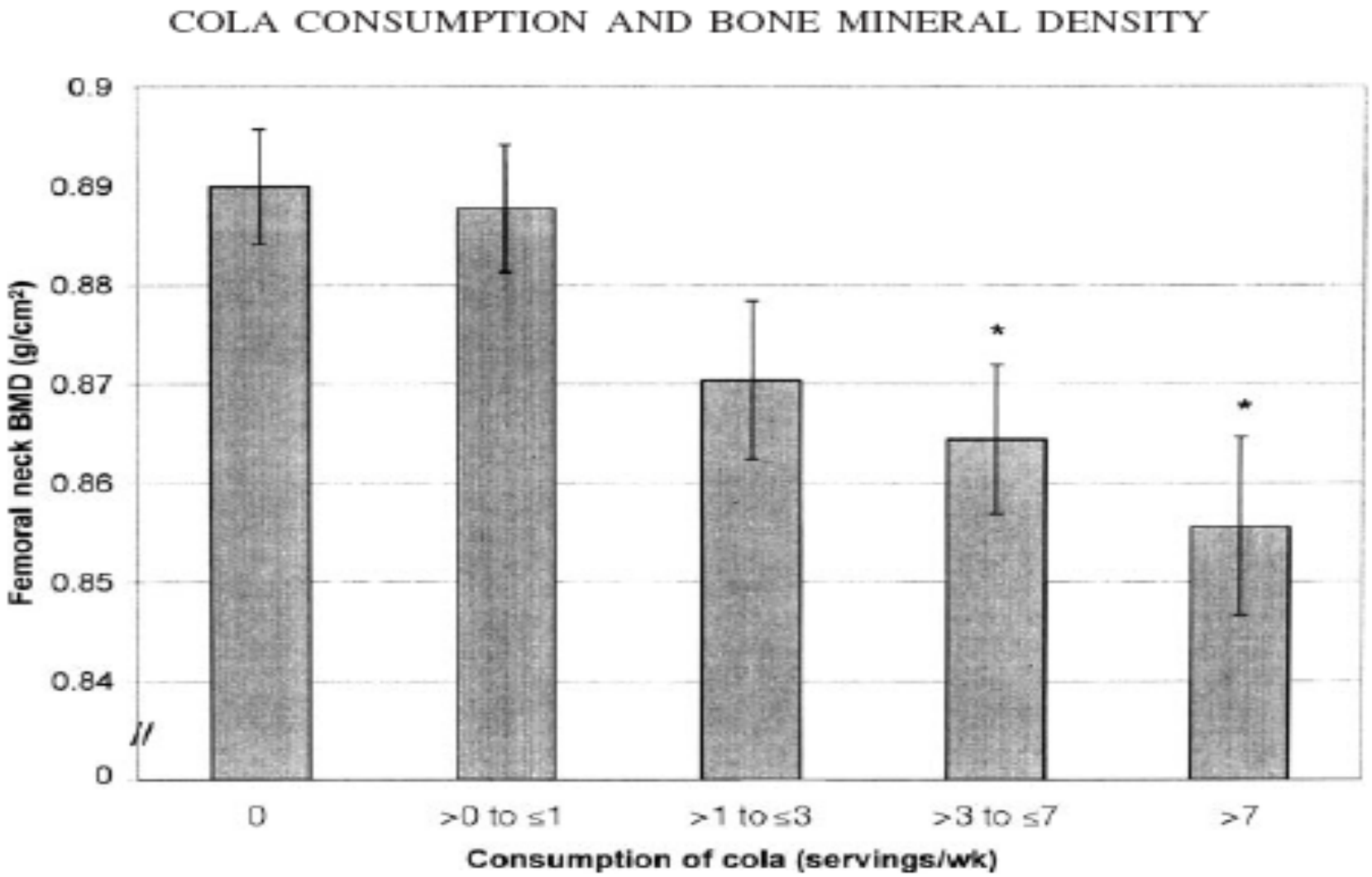
Johnson JB et al Free Radic Biol 2007;42:665-674





COLA C0NSUMPTION & BONE DENSITY

Tucker K et al Am J Clin Nutr 2006;84:936-942



DAIRY-INDUCED INFLAMMATION

- **Dietary proteins of cow´s milk induce inflammation:**
- release inflammatory mediators
- increase intestinal permeability
- induce leakage of albumin/ hyaluronan

Jalonen T J Allerg Clin Immunol 1991;88:737, Isolauri E Gastroenterology 1993;105:1643, Bengtsson U et al. J Clin Exp Allerg 1996;26:197, Allerg Clin Immunol 1997;100:216

ESTROGENS IN MILK

Malekinejad H et al J Agric Food Chem 2006;54: 9785-9791

A dramatic increase in testicular, breast, prostate, ovarian, and corpus uteri , and large bowel cancers.

60-80% of the intake of estrogens originate in the Western world from milk and other dairy foods.

The daily intake of total estrogens through milk is 372 ng, ***"which is dramatically more than currently recognized."***

The content is twice as high in 3.5 % fat milk
- 0 % in non-fat milk & extremely high in butter!

FREE ESTROGENS IN DAIRY pg/g

	E1	E2 - 17β	E3
Whole milk	3.7	**6.4**	9.0
Skimmed milk	20.2	**3.4**	8.2
Whey	3.6	**1.5**	3.0
Cottage cheese	34.9	**10.8**	6.1
Butter	539.4	**82.3**	86.8

- ***Wolford ST, Argoudelis CJ J Dairy Science 1979;62:1458-1463***

METABOLIC SYNDROME IN COWS

- Modern feeds of dairy cows, less forage-based and rich in starch & carbohydrates (corn, maize grains, barley, molasses and dextrose) are likely to induce, also in cows:

Insulin resistance

- **Insulin-resistance observed in calves fed an intensive milk- and lactose diet**
  Hostettler-Allen RL et al J Anim Sci 1994;72:160-173

AGEs IN VARIOUS MILK PRODUCTS

- *Baptista J, Carvalho R*
  Food Res Int
  2004;37:739-747

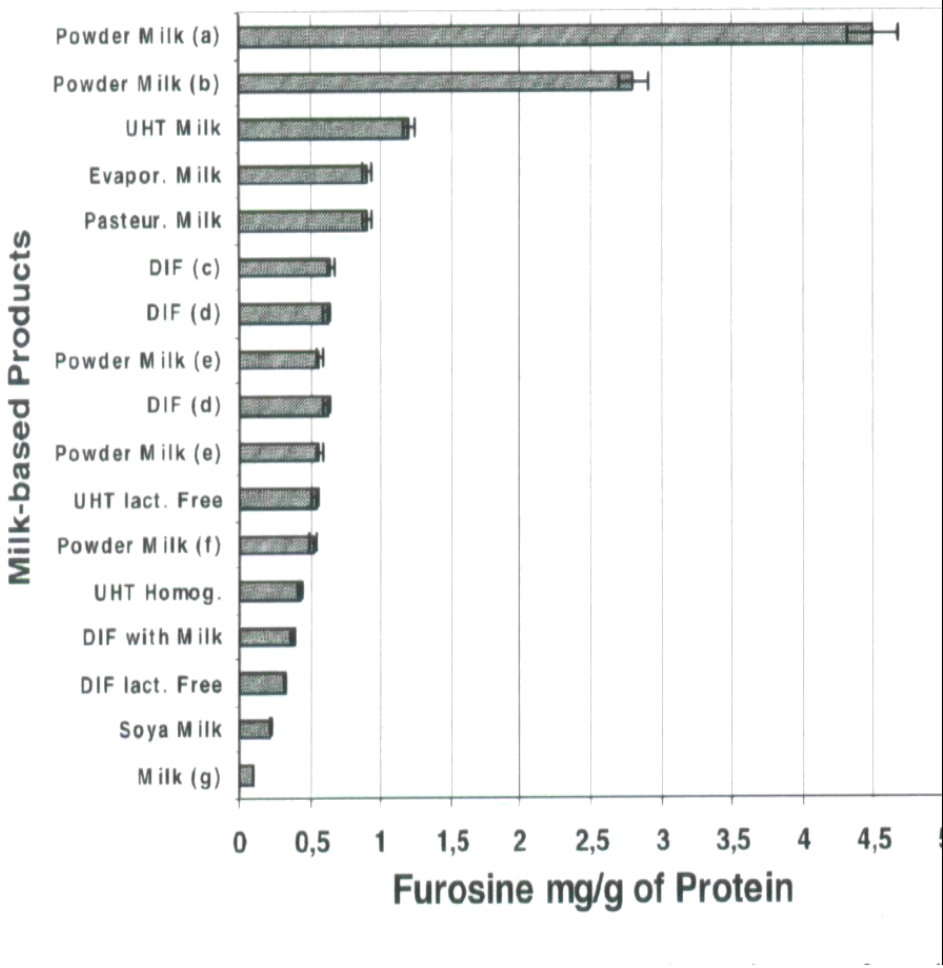


Fig. 4. Relative furosine content in milk-based products referred in Table 4. Quantitative data are based on printout obtained by using a Shimadzu integrator model CR 501, programmed for area normalization method. (a) Powder milk kept 2 years at RT, (b) Powder milk kept 1 year at RT, (c) DIF with whey plus casein, (d) DIF with hydrolyzed whey, (e) Powder milk kept 1 year at 4 °C, (f) Powder milk (fresh), (g) Raw (whole) bovine milk.

DIET AND BREAST CANCER

Carroll KK Cancer Res 1975;35:3374-3383

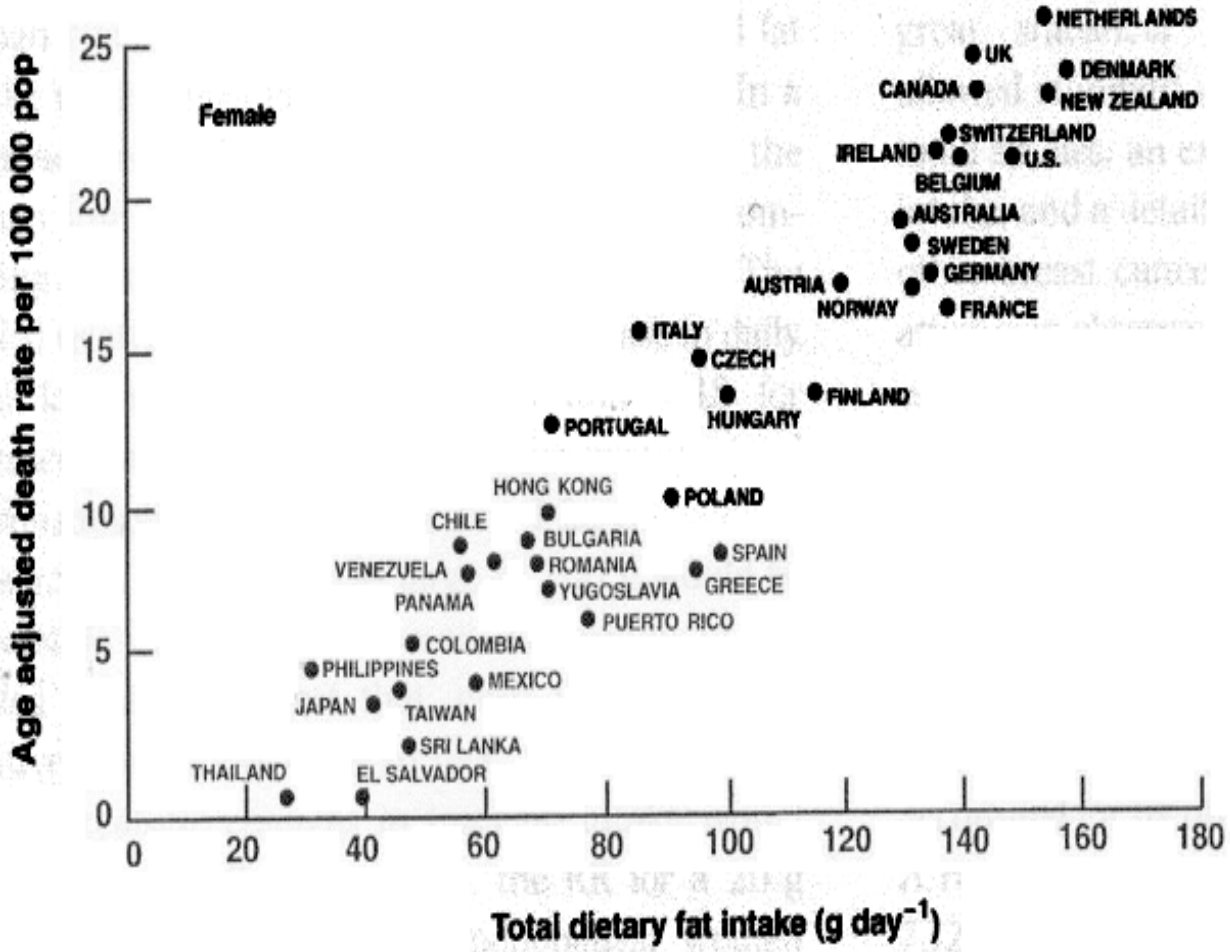


Fig. 1 Relation between national per capita fat intake and breast cancer mortality rate (from Carroll, 1975, reproduced with permission).

 Journal of Internal Medicine 249: 395–411

BOVINE MILK & TESTICULAR CANCER

Ganmaa D et al. Int J Cancer 2002;98:262-267

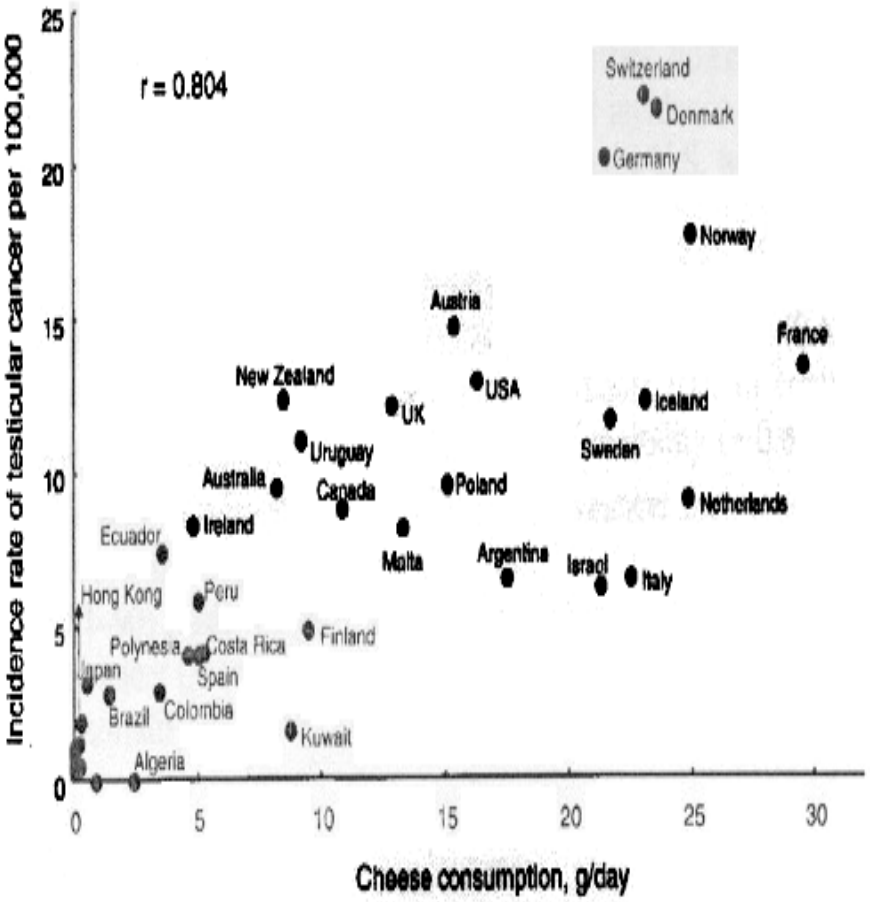


FIGURE 1 – Correlation between testicular cancer incidence rates at ages 20–39 years and *per capita* cheese consumption (1961–65) in 42 countries. Polynesia, French Polynesia.

TABLE I – CORRELATION COEFFICIENTS BETWEEN TESTICULAR CANCER INCIDENCE RATE AT AGES 20–39 (1988–92) AND FOOD CONSUMPTION[1]

	Correlation coefficient		
	1961–65	1961–70	1961–90
Animal fats	0.770[4]	0.764[4]	0.767[4]
Butter	0.558[4]	0.583[4]	0.626[4]
Cheese	0.804[4]	0.792[4]	0.769[4]
Eggs	0.616[4]	0.609[4]	0.604[4]
Meat	0.655[4]	0.660[4]	0.686[4]
Fish	0.093	0.066	0.045
Milk	0.741[4]	0.736[4]	0.745[4]
Cereals	−0.358[2]	−0.395[3]	−0.468[3]
Pulses	−0.442[3]	−0.441[3]	−0.486[3]
Fruits	0.333[2]	0.355[2]	0.334[2]
Vegetables	0.103	0.090	0.079
Vegetable oils	0.478[3]	0.503[4]	0.447[3]
Alcohol	0.495[4]	0.514[4]	0.602[4]
Coffee	0.578[4]	0.574[4]	0.606[4]
Tea	0.058	0.072	0.078

[1]Average values during 1961–65, 1961–70, and 1961–90.–[2]$p < 0.05$.–[3]$p < 0.01$.–[4]$p < 0.001$.

BOVINE MILK & PROSTATIC CANCER

Ganmaa D et al. Int J Cancer 2002;98:262-267

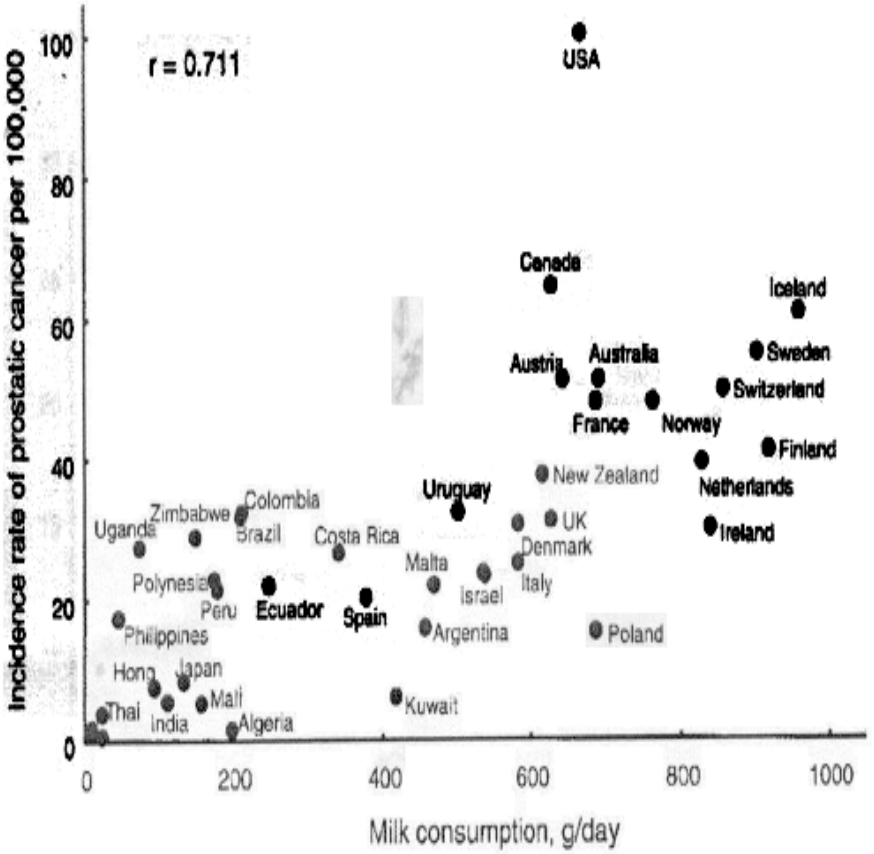


FIGURE 2 – Correlation between the age-adjusted incidence rates of prostatic cancer and *per capita* milk consumption (1961–90) in 42 countries. Hong, Hong Kong; Polynesia, French Polynesia; Thai, Thailand.

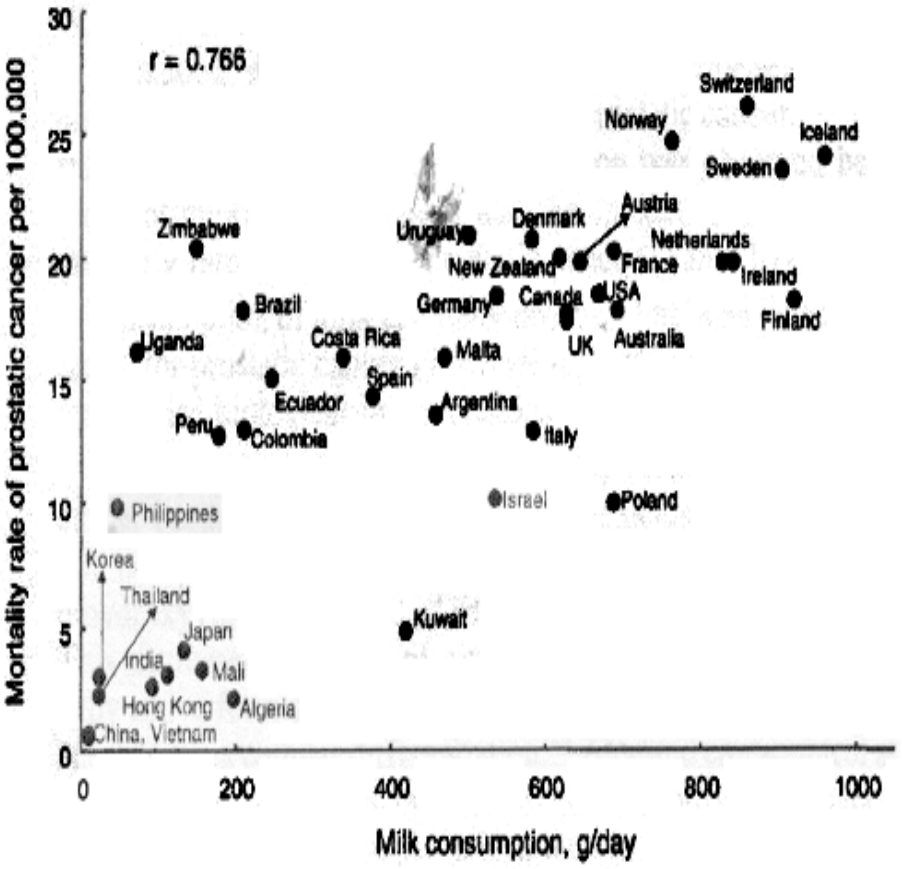


FIGURE 3 – Correlation between the age-adjusted mortality rates of prostatic cancer and *per capita* milk consumption (1961–90) in 41 countries.

BOVINE MILK & TYPE 1 DIABETES

Dahl-Jörgensen K et al Diabetes Care 1991;14:1081-1083

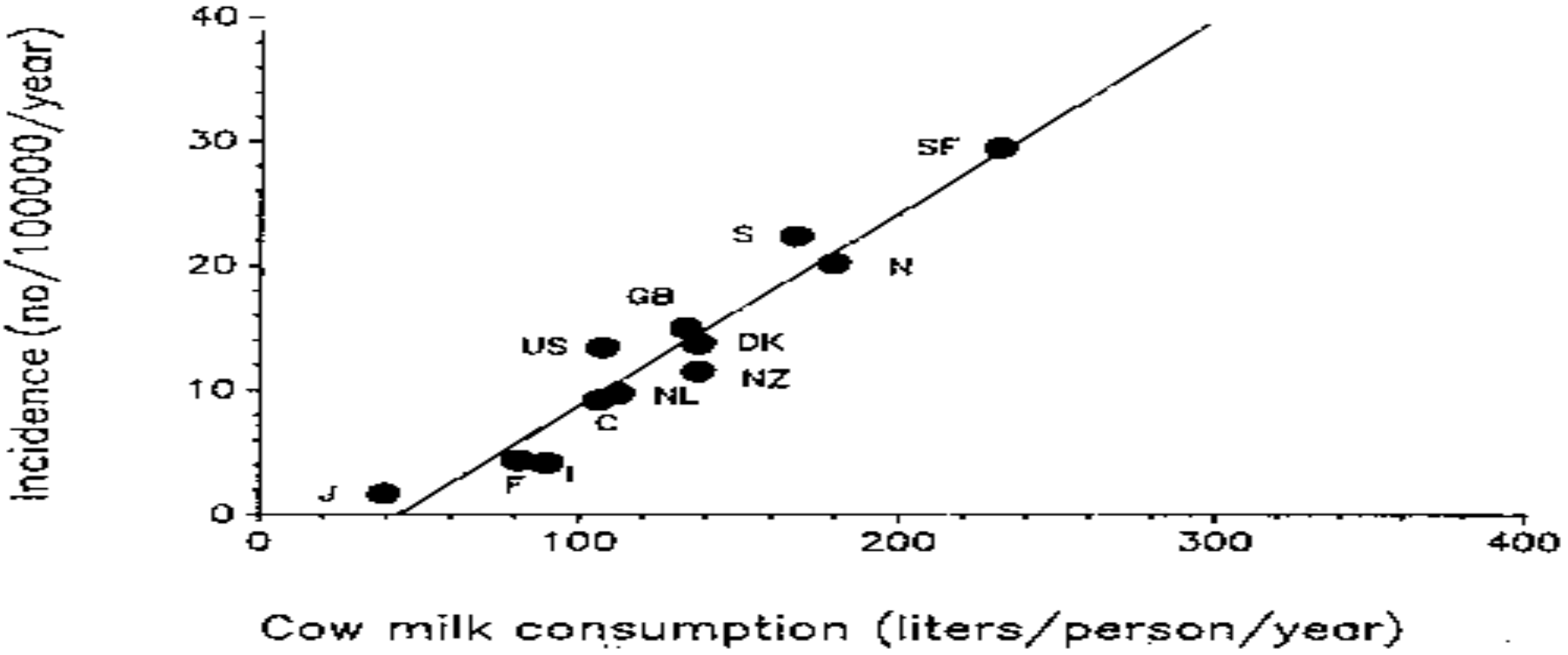
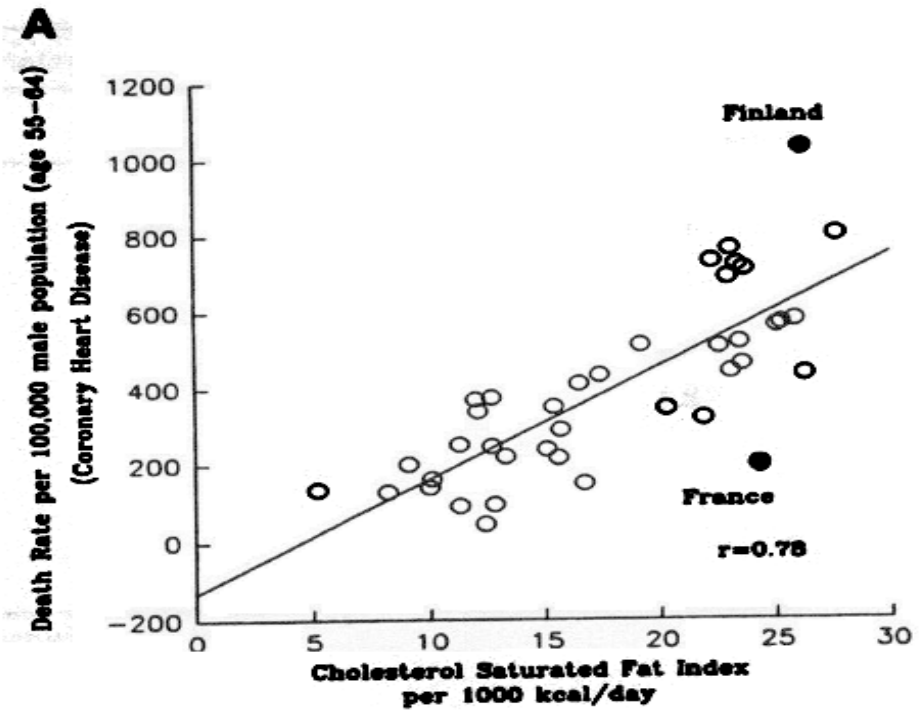
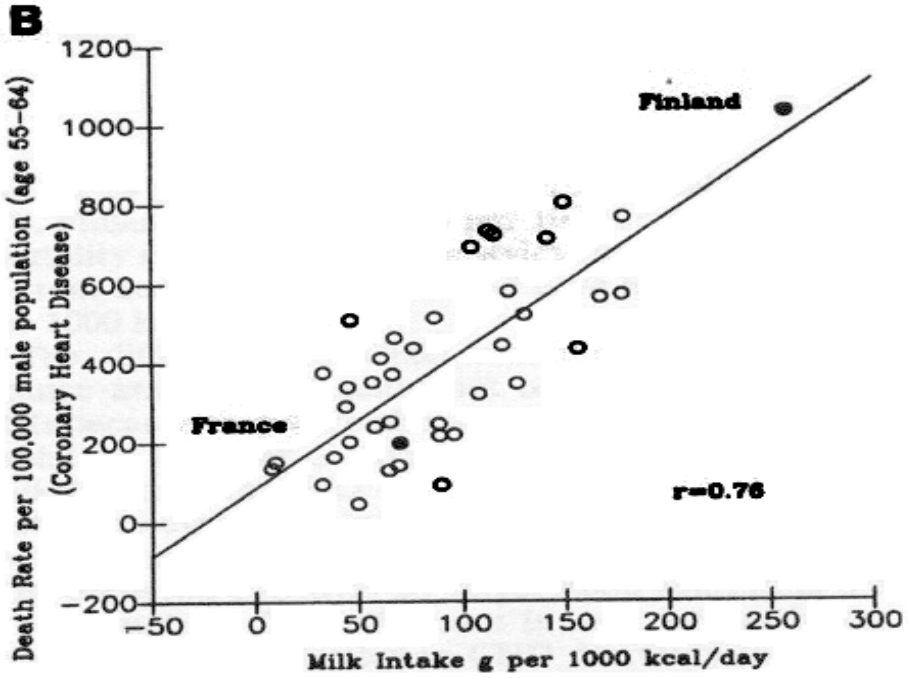


FIG. 1. Mean yearly incidence of insulin-dependent diabetes mellitus in children 0–14 yr of age by average fluid cows' milk consumption per person per yr in different countries. J, Japan; F, France; I, Israel; C, Canada; US, United States; NL, Netherlands; NZ, New Zealand; GB, Great Britain; DK, Denmark; N, Norway, S, Sweden; and SF, Finland. Incidence, −6.77 + 0.16 × consumption, $R^2 = 0.94$.

BOVINE MILK & CORONARY HEART DISEASE

Artaud-Wild SM et al.
Circulation
1993;88:2771-2779





AGE IN VEGETARIAN DIET

Fluorescent AGE:

Omnivorous (n=19): 9.9±0.5

Vegans (n=9): 10.8±0.7

Ovolacto-vegetarians (n=19): 13.1±0.8*

Chemical AGE (CML)

Omnivorous (n=19): 427.1±15.0

Vegans (n=9): 514.8±24.6*

Ovolacto-vegetarians (n=19): 525.7±29.5**

Sebekova K et al Eur J Nutr 2001;40:275–281

DRUGS & RESISTANCE TO DISEASE

- **Chemicals** incl. pharmaceutical drugs suppress innate immune functions.
- **Antibiotics suppress:**
  - **Lymphocyte proliferation**
  - **Macrophage functions** such as: chemiluminescence response, chemotactic motility, bactericidal & cytostatic ability

Roszkowski K et al. Zeitschr Bakteriol Hyg 1988;270:270-279

Pulverer G et al. Zentralbl Bakteriol 1990;272:467-476

STRESS-INDUCED INFECTIONS

- **Potentially pathogenic microorganisms (PPMs) change under stress their phenotype and become life-threatening pathogens**

  Alverdy JC et al. Crit Care Med. 2003;31:598-607

- **Luminal release of noradrenaline is a strong inducer of virulence of luminal bacteria**

  Kinney KS Life Science 2000;67:3075-3085

DRUGS & BACTERIAL GROWTH

- **Noradrenaline** increases the growth of *E coli* and production of *Shiga*-like toxins

- **β-endorphins** increase the growth of gram-positives such as *Staph aureus*

- **6-hydroxy-dopamine** increases the total number of bacteria in cecum with 3-4 logs

Lyte M, Bailey MT J Surg Res 1997;70:195-201

ADRENALIN & CLOSTRIDIAL GROWTH

Cooper EV Lancet 1946;24:459-461

TABLE I—EFFECT OF INJECTING 1/8000 ADRENALINE WITH WASHED *Cl. welchii*

Dose of bacilli	Guineapigs dying of gas-gangrene	
	Test series (bacilli + adrenaline)	Control series (bacilli + broth-saline)
40,000,000 ..	3/3	2/3*
4,000,000 ..	3/3	0/3
400,000 ..	3/3	0/3
40,000 ..	3/3	0/3
4000 ..	2/3	0/3
0 ..	0/3	..

* 2/3 = of three guineapigs injected, two died.

PN & INFECTION

A significant increase in mortality (63% vs 26%)

in patients with burns, fed with

parenteral nutrition

Herndon DN et al . J Burn Care Rehabil 1989;10:309–313

EN & INFECTION

Significant increase in bacterial translocation in mice fed Vivonex (53%), Criticare (67%), or Ensure (60%) vs chow-fed (0%) ($p < .05$)

All three diets induced loss of jejunal and ileal mucosal protein content, Intestinal microbial overgrowth & translocation

Haskel Y et al Crit Care Med 1994;22:108-113

ANTI-INFLAMMATORY NUTRITION

A SHIELD AGAINST ACUTE AND CHRONIC DISEASE

Bengmark S JPEN J Parenter Enteral Nutr. 2006;30:45-51

0148-6071/06/3001-0045$03.00/0
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Review

Curcumin, An Atoxic Antioxidant and Natural NFκB, Cyclooxygenase-2, Lipooxygenase, and Inducible Nitric Oxide Synthase Inhibitor: A Shield Against Acute and Chronic Diseases

Stig Bengmark, MD, PhD, FRACS (hon), FRCPS (hon)

From the Institute of Hepatology, University College, London Medical School, London, United Kingdom

ABSTRACT. *Background:* The world suffers a tsunami of chronic diseases, and a typhoon of acute illnesses, many of which are associated with the inappropriate or exaggerated activation of genes involved in inflammation. Finding therapeutic agents which can modulate the inflammatory reaction is the highest priority in medical research today. Drugs developed by the pharmaceutical industry have thus far been associated with toxicity and side effects, which is why natural substances are of increasing interest. *Methods:* A literature search (PubMed) showed almost 1500 papers dealing with curcumin, most from recent years. All available abstracts were read. Approximately 300 full papers were reviewed. *Results:* Curcumin, a component of turmeric, has been shown to be non-toxic, to have antioxidant activity, and to inhibit such mediators of inflammation as NFκB, cyclooxygenase-2 (COX-2), lipooxygenase (LOX), and inducible nitric oxide synthase (iNOS). Significant preventive and/or curative effects have been observed in experimental animal models of a number of diseases, including arteriosclerosis, cancer, diabetes, respiratory, hepatic, pancreatic, intestinal and gastric diseases, neurodegenerative and eye diseases. *Conclusions:* Turmeric, an approved food additive, or its component curcumin, has shown surprisingly beneficial effects in experimental studies of acute and chronic diseases characterized by an exaggerated inflammatory reaction. There is ample evidence to support its clinical use, both as a prevention and a treatment. Several natural substances have greater antioxidant effects than conventional vitamins, including various polyphenols, flavonoids and curcumenoids. Natural substances are worth further exploration both experimentally and clinically. (*Journal of Parenteral and Enteral Nutrition* 30:45–51, 2006)

ENTERAL NUTRITION & INFLAMMATION

Compared standard (**Nutrison**) & a immunomodulatory (**Stresson**) nutrition in malnourished patients after pancreaticoduodenectomy.

Standard nutrition lead to significant elevations of PRO-INFLAMMATORY cytokines:

TNF-alpha: day 3 (P=0.006), **day 7** (P<0.001) &

IL-1beta: day 7 (P<0.001) **day 14** (P=0.022)

Immunomodulatory nutrition lead to significant elevations in ANTI-INFLAMMATORY cytokines:

IL-8: day 1 (P=0.011) **days 3, 7, 10, & 14** (P<0.001), **IL-10: days 3 &10** (P<0.001)

IL-1ra/s : day 7 (P<0.001), **IL-6: day 10** (P=0.017)

Slotwinski R et al. JOP. J Pancreas 2007; 8:759-769

IMMUNONUTRITION IN SURGERY

1 lit/d Impact to elective major abd. surgery patients:

1. 5 days preop + 7 days postop

2. only postop 7 days

The length of IMU/ICU stay , hosp stay & infect rate:

PRE+POSTOP	**1.9 ±1.3 days**	**19.7 ±2.3 days**	**2/14 (14%)**
ONLY POSTOP	**5.9 ±0.8 days**	**29.1 ±3.6 days**	**10/15 (67%)**

TNF-alpha (postop days 1 and 3) & CRP (postop day 7) were significantly lower in the preop+postop treated ($p < .01$)

Giger U et al Ann Surg Oncol 2007;14:2798-2806

TURMERIC - Curcumin

Turmeric suppresses genes that ratchet up inflammation.

ONE EXAMPLE:

- **Name of gene:** Cox-2
- **Function of gene:** Makes inflammatory compounds
- **Long-term effect:** Could help ward off colon cancer and Alzheimer's

CURCUMIN-REDUCED SEPSIS

Curcumin pretreatment for 3 d before induction of sepsis by cecal ligation and puncture

-**Prevents cellular alterations in macrophages**

- **Decreases expression of TNF-α,**

- Down-regulates PPAR-γ in organs (liver) &

- Reduces tissue injury and mortality

Siddiqui AM et al Crit Care Med 2006 34:1874-1882

Curcumin attenuates endotoxin-induced coagulopathy & prevents disseminated intravascular coagulation (DIC)

Chen HW et al J Endotoxin Res 2007;13:15-23

CURCUMIN AGAINST AGING

Lipid peroxidation and lipofuscin increase & SOD, GPx and Na+, K+, -ATPase decrease with ageing.

Bala K et al Biogerontol 2006;7:81-89

Table 1. Percent change of different parameters studied in different regions of the brain, taking control as 100% in 6 and 24-month-old curcumin-treated rats.

Parameters	Brain regions (curcumin-treated animals)							
	Cortex		Hippocampus		Cerebellum		Medulla	
	6 m	24 m	6 m	24 m	6 m	24 m	6 m	24 m
Lipid peroxide ↓	42.5	32.4	20.0	28.8	45.0	17.4	50.0	23.3
Lipofuscin ↓	35.7	24.0	35.3	18.0	39.0	60.0	11.1	40.4
SOD ↑	37.0	45.0	37.5	40.0	36.7	15.0	37.0	34.0
GPx ↑	24.3	15.3	15.4	50.0	96.2	75.5	56.6	266.0
Na^+, K^+, -ATPase ↑	16.6	40.0	24.4	20.5	10.2	16.5	22.5	11.1

TURMERIC/CHILI COCKTAIL

½ GLAS OF FRUIT JUICE SUCH AS APPLE, PINEAPPLE

1 HEAPFUL TABLESPOON TURMERIC

¼ TEASPOON CHILI (CAYENNE) PEPPER

1 TABLESPOON APPLE CIDER VINEGER

1 TABLESPOON FRESH LEMON JUICE

MIX, DRINK ONCE OR TWICE A DAY

RESTORING TH1 IMMUNITY – SULFORAPHANE

Kim H-J et al J Allerg Clin Immunol 2008 March 6 E-pub

Redox equilibrium of dendritic cells (DCs) is a key factor in maintaining protective cellular immunity.

The Nrf2 pathway is the most sensitive oxidative stress response, regulating the transcriptional activation of > 200 antioxidant and protective genes

In the so-called phase II response.

The Nrf2 agonist Sulforaphane & the thiol precursor N-acetyl cysteine (NAC)

- **boosts the GSH levels**
- **restores redox equilibrium &**
- **upregulates TH1 immunity in aging**

Cellular immunity is also correctable by the Nrf2 agonist, a-lipoic acid.

DIABETES & SOY INTAKE

Azadbakht L et al Diabetes Care 31:648-654, 2008

20 pat consumed **35% animal proteins**, **35% textured soy protein**, and 30% vegetable proteins &

21 pat a diet containing **70% animal proteins** and **30% vegetable proteins** for **4 years**. Mean change soy group vs control:

fasting plasma glucose –18 ± 3 vs. 11 ± 2 mg/dl *P* = 0.03

total cholesterol –23 ± 5 vs. 10 ± 3 mg/dl *P* = 0.01

LDL cholesterol –20 ± 5 vs. 6 ± 2 mg/dl *P* = 0.01

serum triglyceride –24 ± 6 vs. –5 ± 2 mg/dl *P* = 0.01

Serum CRP levels 1.31 ± 0.6 vs. 0.33 ± 0.1 mg/l *P* = 0.02

Proteinuria –0.15 ± 0.03 vs. 0.02 ± 0.01 g/day *P* = 0.001

urinary creatinine (–1.5 ± 0.9 vs. 0.6 ± 0.3 mg/dl *P* = 0.01

MULTIFIBRE IN ACUTE PANCREATITIS

30 severe acute pancreatitis patients received EN with or without 24 g/d multifibre:

Median duration with multifibre:

of EN was 8 ±4 (6-12) vs 10 ± 4 (6-13) days

to APACHE II normalization (< 8)
was 4 ± 2 vs 6.5 ± 3 days (P < 0.05)

To CRP normalization
was 7 ± 2 vs 10 ± 3 days (P < 0.05)

Karakan T et al World J Gastroenterol 2007; 13:2733-2737

THE ROLE OF THE GUT

BIOECOLOGICAL CONTROL

Bengmark S Anesthesiol Clin N Amer 2006;24: 299-323

ELSEVIER
SAUNDERS

Anesthesiology Clin N Am
24 (2006) xxx–xxx

ANESTHESIOLOGY
CLINICS OF
NORTH AMERICA

Bioecologic Control of Inflammation and Infection in Critical Illness

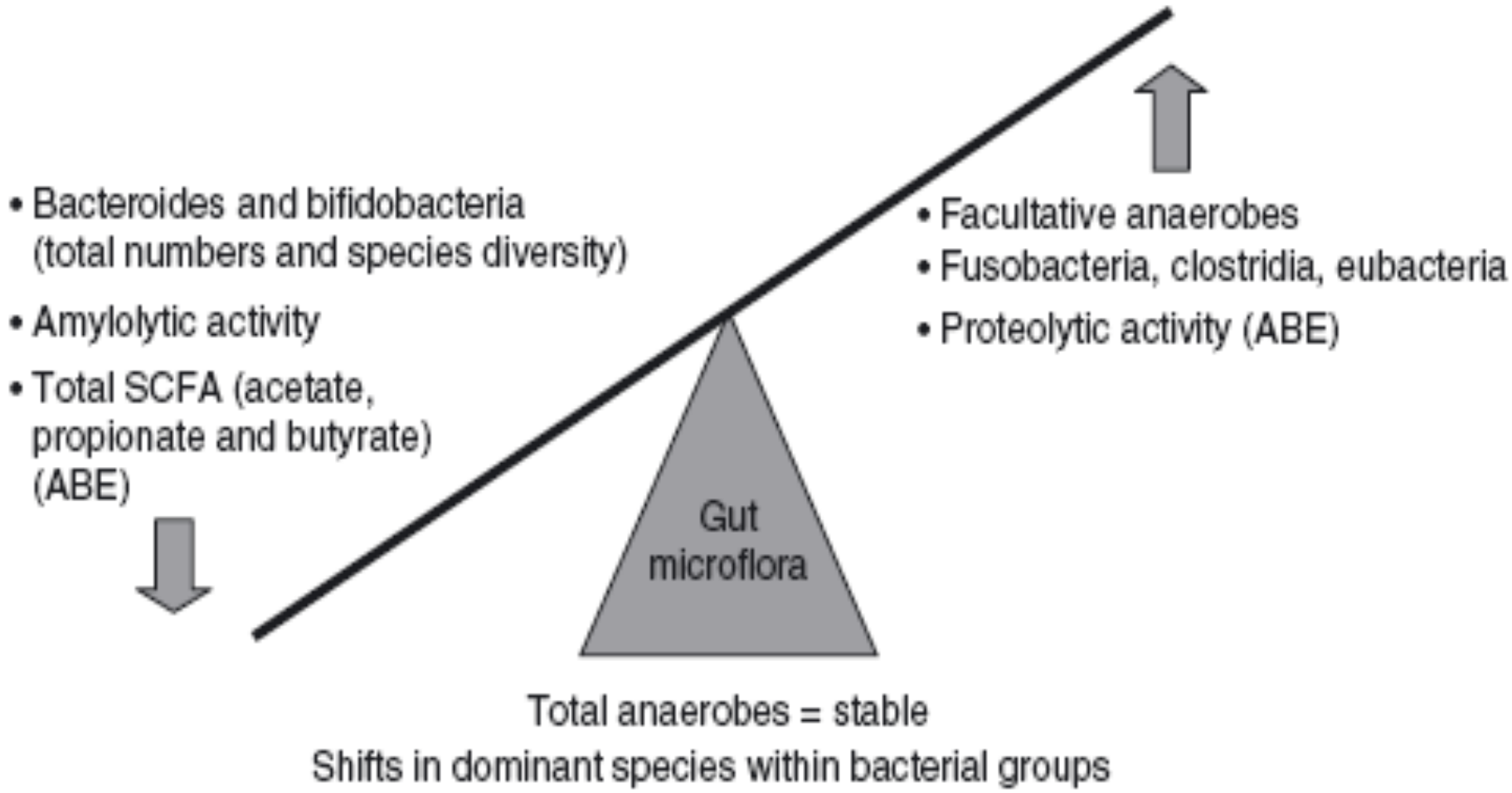
Stig Bengmark, MD, PhD*

Institute of Hepatology, University College London Medical School, 69-75 Chenies Mews, London WC1E 6HX, UK

Advanced surgical and medical treatments and medical and surgical emergencies are, despite some breathtaking advances in medical-pharmaceutical and surgical treatment, still affected by an unacceptably high rate of morbidity and mortality. Worse, the rate of both morbidity and mortality in critical illness (CI) is quickly increasing and has done so for several decades. With a documented rate

GUT FLORA IN AGING

Woodmansey EJ Appl Microbiol 2007;102:1178-1186



AGING & BARRIER FUNCTION

Changes of microbiota composition

Deficient epithelial integrity

Deficient protective commensals

Reduced barrier components: sIgA, mucins, defensins, gastric acid etc and often

Chronic activation of the immune systems by persistent viral infections, in particular cytomegalovirus (CMV)

CMV infections, esp. in the elderly, associated to changes of T cell immunity **=> low ratio naive/memory T cells.**

Vasto S et al. Immun Ageing 2006;3:2.

AGING AND FLORA

Blood samples and colonic biopsies from elderly subjects (90-99 years) show significantly down-regulated transcript levels of receptors such as:

- Toll-like receptors (TLRs)

- Nucleotide-binding &

- Oligomerization domain-like receptors (NLRs)

Which "may contribute to the lack of effective recognition of invading pathogens or the commensal flora."

Rosenstiel P et al Genes Immun. 2008 E-pub Jan 24

LAB CONSUMPTION BY ELDERLY

improves specific immune functions:

Increasing natural killer cell activity

Takeda K, Okumura K. J Nutr 2007; 137:791S–793S

Increasing phagocytic activity of PBMCs

Gill HS et al. Am J Clin Nutr 2001; 74:833–839.

Decreasing macrophages-induced TNFα

Matsumoto M, Benno Y. Biosci Biotechnol Biochem 2006; 70:1287–1292

Reducing the incidence of winter infections

Turchet P, et al. J Nutr Health Aging 2003;7:75–77

PROBIOTICS IN ATHLETES

Probiotics, reported to:

- **correct interferon-γ deficiencies in athletes**

Clancy RC et al Brit J Sports Med 2006;40:351-3 54

- **shortened the duration of GI episodes in marathon runners**
- **no effect on respiratory infections or GI symptoms**

Kekkonen RA et al Int J Sport Nutr Exer Metab 2007;17:352-363

***L. fermentum VRI-003* in a dose of 1.2 x 10.10 CFU elicited**

- **a two-fold (p=0.07) increase in whole-blood IFN-γ**
- **reduced severity of illness p=0.06**
- **reduced to < half the days with respiratory symptoms (30 d vs 72 d, p=0.00006)**

Cox AJ et al Br J Sport Med 2008 E-pub

REDUCED INFECTION RATE

After pancreatdoudenectomy

Probiotic treatment (=lactic acid bacteria)

from 53 % => 23 % (P = 0.02)

Nomura T et al Hepatogastroenterol 2007;54:661-663

Synbiotic treatment (=lactic acid bacteria + fibres)

from *40 %* => 12.5 % (P = 0.05)

Rayes N et al Ann Surg 2007;246:36-41

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PROBIOTIC 2000 IN CHRONIC LIVER DISEASE

One month supply of Synbiotic 2000 reduces:

Mucosal pH

PPM flora: *E. coli* ($p<0.001$) *Staphylococcus* ($p<0.01$) and *Fusobacterium* ($p<0.05$),

Endotoxin, ammonia/s, ALT/s, bilirubin/s

Increases:
albumin/s and prothrombin

Improves: **Child classification** &
degree **of encephalopathy**/psychometric test in half of the patients

Qing-Liu et al. Hepatology 2004; 39:1441-1449

SYNBIOTIC 2000

Medipharm AB, Kågeröd, Sweden & Des Moines, USA

- **10^{10} of *Pediococcus pentosaceus 5-33:3***
- **10^{10} of *Leuconostoc mesenteroides 32-77:1***
- **10^{10} of *Lactobacillus paracasei sbsp. paracasei***
- **10^{10} of *Lactobacillus plantarum 2362***

- **2.5 g of betaglucan**
- **2.5 g of inulin**
- **2.5 g of pectin**
- **2.5 g of resistant starch**

LAB IN SYNBIOTIC 2000

- **Induce several bioactive proteins – five cross-react with stress proteins - all**
- **Transcribe NF-κB – to the largest extent *L plantarum* and *L paracasei*.**
- **Produce pro-inflammatory cytokines (IL-1β, IL-8) and anti-inflammatory (IL-10), to a large extent by *L plantarum*, and less by *Leuconostoc mesenteroides*.**

Ljungh Å, Microb Ecol Health Dis 2002;3, Suppl 4:4 Kruszewska D et al Microecol. Ther. 2002;29:37

LAB IN SYNBIOTIC 2000 cont

- **Produce Antioxidants,** espec.
  Lb plantarum **&**
  Pediococcus pentosaceus
  Ljungh Å, Microb Ecol Health Dis 2002;3, Suppl 4:4
  Kruszewska D et al Microecol. Ther. 2002;29:37
- **Induce Heat Shock proteins** espec.
  Leuconostoc mesenteroides and
  Lb paracasei subsp paracasei
  Eleine Petrof, personal communication
- **Induce Beta-defensins** espec.
  Pediococcus pentosaceus and
  Lb paracasei subsp paracasei
  Wehkamp J et al Infect Immun. 2004;72:5750-5758

PROBIOTICS IN CLP-INDUCED LUNG INJURY

Lung injury induced by ceacal ligation and puncture (CLP), two studies:

1. Pretreatment with Synbiotic 2000 during 3 days before CLP

Tok D et al J Trauma 2007;62:880-885

2. Subcutaneous injection of live Lactic acid bacteria in Synbiotic 2000

Ilkgul O et al. Br J Int Care 2005;15:52-57

MYEOLOPEROXIDASE – MPO

Tok D et al J Trauma 2007;62:880-885

U/g

- Synbiotic 2000 25.62±2.19
- Only LAB 26.75±2.61
- Only the fibres 56.59±1.73
- Placebo 145.53±7.53

$p < 0.05$

MALONALDEHYDE – MDA

Tok D et al J Trauma 2007;62:880-885

nmol/mg

- Synbiotic 2000 0.22±1,31
- Only LAB 0.28±3,55
- Only the fibres 0.48±5,32
- Placebo 0.67±2,94

$p < 0.05$

NITRIC OXIDE

Tok D et al J Trauma 2007;62:880-885

micromol/g

- Synbiotic 2000 17.16±2,03
- Only LAB 8.91±2,24
- Only the fibres 47.71±3,20
- Placebo 66.22±5,92

$p < 0.05$

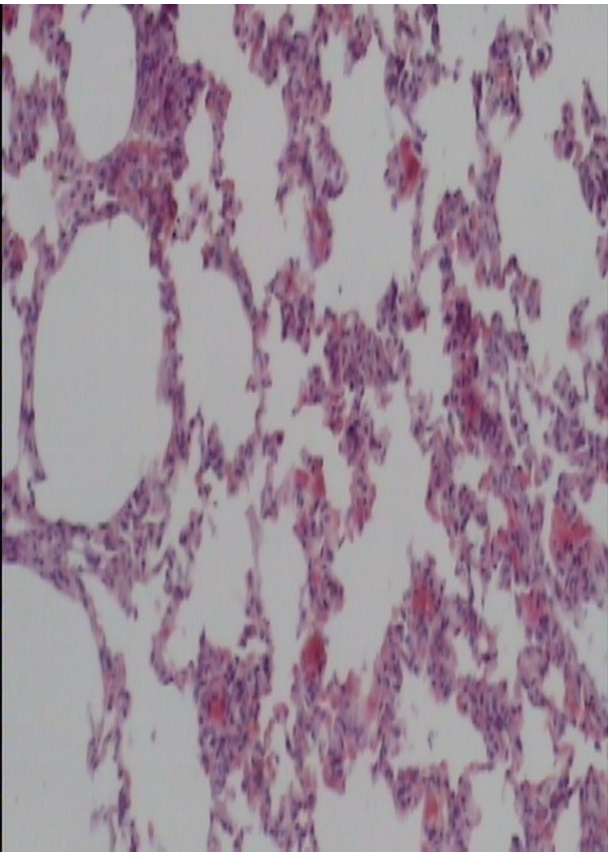
NEUTROPHILS IN LUNG TISSUE

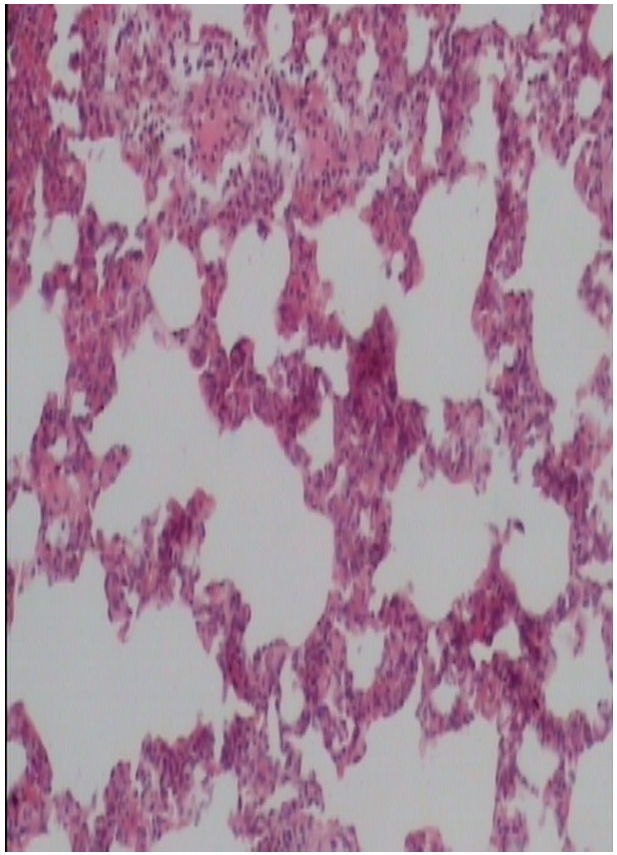
Tok D et al J Trauma 2007;62:880-885

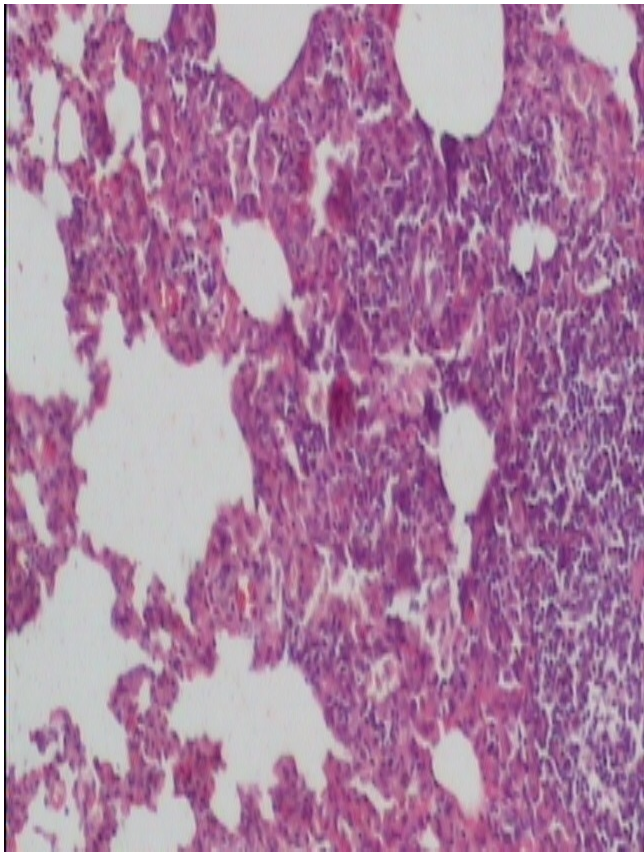
- Synbiotic 2000 9.00±0.44
- Only LAB 8.40±0.42
- Only the fibres 31.20±0.98
- Placebo 51.10±0.70
- $p < 0.05$

SYNBIOTIC 2000 IN LUNG INJURY

Ilkgul O et al Br J Int Care. 2005;15:52-57







- **Placebo** **Only fibres** **Synbiotic 2000**

SYNBIOTIC 2000 IN CHRONIC LIVER DISEASE

One month supply of Synbiotic 2000 reduces:

Mucosal pH

PPM flora: *E. coli* ($p<0.001$) *Staphylococcus* ($p<0.01$) and *Fusobacterium* ($p<0.05$),

Endotoxin, ammonia/s, ALT/s, bilirubin/s

Increases:
albumin/s and prothrombin

Improves: **Child classification** &
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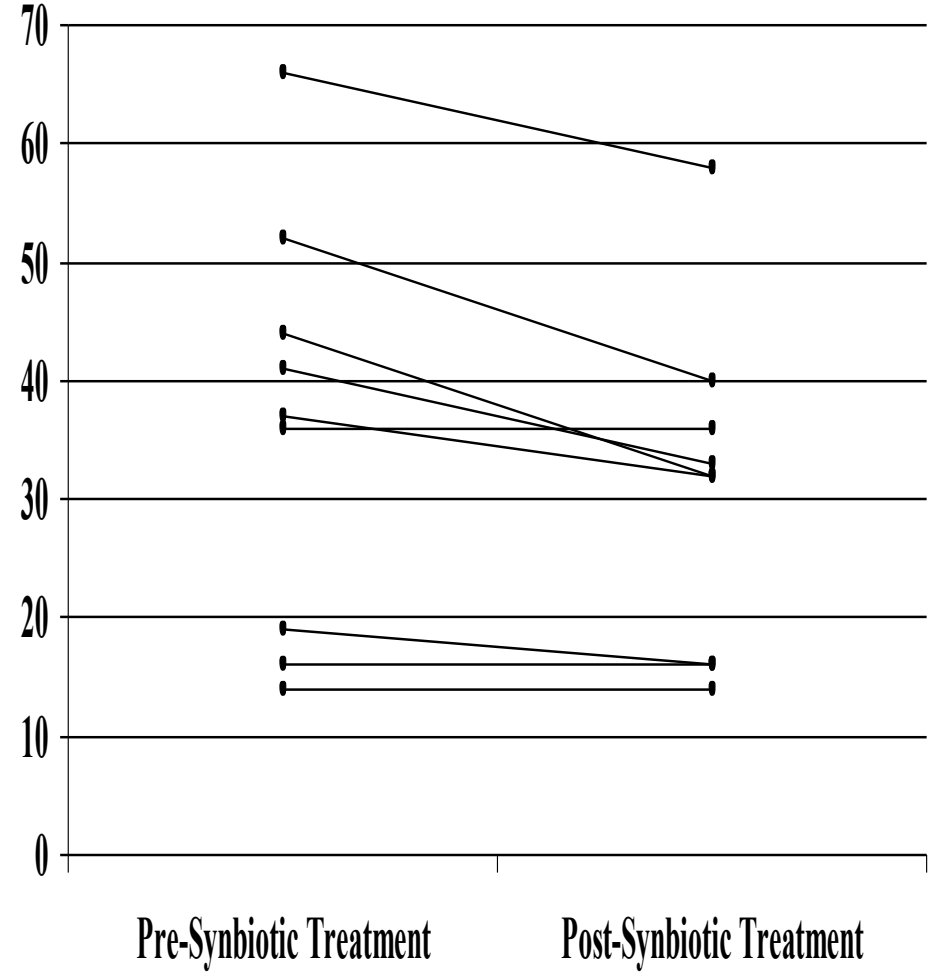
Qing-Liu et al. Hepatology 2004; 39:1441-1449

LIVER FUNCTION CHANGES

Riordan SM et al Microb Ecol Health Dis 2007;19:7-16

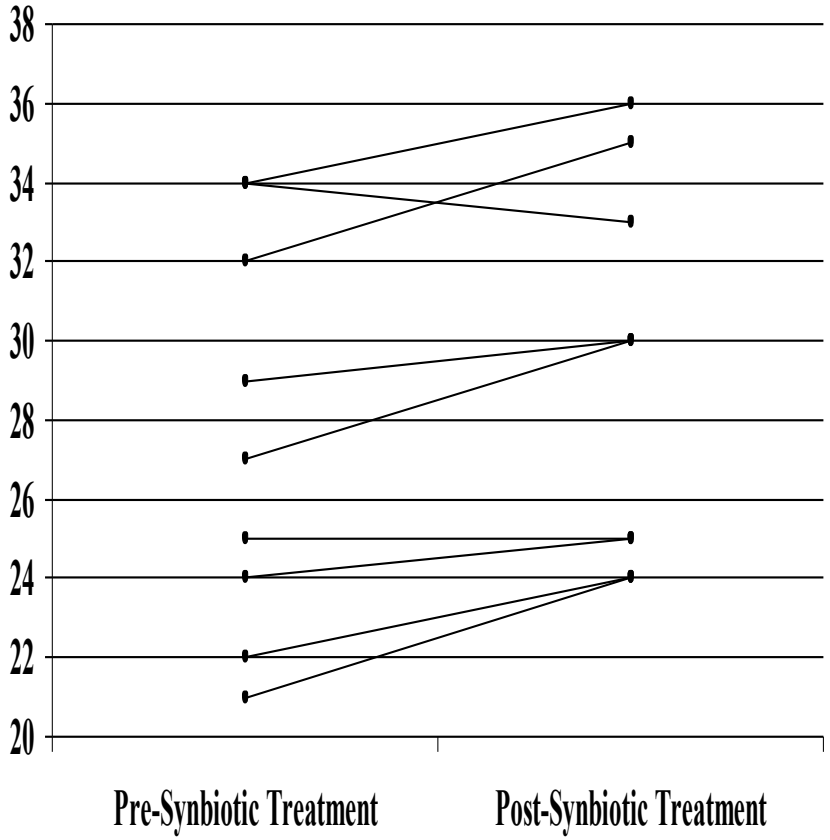
Serum Bilirubin (umol/L)

P=0.002



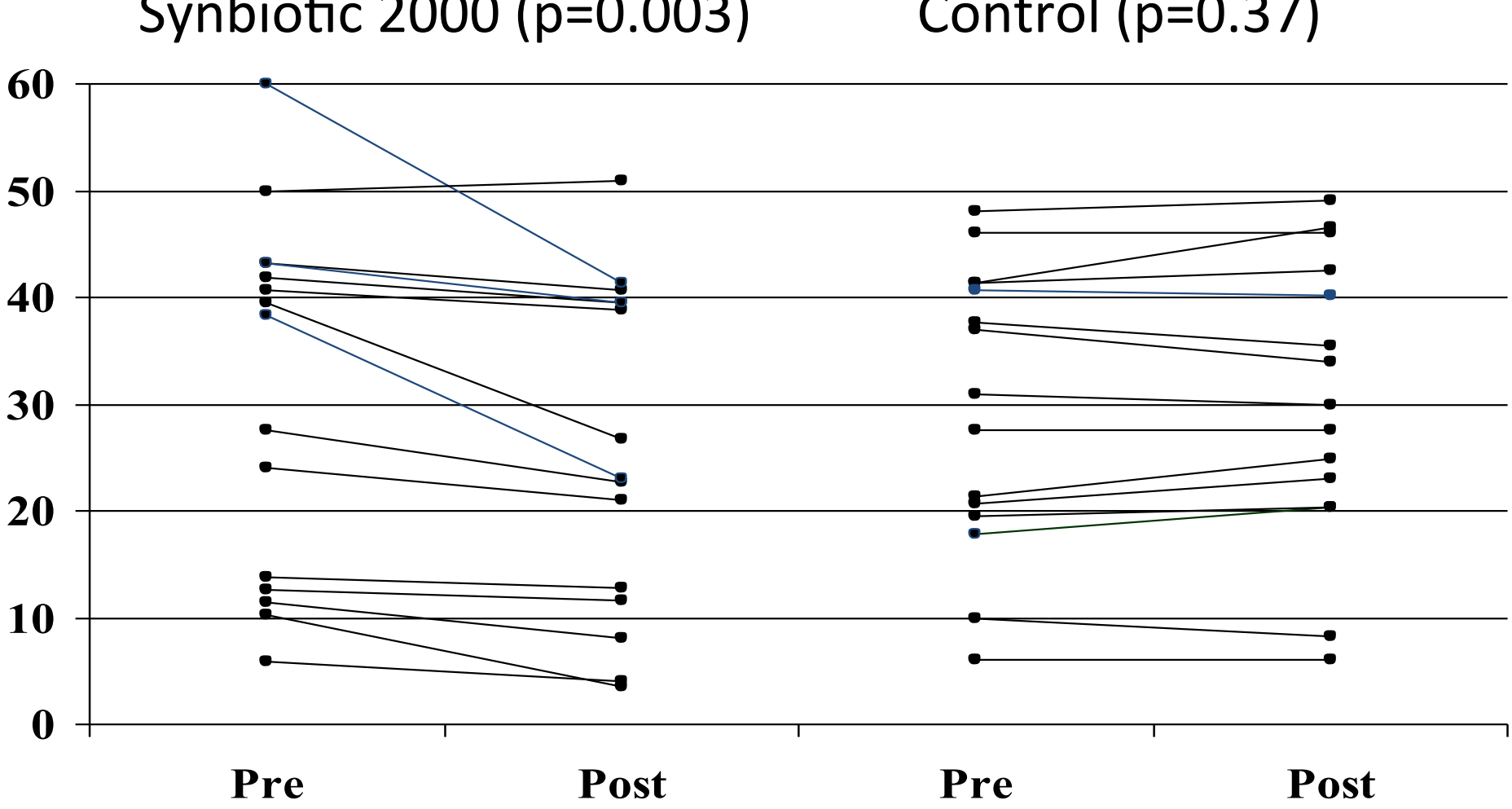
Serum Albumin (g/L)

P=0.003



Indocyanine Green Retention at 15 mins

Riordan SM et al Microb Ecol Health Dis 2007;19:7-16



PROBIOTIC 2000 IN LIVER TRANSPLANTATION

50 to 85 % of transplant patients develop nosocomial infections within 30 days.

Synbiotic 2000 or Only fibres daily
from the day before surgery +
during 14 postop. days

30 day-infection rate:

Synbiotic 2000 1/33 - 3 %

Only fibres 17/33 - 51 %

Rayes N et al. Am J Transplant 2005;5:125-131

PROBIOTIC 2000 IN LIVER TRANSPLANTATION

Isolated bacteria:	Synbiotic	Fibres only
Enterococcus faecalis	1	11
Escherichia coli	0	3
Enterobacter cloacae	0	2
Pseudomonas aeruginosa	0	2
Staphylococcus aureus	0	1
	(total 1)	(total 18)

Rayes N et al. Am J Transplant 2005;5:125-131

SYN. 2000 IN ABD. CANCER

- **The incidences of postoperative bacterial infections were**
  Parenteral Nutrition 47 %,
  EN + fibres 20 %
  EN + Synbiotic 2000 7 %
- **Significant improvements in prealbumin, C-reactive protein, serum cholesterol, serum endotoxin, white cell blood count, and IgA**
  Han Chunmao et al. In press

SYNBIOTICS IN SEVERE ACUTE PANCREATITIS 1

Oláh A el al. Br. J. Surg 89:1103-1107

Trial in 45 patients, heatkilled (A) or live (B*) Lactobacillus plantarum 299* and 10 g oat fibre during days.

<u>Pancreatic sepsis (inf necroses/abscesses):</u>

A. 7/23 patients (30 %)

B. 1/22 patients (4.5 %)

p=0.023 *

***<u>Mean length of stay</u>*:**

A. 21.4 days

B. 13.7 days – ns

No statistically significant differences in number of chest infections (2+2),

SIRS (6&11)

MOF (2&2).

***The only infection in the synbiotic treated group occured on the 15th day, <u>e.g. 8 days after conclusion of supply of LAB and fibre</u>**

SYNBIOTICS IN ACUTE PANCREATITIS 2

Oláh A et al Hepato-gastroenterology 2007;54:36-41

	Synbiotic 2000	Fibres Only	
Total number of infections	9/33 (27 %)	15/29 (52 %)	
Pancreatic abscesses	2	2	
Infected necrosis	2	6	
Chest infections	2	4	
Urinary infections	3	3	
SIRS	3	5	
MOF	5	9	
SIRS + MOF	8	14	p<0.05
Late (>48h) MOF	1	5	
Complications	9/33	15/29	p<0.05
Surgical drainage	4/33 (12 %)	7/29 (24 %)	
Mean hospital stay	14.9 ±6.5	19.7±9.3	
Dead	2/33 (6 %)	6/29 (18 %)	

SYNBIOTICS IN ACUTE PANCREATITIS

Oláh A et al Hepato-gastroenterology 2007;54:36-41

Isolated Microorganisms:	**SYNBIOTIC 2000**	**Fibres Only**
Pseudomonas aeruginosa	1	4
Enterococcus faecalis	1	2
Enterobacter spp	1	1
Streptococcus spp	2	-
Staphylococcus aureus	1	1
Enterococcus faecium	1	-
Candida spp	-	2
Staphylococcus haemolyticus	-	1
Serratia spp	-	2
Klebsiella spp	-	1
Escherichia coli	-	1
Stenotrophomonas maltophilia	-	1
Citrobacter freundii	-	1
	(Total 7)	**(Total 17)**

SYN. 2000 IN TRAUMA PATIENTS

Spindler-Vesel A et al. JPEN 2007;31:119-126

• **Number of chest infections:**		
• **Synbiotic 2000**	**1/14**	**7 %**
• Only fibres	11/28	39 %
• Nutricomp peptide	10/21	48 %
• Glutamine	12/37	32 %
• **Total number of infections:**		
• **Synbiotic 2000**	**2/14**	**14 %**
• Only fibres	16/28	57 %
• Nutricomp peptide	11/21	52 %
• Glutamine	19/37	51 %

Both glutamine and Synbiotic 2000 down-regulated Il-6 but not Il-8 and TNF.

SYNBIOTIC 2000 IN SEVERE TRAUMA

Kotzampassi K et al. World J Surgery 2006;30:1848-1855

- 102 patients with multiple trauma treated 5 days with either Synbiotic 2000 Forte or placebo.

  Synbiotic-treated patients exhibited:

  Reduced rate of infections
  (P = 0.01)
  Reduced rate of SIRS, severe sepsis
  (P = 0.02) & mortality.
  Reduced number of days on mechanical ventilation (P= 0.001).
  Reduced ICU stay (P = 0.01)

SYNBIOTIC 2000 IN PANCREATECTOMY

- **Patients with infection:**
  Synbiotics 2000 5/40 (12.5%)
  Only fibres 16/40 (40%) p< 0.05

Rayes N et al. Ann Surg 2007;246:36-41

	Synbiotic 2000	Only fibres
Wound infections	4	6
Peritonitis	0	5
Pneumonia	0	4
Urinary	1	1
Sepsis	0	2
Cholangitis	0	1
Empyema	0	1
Total infections	**5**	**20**

SYNBIOTIC 2000 IN PANCREATECTOMY

Rayes N et al. Ann Surg 2007;246:36-41

	Synbiotic 2000	Only fibers
Enterobacter cloacae	2	8
Enterococcus faecalis/faecium	1	7
Escherichia coli	0	7
Klebsiella pneumoniae	2	2
Proteus mirabilis	1	1
Staphylococcus aureus	0	2
Total	**6**	**27**

LAB & ANTIBIOTIC-INDUCED DIARRHOEA

135 elderly hospital patients on antibiotics consumed 100 g (97 ml) of a probiotic drink twice a day during a course of antibiotics and for one week after the course finished

7/57 (12%) of the probiotic group compared to 19/56 (34%) in the placebo group developed diarrhoea (P=0.007)

No one in the probiotic group and 9/53 (17%) in the placebo group had diarrhoea caused by *C difficile* (P=0.001).

Hickson M et al BMJ 2007;335:80

PROBIOTIC CONTROL OF INFLAMMATION - *L lactis*

Desirable strains improve immune function by:

- **increasing the number of IgA-producing plasma cells**
- **increasing/ improving phagocytosis, &**
- **increasing the proportion of Th1 cells and NK cells**

Ouwehand AC et al Antonie Van Leeuwenhoek 2002;82:279–289

The *in vitro* ability to induce production of cytokines by 46 strains of *L. lactis* selected from about 2600 LAB strains was studied.

Great inter-strain differences in induction of IL-6 and IL-12 and in TNF-α.

IL-6 varied between 0 and 138 (ng/ml)

IL-12 varied between 0 and 37.3 (ng/ml) &

TNF-α varied between 0 and > 20.0(ng/ml)

Suzuki Ch et al Int J Food Microbiol 2008 E-pub

IMMUNE MODULATION – *L lactis*

Suzuki C et al Int J Food Microbiol 2008

Strains	IL-6 (ng/ml)	IL-12 (ng/ml)	TNF-α (ng/ml)
S63	138	37	20
P79	100	23	10
H-17	118	3	12
H45	4	2	0.33
O 62	4	2	0
G50	10	2	16
1257	0.29	1	0.23
ATCC19435	21	5	0
O19	0	0	0
O20	0	0	0
LPS	**170**	**8**	**4**

THE GREAT Ps

- ***Plantarum***
- ***Paracasei***
- ***Pediococcus pentosaceus***

Lb paracasei – the master?

- the strongest inducer of Th1 & repressor of Th2 cytokines
  when more than 100 strains are compared
  Fujuwara D et al. Allergy Immunol 2004;135:205-215

Lb paracasei

- **Induces cellular immunity**
- **Stimulates production of suppressive cytokines – TGFβ and Il-10 & suppresses CD4 T-cells**
- **Suppresses in vivo and in vitro Th2 activity**
  v. der Weid et al Clin Lab Immunol 2001;8:695-701
  Ibnon-Zekri et al Infect Immun 2003;71:428-436
- **Suppresses splenocyte proliferation**
  Nagler-Anderson Crit Rev Immun 2000;20:103-120
- **Decreases antigen-specific IgE and IgG1**
  Prioult et al Clin Diagn Immunol 2003;10:787-792

EFFECTS OF LAB ON PERMEABILITY & PAIN

Compared in animals effects of three probiotic strains: *Bifidobacterium lactis* NCC362, *Lactobacillus johnsonii* NCC533, and *Lactobacillus paracasei* NCC2461

on stress-induced changes in gut permeability & on sensitivity to colorectal distension (CRD)

Only *Lb paracasei* reduced significantly visceral pain & restored normal gut permeability.

Only *Lb paracasei* prevented visceral hyperalgesia.

Eutamene H et al. J Nutr. 2007;137:1901-1907

LAB & POST-INFECTIVE GUT DYSFUNCTION

Rats received either *Lactobacillus paracasei*, *Lactobacillus johnsonii*, *Bifidobacterium longum*, or *Bifidobacterium lactis during* days 10 to 21 after *Trichinella spiralis* - induced infection.

Lb paracasei but **NOT the other LAB**

- **attenuated muscle hypercontractility**
- **reduced the infection-associated Th- 2 response &**

muscle levels of TGF-β, COX-2 and

CONTROL OF PATHOGENS

- **The ability of 50 different LAB to control 23 different pathogenic *Clostridium difficile***

  27 were totally ineffective

  18 antagonistic to some

  5 effective against all:

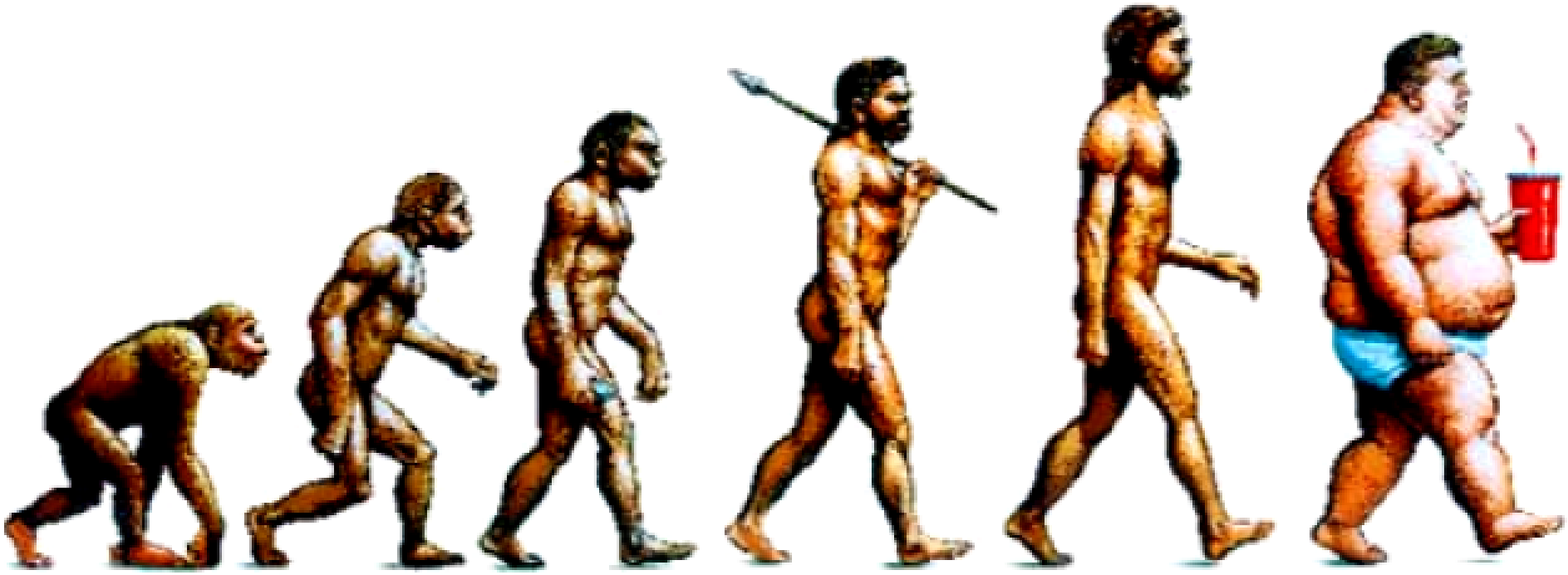
  2 strains - ***Lb paracasei* subsp *paracasei***

  3 strains - *Lb plantarum*

  Naaber P et al. Med Microbiol 2004;53:551-554.

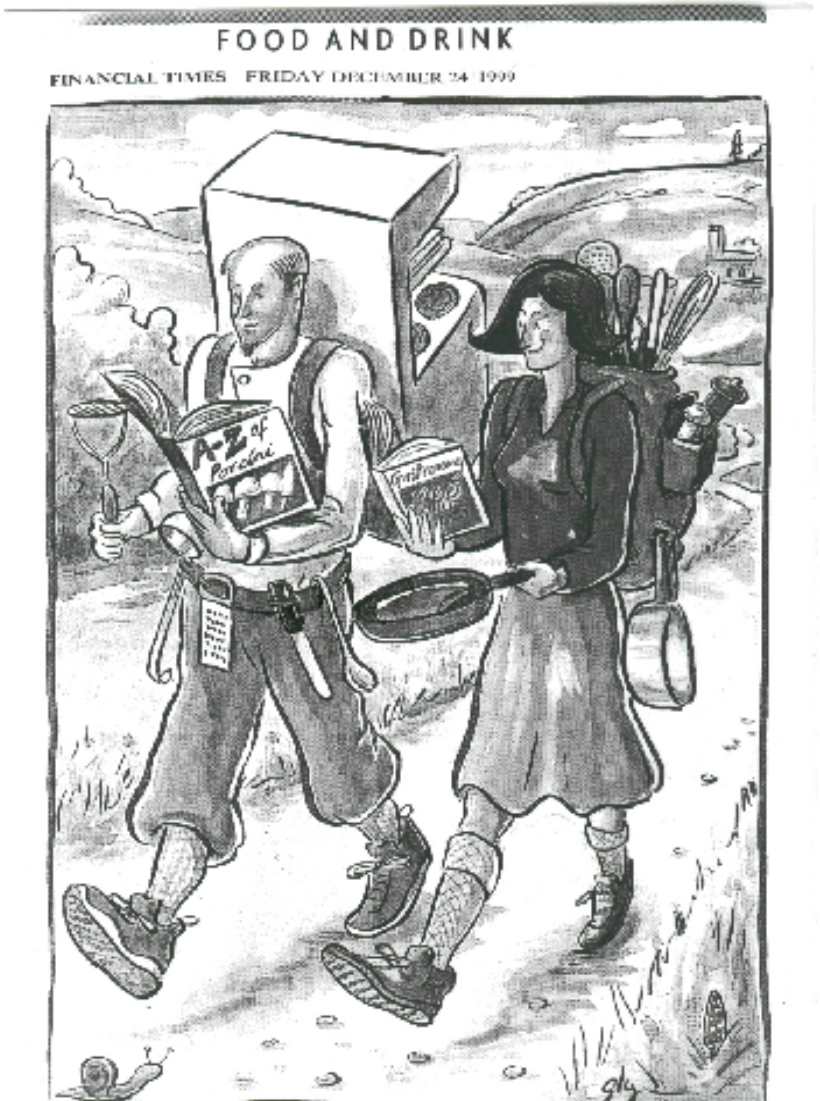
CONCLUSIVE REMARKS

“The Shape of Things to Come”



MAJOR HEALTH THREATS & life expectancy

- Reduced physical activity ? Years
- Alcohol abuse 4-5 years
- Tobacco abuse 8-10 years
- Food abuse up to 20-25 years



BENEFITS OF HEALTHY LIFESTYLE

- **High intake of fruit, vegetables, fish, olive oil**
- **Low intake of sugar, starchy and dairy products (Mediterranean diet) 0.77**
- **Restricting alcohol 0.65**
- **Avoiding tobacco 0.65**
- **Combination of all 0.35**
- **91 % reduction in diabetes, 83 % in coronary vascular disease & 71 % in large bowel cancer**

PREVENTION OF AGING AND DISEASE?

1. Rich resh fruits & vegetables
2. Abstaining from AGE/Ale rich food

3. Stimulation of flora

EASE INFLAMMATION

- **E** = ELIMINATE/MINIMIZE intake of proinflammatory drugs & nutrients

  A = ADD physical exercise & stress control to the extent possible

  S = SUPPLEMENT "anti-inflammatory" nutrients: omega-3, various B & D vitamins, zinc

  E = EAT/FEED non-processed fruit and vegetable juices.

Methuselah of the 3rd millenium

- ***"Twenty years ago the idea of postponing aging,……was weird and off-the-wall. Today there are good reasons for thinking it is fundamentally possible."*** (Michael Rose, professor of evolutionary biology, University of California, Irvine)
- ***"The first person to live to be 1000 years old is certainly alive today …whether they realize it or not ……. most people now 40 years or younger can expect to live for centuries."***

(Aubrey de Grey, Cambridge University geneticist.)

THANK YOU!

s.bengmark@ucl.ac.uk