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

SPIRITUAL HARMONY

(control of stress)

PHYSICAL EXERCISE — PROPER NUTRITION
A WORLD-WIDE EPIDEMIC
TSUNAMI OF CHRONIC DISEASES (ChDs)


• 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

“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

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

Immune Deficiencies – Elderly Patients with Colorectal Cancer

- Immuno-reactivity impaired in under-nourished patients.
- Preoperatively: high age, low BMI, high levels of IL-1 receptor antagonist (IL-1Ra).
- Postoperatively: Exaggerated IL-6 increase & increased postoperative loss of body weight.

EXAGERRATED INFLAMMATION
– THE CAUSE!
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>
<thead>
<tr>
<th>Disease</th>
<th>Incidence (n persons)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic disease</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 million</td>
</tr>
<tr>
<td>Arthritis</td>
<td>40 million</td>
</tr>
<tr>
<td>Migraine</td>
<td>23 million</td>
</tr>
<tr>
<td>Cancer</td>
<td>40% of Americans in their lifetimes (1 million/y)</td>
</tr>
<tr>
<td><strong>Drug-induced disease</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td>1 million</td>
</tr>
<tr>
<td>Drug-induced parkinsonism</td>
<td>61 000</td>
</tr>
<tr>
<td>Automobile accidents due to prescription drugs</td>
<td>16 000</td>
</tr>
<tr>
<td>Drug-induced memory problems</td>
<td>163 000</td>
</tr>
<tr>
<td>Hip fractures caused by drug-induced falls</td>
<td>32 000</td>
</tr>
<tr>
<td>Prescription drug abuse</td>
<td>6 million</td>
</tr>
<tr>
<td>Medical accidents</td>
<td>97 000</td>
</tr>
</tbody>
</table>
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
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

Table 2

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PS (n = 11)</td>
</tr>
<tr>
<td>Total proteins (g/dL)</td>
<td>5.2 ± 0.7‡</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>2.1 ± 0.6§</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>14.8 (6.1–23.4)§</td>
</tr>
<tr>
<td>α1-acid glycoprotein (g/L)</td>
<td>1.9 ± 0.3§</td>
</tr>
<tr>
<td>Leukocytes (cell/mm³)</td>
<td>13 100 (5900–22 400)‡</td>
</tr>
<tr>
<td>Lymphocytes (cell/mm³)</td>
<td>2180 ± 1300</td>
</tr>
</tbody>
</table>

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
FIGURE 2. Representation of the progressive decline of the functional capacities with aging, a decline that begins for most around age 30. Cross-sectional data for male participants 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

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 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.


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

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

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 0.51; 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, Lithuania; 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
Older persons have significantly:
- lower plasma zinc
- higher inflammatory cytokines & IL-10,
- higher levels of oxidative stress markers & of endothelial cell adhesion molecules

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

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
<table>
<thead>
<tr>
<th>Food</th>
<th>Zinc (mg/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat germ</td>
<td>18</td>
</tr>
<tr>
<td>Dry yeast</td>
<td>14</td>
</tr>
<tr>
<td>Sesami seed</td>
<td>10.2</td>
</tr>
<tr>
<td>Flaxseed, dry</td>
<td>7.8</td>
</tr>
<tr>
<td>Pumpkin seed</td>
<td>7.5</td>
</tr>
<tr>
<td>Squash seed</td>
<td>7.5</td>
</tr>
<tr>
<td>Cacao</td>
<td>7.0</td>
</tr>
<tr>
<td>Pecan nuts</td>
<td>5.5</td>
</tr>
<tr>
<td>Sunflower seeds</td>
<td>5.1</td>
</tr>
<tr>
<td>Liver</td>
<td>4-7</td>
</tr>
<tr>
<td>Beef</td>
<td>4-6</td>
</tr>
<tr>
<td>Soy protein</td>
<td>4.4</td>
</tr>
<tr>
<td>Brazil nuts</td>
<td>4.2</td>
</tr>
<tr>
<td>Peas</td>
<td>3.8</td>
</tr>
<tr>
<td>Lentils</td>
<td>3.1</td>
</tr>
<tr>
<td>Peanuts</td>
<td>3.1</td>
</tr>
<tr>
<td>Bacon</td>
<td>3.0</td>
</tr>
<tr>
<td>Walnuts</td>
<td>3.0</td>
</tr>
<tr>
<td>Flour</td>
<td>3.0</td>
</tr>
<tr>
<td>Cheese</td>
<td>2-3</td>
</tr>
<tr>
<td>French fries</td>
<td>0.4</td>
</tr>
<tr>
<td>Milk</td>
<td>0.4</td>
</tr>
<tr>
<td>Cream</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Acute and "chronic" phase reaction—a mother of disease

Stig Bengmark

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

Received 23 July 2004

Summary  The world is increasingly threatened by a global epidemic 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 function of the innate immune system is severely impaired. This review discusses 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”

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

THE IMMUNE SYSTEM

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

<table>
<thead>
<tr>
<th>20–30%</th>
<th>70–80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>Small intestine 6–7 m</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Large intestine 1.5 m</td>
</tr>
<tr>
<td>(N = 500–1000)</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
</tr>
</tbody>
</table>
THE INFLAMMATION BALANCE

> 2 mill different molecules in absolute balance

homeostasis

Cannon WB The autonomic nervous system: an interpretation 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
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)

<table>
<thead>
<tr>
<th></th>
<th>1973</th>
<th>2008 (estim)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn syrup</td>
<td>0.5 kg (1448 cal)</td>
<td>20 kg (62205 cal)</td>
</tr>
<tr>
<td>Sugar</td>
<td>32 kg (122873 cal)</td>
<td>21 kg (80747 cal)</td>
</tr>
<tr>
<td>Cheese</td>
<td>4.5 kg (18276 cal)</td>
<td>14.5 kg (58435 cal)</td>
</tr>
<tr>
<td>Total</td>
<td>142577 calories</td>
<td>201387 calories</td>
</tr>
</tbody>
</table>

Increase: 58790 calories

* the calories needed for 70 marathon runs
** the calories needed for 20 marathon runs
“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 (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 n mol/mg (p<0.05).

Tanuma N et al Brain Dev. 2008 Feb 13
Fig. 1. Age-related difference in insulin resistance in 466 healthy subject.
Table 1
Plasma oxidative stress and vitamin E levels in aged subjects (AS) and in centenarians (C)

<table>
<thead>
<tr>
<th></th>
<th>AS ($n = 30$)</th>
<th>C ($n = 22$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBARS (mmol MDA/ml plasma)</td>
<td>$0.51 \pm 0.07$</td>
<td>$0.39 \pm 0.04^*$</td>
</tr>
<tr>
<td>LPO (pmol/l)</td>
<td>$0.39 \pm 0.05$</td>
<td>$0.31 \pm 0.03^*$</td>
</tr>
<tr>
<td>Vitamin E (pmol/l)</td>
<td>$25 \pm 3$</td>
<td>$29 \pm 4^*$</td>
</tr>
</tbody>
</table>

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
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 >12,500 articles about the related HbA1c, 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, seems 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 autofluorescing
  - induce inflammation & infection
  - reduce antioxidant defense
  - weaken immune system
  - impair DNA repair mechanisms
  - induce tissue accumulation of toxins & accelerate the development of various diseases

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).

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

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

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
- Cardiovascular disease

- Cataract
- Glaucoma
- Macula degeneration
- Diabetes
- Hormone deficiencies
- Polycystic Ovary Syndrome
- Liver cirrhosis
- Chronic pulmonary disorders
- Rheumatoid diseases
- Fibromyalgia
- 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 associated 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


![Graph showing % Change in weight vs Week](image_a)

![Graph showing Peak Flow (L/min) vs Week](image_d)
COLA CONSUMPTION & BONE DENSITY

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

![Graph showing the relationship between cola consumption and bone mineral density.](image-url)
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
ESTROGENS IN MILK


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!
<table>
<thead>
<tr>
<th></th>
<th>E1</th>
<th>E2 - 17β</th>
<th>E3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole milk</td>
<td>3.7</td>
<td>6.4</td>
<td>9.0</td>
</tr>
<tr>
<td>Skimmed milk</td>
<td>20.2</td>
<td>3.4</td>
<td>8.2</td>
</tr>
<tr>
<td>Whey</td>
<td>3.6</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Cottage cheese</td>
<td>34.9</td>
<td>10.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Butter</td>
<td>539.4</td>
<td>82.3</td>
<td>86.8</td>
</tr>
</tbody>
</table>

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

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

BOVINE MILK & TESTICULAR CANCER

**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>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal fats</td>
<td>0.770⁴</td>
<td>0.764⁴</td>
<td>0.767⁴</td>
</tr>
<tr>
<td>Butter</td>
<td>0.558⁴</td>
<td>0.583⁴</td>
<td>0.626⁴</td>
</tr>
<tr>
<td>Cheese</td>
<td>0.804⁴</td>
<td>0.792⁴</td>
<td>0.769⁴</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.616⁴</td>
<td>0.609⁴</td>
<td>0.604⁴</td>
</tr>
<tr>
<td>Meat</td>
<td>0.655⁴</td>
<td>0.660⁴</td>
<td>0.686⁴</td>
</tr>
<tr>
<td>Fish</td>
<td>0.093</td>
<td>0.066</td>
<td>0.045</td>
</tr>
<tr>
<td>Milk</td>
<td>0.741⁴</td>
<td>0.736⁴</td>
<td>0.745⁴</td>
</tr>
<tr>
<td>Cereals</td>
<td>-0.358²</td>
<td>-0.395³</td>
<td>-0.468³</td>
</tr>
<tr>
<td>Pulses</td>
<td>-0.442³</td>
<td>-0.441³</td>
<td>-0.486³</td>
</tr>
<tr>
<td>Fruits</td>
<td>0.333²</td>
<td>0.355²</td>
<td>0.334²</td>
</tr>
<tr>
<td>Vegetables</td>
<td>0.103</td>
<td>0.090</td>
<td>0.079</td>
</tr>
<tr>
<td>Vegetable oils</td>
<td>0.478³</td>
<td>0.503⁴</td>
<td>0.447³</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.495⁴</td>
<td>0.514⁴</td>
<td>0.602⁴</td>
</tr>
<tr>
<td>Coffee</td>
<td>0.578⁴</td>
<td>0.574⁴</td>
<td>0.606⁴</td>
</tr>
<tr>
<td>Tea</td>
<td>0.058</td>
<td>0.072</td>
<td>0.078</td>
</tr>
</tbody>
</table>

¹Average 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**

**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.
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

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
### 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

ADRENALIN & CLOSTRIDIAL GROWTH

Cooper EV Lancet 1946;24:459-461

<table>
<thead>
<tr>
<th>Dose of bacilli</th>
<th>Guineapigs dying of gas-gangrene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test series (bacilli + adrenaline)</td>
</tr>
<tr>
<td>40,000,000</td>
<td>3/3</td>
</tr>
<tr>
<td>4,000,000</td>
<td>3/3</td>
</tr>
<tr>
<td>400,000</td>
<td>3/3</td>
</tr>
<tr>
<td>40,000</td>
<td>3/3</td>
</tr>
<tr>
<td>4000</td>
<td>2/3</td>
</tr>
<tr>
<td>0</td>
<td>0/3</td>
</tr>
</tbody>
</table>

* 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

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

ANTI-INFLAMMATORY NUTRITION
A SHIELD AGAINST ACUTE AND CHRONIC DISEASE

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

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 l/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)

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)

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.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Brain regions (curcumin-treated animals)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortex</td>
</tr>
<tr>
<td>Lipid peroxide ↓</td>
<td></td>
</tr>
<tr>
<td>42.5</td>
<td>32.4</td>
</tr>
<tr>
<td>Lipofuscin ↓</td>
<td></td>
</tr>
<tr>
<td>35.7</td>
<td>24.0</td>
</tr>
<tr>
<td>SOD ↑</td>
<td></td>
</tr>
<tr>
<td>37.0</td>
<td>45.0</td>
</tr>
<tr>
<td>GPx ↑</td>
<td></td>
</tr>
<tr>
<td>24.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Na+, K+, -ATPase ↑</td>
<td></td>
</tr>
<tr>
<td>16.6</td>
<td>40.0</td>
</tr>
</tbody>
</table>
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
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, α-lipoic acid.
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 $-18 \pm 3$ vs. $11 \pm 2$ mg/dl $P = 0.03$
total cholesterol $-23 \pm 5$ vs. $10 \pm 3$ mg/dl $P = 0.01$
LDL cholesterol $-20 \pm 5$ vs. $6 \pm 2$ mg/dl $P = 0.01$
serum triglyceride $-24 \pm 6$ vs. $-5 \pm 2$ mg/dl $P = 0.01$
Serum CRP levels $1.31 \pm 0.6$ vs. $0.33 \pm 0.1$ mg/l $P = 0.02$
Proteinuria $-0.15 \pm 0.03$ vs. $0.02 \pm 0.01$ g/day $P = 0.001$
urinary creatinine $-1.5 \pm 0.9$ vs. $0.6 \pm 0.3$ 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
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

- Bacteroides and bifidobacteria (total numbers and species diversity)
- Amylolytic activity
- Total SCFA (acetate, propionate and butyrate) (ABE)

Gut microflora

- Facultative anaerobes
- Fusobacteria, clostridia, eubacteria
- Proteolytic activity (ABE)

Total anaerobes = stable
Shifts in dominant species within bacterial groups
AGING & BARRIER FUNCTION

Changes of microbiota composition
Deficient epithelial integrity
Deficient protective commensals
Reduced barrier components: slgA, 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.

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.”

LAB CONSUMPTION BY ELDERLY improves specific immune functions:
Increasing natural killer cell activity
Increasing phagocytic activity of PBMCs
Decreasing macrophages-induced TNFα
Matsumoto M, Benno Y. Biosci Biotechnol Biochem 2006; 70:1287–1292
Reducing the incidence of winter infections
PROBIOTICS IN ATHLETES

Probiotics, reported to:
- correct interferon-γ deficiencies in athletes
- shortened the duration of GI episodes in marathon runners
- no effect on respiratory infections or GI symptoms

*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

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)
REDUCED INFECTION RATE

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)
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 
  \textit{L plantarum} and \textit{L paracasei}.

• Produce pro-inflammatory cytokines (IL-1β, IL-8) and anti-inflammatory (IL-10), to a large extent by \textit{L plantarum}, and less by \textit{Leuconostoc mesenteroides}.

 LAB IN SYNBIOTIC 2000 cont

• **Produce Antioxidants**, espec. *Lb plantarum* & *Pediococcus pentosaceus*

• **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*
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
MYELOPEROXIDASE – 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

<table>
<thead>
<tr>
<th>Group</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synbiotic 2000</td>
<td>17.16±2.03</td>
</tr>
<tr>
<td>Only LAB</td>
<td>8.91±2.24</td>
</tr>
<tr>
<td>Only the fibres</td>
<td>47.71±3.20</td>
</tr>
<tr>
<td>Placebo</td>
<td>66.22±5.92</td>
</tr>
</tbody>
</table>

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


- 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 & degree of encephalopathy/psychometric test in half of the patients

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*

Synbiotic 2000 (p=0.003)  Control (p=0.37)
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 %

**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) |

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

**Pancreatic sepsis**

(inf necroses/abscesses):

A. 7/23 patients (30 %)
B. 1/22 patients (4.5 %)

p=0.023 *

**Mean length of stay:**

A. 21.4 days
B. 13.7 days – ns

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

No statistically significant differences in number of chest infections (2+2), SIRS (6&11), MOF (2&2).
## SYNBIOTICS IN ACUTE PANCREATITIS 2

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

<table>
<thead>
<tr>
<th></th>
<th>Synbiotic 2000</th>
<th>Fibres Only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of infections</strong></td>
<td><strong>9/33 (27%)</strong></td>
<td><strong>15/29 (52%)</strong></td>
</tr>
<tr>
<td>Pancreatic abscesses</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Infected necrosis</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Chest infections</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Urinary infections</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>SIRS</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>MOF</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>SIRS + MOF</td>
<td>8</td>
<td>14 p&lt;0.05</td>
</tr>
<tr>
<td>Late (&gt;48h) MOF</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Complications</td>
<td>9/33</td>
<td>15/29 p&lt;0.05</td>
</tr>
<tr>
<td>Surgical drainage</td>
<td>4/33 (12%)</td>
<td>7/29 (24%)</td>
</tr>
<tr>
<td>Mean hospital stay</td>
<td><strong>14.9 ±6.5</strong></td>
<td><strong>19.7±9.3</strong></td>
</tr>
<tr>
<td>Dead</td>
<td>2/33 (6%)</td>
<td>6/29 (18%)</td>
</tr>
</tbody>
</table>
SYNBIOTICS IN ACUTE PANCREATITIS

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

<table>
<thead>
<tr>
<th>Isolated Microorganisms</th>
<th>SYNBIOTIC 2000</th>
<th>Fibres Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Candida spp</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Serratia spp</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

(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:**

<table>
<thead>
<tr>
<th></th>
<th>Synbiotic 2000</th>
<th>Only fibres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infections</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Urinary</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Empyema</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total infections</strong></td>
<td><strong>5</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

**SYNBIOТИC 2000 IN PANCREATECTOMY**  

<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>Synbiotic 2000 Only fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Enterococcus faecalis/faecium</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Strains</th>
<th>IL-6 (ng/ml)</th>
<th>IL-12 (ng/ml)</th>
<th>TNF-α (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S63</td>
<td>138</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>P79</td>
<td>100</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>H-17</td>
<td>118</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>H45</td>
<td>4</td>
<td>2</td>
<td>0.33</td>
</tr>
<tr>
<td>O 62</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>G50</td>
<td>10</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>1257</td>
<td>0.29</td>
<td>1</td>
<td>0.23</td>
</tr>
<tr>
<td>ATCC19435</td>
<td>21</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>O19</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>O20</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LPS</td>
<td>170</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>
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

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
- Suppresses splenocyte proliferation
  Nagler-Anderson Crit Rev Immunol 2000;20:103-120
- Decreases antigen-specific IgE and IgG1
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 PGE2

Verdú EF et al. Gastroenterology 2004;127:826-837
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*

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

The danger of wallowing in the past