Microbiota, immune development and immune functions

Stig Bengmark, MD, PhD

UCL, London University, United Kingdom, www.bengmark.se
“These studies have also given us weapons for fighting disease and reducing human suffering, weapons not less sharp than the surgeon's knife”

Albert Szent-Györgyi:
BIOLOGICAL OXIDATION AND VITAMINS
Harvey Lecture, May 18, 1939
“Research is to see what everybody else has seen, and to think what nobody else has thought”

Albert Szent-Györgyi
Nobel Prize laurate
1937
(Ascorbic acid)
Ignaz Semmelweis, 1818 – 1865

Chief of first Maternity Clinic in Vienna 1946 -
Thesis 1961: Die Ätiologie, der Begriff und die Prophylaxis des Kindbettfiebers
Puerperal fever, Yearly mortality rates
Puerperal fever
Monthly mortality rates 1841-1849
STAGES OF SUCCESS

• First – ridiculed
• Second – violently opposed
• Third – accepted as self-evident & honoured

Arthur Schopenhauer (1788-1860)
One of the greatest philosophers of the 19th century
• AE Baue 1983 – ”MOF, MODS, SIRS - without identifiable infections”
  Faist E et al J. Trauma 1983;23;775-787
• J Goris 1986 - “auto-destructive inflammatory response”
  Goris RJ et al Arch. Surg 1986;121:897-901
• Marshall JC 1993 – “the gut – the undrained abscess”
• Alverdy J 2003 – “Potentially pathogenic microorganisms (PPMs), normally indolent colonizers, change under stress their phenotype and become life-threatening pathogens”
INFLAMMATION & INFECTION

• It is inflammation that 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
CYTOKINE REACTION IN LIVER TRANSPLANTATION

More than six-fold increase in TNF-alpha and IL-6 at the end of the operation indicates that the patient will develop infections.

SYSTEMIC INFLAMMATION

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

Individuals without obvious disease, with higher levels of inflammatory markers/s:
C-reactive protein, fibrinogen, factor VIII activity, interleukin-6 and TNF-α etc.
are candidates to develop chronic diseases & complications to disease and treatments
A MOTHER OF DISEASE

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

Acute and “chronic” phase reaction—a mother of disease

Stig Bengmark

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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, ORIGIN & MANIFESTATIONS

• Low intake of antioxidants, plant fibres (fruits and vegetables)

• High intake of heat- and storage-induced glycated (AGEs), lipoxidated molecules (ALEs)

• High intake of proteotoxins; casein, gluten, zein etc.

will lead to:
- Reduced numbers & diversity of microbiota
- Increased translocation through membranes: leaky gut, leaky airways, leaky skin, leaky vagina, leaky eye cavity, leaky nose, leaky placenta, leaky blood-brain barrier etc.
DESTABILIZING FACTORS

Excess of refined processed foods e.g. foods rich in IGF-1, and IGF-1 promoting & Toll-stimulatory foods:

- increase expression of inflammatory messengers
- reduce microbiota
- increase membrane leakages
- destabilize the immune system

Contributory are: Lack of physical activity, mental and physical stress, Vitamin D deficiency, lack of anti-inflammatory minerals; Mg, Zn, Se, lack of omega-3 fatty acids etc.
THE OBESITY EPIDEMIC

THE GLOBAL OBESITY PROBLEM

An obese adult is classified as having a Body Mass Index equal to or greater than 30

SOURCE: World Health Organization, 2005
Increase of ChDs 1850 – 2005 in parallel to:
100 % increase in per person intake of saturated fats
1500 % production of milk/cow (2 l/d => 30 l/d )
10000 % increase in refined sugar intake (1 lb => 100 lb)

Figure 1. Scheme of the relative percentages of different dietary fatty acids (saturated fatty acids and n-6 and n-3 unsaturated fatty acids) in the diet and possible changes subsequent to industrial food processing, involving animal husbandry and hydrogenation of fatty acids. (Reprinted from Leaf and Weber), (14).
Vitamin D deficiencies (< 30 nmol/L) in Westerners undergoing surgery:

- 95% of Afro-Americans undergoing renal transplantation
  *Tripathy SS et al Transplantation 2008;85: 767–770*

- 85% of patients undergoing hip or knee replacement
  *Breijawi N et al Eur Surg Res 2009;42:1–10*

- 77% of chronic pancreatitis patients
  *Dujsikova H et al Pancreatology 2008;8:583–586*

- 67% of renal transplantation patients
  *Ducloux D et al Transplantation 2008;85: 1755–1759*

- 57% obesity surgery patients (79% in black and Hispanic)
  *Gemmel K et al Surg Obes Rel Dis 2009,5, 54–59*
VITAMIN D DEFICIENCY & DISEASE

- Aging
- Allergy
- Alzheimer’s disease
- Asthma
- Athletic performance
- Autism
- Cancer
- Cavities
- Colds
- Crohn’s disease
- Cystic fibrosis
- Depression
- Diabetes 1 and 2
- Eczema
- Heart disease
- Hearing loss
- Hypertension
- Infertility
- Influenza
- Insomnia
- Macular degeneration
- Migraines
- Multiple Sclerosis
- Muscle pain
- Myopia
- Obesity
- Periodontal disease
- Pre-eclampsia
- Psoriasis
- Rheumatoid diseases
- Schizophrenia
- Seizures
- Septicemia
- Tuberculosis
48/54 of Swedish depressed adolescents had below normal vitamin D levels (< 41 nmol/L) & were supplemented vitamin D3 over 3 months (mean: 91 nmol/L, p < 0.001)

- Depressed feeling (p < 0.001)
- Irritability (p < 0.05)
- Tiredness (p < 0.001)
- Mood swings (p < 0.01)
- Sleep difficulties (p < 0.01)
- Weakness (p < 0.01),
- Ability to concentrate (p < 0.05)
- Pain (p < 0.05)
VITAMIN D DEFICIENCY – COSTS

Gant WB et al Prog Biophys Mol Biol 2009;99:104-113

36 % of direct and 28 % of indirect Health Costs are associated with vitamin D deficiency.

Examples:
Cardiovascular 13.5 and 7.5 resp
Infections incl influenza 7 and 6.5 resp
Type 2 diabetes 7 and 2.4 resp
Cancer 6.4 and 9.6 resp
Osteoporosis 1.5 and 0.5 resp
Multiple sclerosis 1 and 0.2 resp
to all European to 40 ng/mL would reduce the direct economic burden of disease by 11.4%, or EUR 105,000,000,000
the indirect economic burden of disease by 6.4% or EUR 82,000,000,000
the total reduction in economic burden of disease by 17.7%, or EUR 187,000,000,000
LEAKY BARRIERS

- Gastrointestinal tract
- Airways
- Skin
- Oral cavity
- Vagina
- Nose
- Eye cavity
- Placenta
- Blood brain barriers

Maccaferri S et al
Dig Dis 2011;29:525-530
Study of 338 patients with thermic injuries. The microbes most commonly cultivated in both blood and at the burned skin surfaces were

*Acinetobacter baumannii* (47%) & *Pseudomonas aeruginosa* (37 %)

Other frequently isolated microorganisms were: *Staphyloccoccus epidermidis* MRSE (20%) & *Staphyloccoccus aureus* MRSA (19 %)
LEAKY PLACENTA

A shocking 9/20 (45 %) of umbilical cord blood, cultivated from healthy neonates born by cesarean section, demonstrated positive growth:

Enterococcus faecium, Propionibacterium acnes, Staphylococcus epidermidis & Streptococcus sanguinis


Other bacteria in amniotic infections: Fusobacterium nucleatum, (common oral species, being the most frequently isolated), Fusobacterium nucleatum, Peptostreptococcus spp, Porphyromonas and Prevotella spp., Eubacterium spp. Eikenella corrodens found in amniotic fluid of women with preterm labour.
Fibre intake, transit-time & stool weight.

○ = Vegetarians, vegans, and African boarding-school (mixed diet).

● = African villagers (high-residue diet).

▲ = English boarding-school and British Navy (low-residue diet).
VEGETABLE CONSUMPTION & HIP FRACTURES

Frassetto L et al
J Nutr 2001;40:200-213
ripened fruits = RF
unripened fruits = UF
young leaves = YL
seeds, flowers
President Bill Clinton – now a vegan radically changed diet, lost 20 lbs. in weight & improved his health, Clinton tells CNN. After experiencing periodic heart problems leading up to the 2004 surgery, the former junk food lover now calls himself a vegan, shunning meat, eggs, dairy and almost all oil saying: "I like the vegetables, the fruits, the beans, the stuff I eat now,“ "I feel good, and I also have … more energy."
Western lifestyle; foods, drugs etc down-regulates immune functions through lack of beneficial microbial products, increases systemic inflammation & induces diseases.

Microbiota contributes anti-inflammatory and/or immunomodulatory products such as: SCFA, polysaccharide A (PSA) and peptidoglycan (PTGN), vitamins, antioxidants etc.

Maslowsk KM, Mackey CR
Nature Immunol 2011;12:5-9
LEAKY GUT – TRANSPORT OF ENDOTOXIN (LPS)

A FAT-RICH MEAL & INFLAMMATION

Erridge E et al  Am J Clin Nutr 2007;86:1286-1292

• Increases circulating leukocytes (neutrophils, lymphocytes, and platelets)

• Activates of the transcription factor nuclear transcription factor B (NF-κB) in mononuclear cells

• Increases expression of tumor necrosis factor- (TNF-) in monocytes

• Alters surface adhesion molecules in neutrophils and monocytes

• Activates Toll-like receptor 4 (TLR4) complex

• Activates platelets and coagulation
FATTY ACIDS & INFLAMMATION


The saturated fatty acid, lauric acid, up-regulates:
- The expression of co-stimulatory molecules (CD40, CD80, and CD86)
- MHC class II,
- Cytokines (IL-12p70 and IL-6) in bone marrow-derived DCs,
- Increases activation of T-cells

The n-3 polyunsaturated fatty acid, docosahexaenoic acid, inhibits:
- TLR4 agonist (LPS)-induced up-regulation of the co-stimulatory molecules
- MHC
- class II, inflammatory cytokine production
- Reduces T-cell activation
PALMITATE & ASTROCYTE INFLAMMATION
(in vitro) Gupta S et al J Neurochem 2012;120 :1060-1071
Live commensal intestinal bacteria present in large numbers in adipose tissue (MAT), mesenteric lymph nodes (MLN) and blood after only one week on a high-fat diet (HFD)
Bacterial debris in human atheroma, earlier considered harmless, seems to contribute to disease progression via TLR-dependent lipid body formation in macrophages.
CHRONIC DEPRESSION & LEAKY GUT

Maes M J Affect Dis 2012 E-pub

Serum IgM and IgA against LPS of gram-negative Enterobacteria: *Hafnia alvei, Pseudomonas aeruginosa, Morganella morganii, Pseudomonas putida, Citrobacter koseri,* and *Klebsiella pneumoniae* measured in 112 depressed patients and 28 normal controls.

- Significantly elevated in acute depression
- Significantly elevated in chronic depression
- Significantly correlated to gastro-intestinal symptoms.
Fig. 2. Possible links between the gut microbiota and metabolism. Details, see main text. Continuous lines, likely pathway; dotted lines, putative pathway.
INFLAMMATION IN OBESE PREGNANT WOMEN

Basu S et al Obesity 2011;19:476-482

(a) Cytokine expression in SVF (FC lean vs. obese)

(b) Expression of LPS-sensitive genes (FC lean vs. obese)

MCP1, IL-8, IL-6, TNF-α, Leptin

CD14, TLR4, TRAM2
HYPOTHESIS: NUTRITION-INDUCED METABOLIC DISORDERS
Cani PD et al Diabetes 2008;57:1470-1481

Bacteria induced metabolic disease hypothesis

- High fat feeding
- Change Gut flora
- Increased permeability
- Increased LPS absorption
- Increased endotoxemia
- Inflammation
- Metabolic disorders

LPS concentration 10 to 50 X higher than those obtained during septic shock

Gram Positive

- Plasma Membrane
- Periplasmic space
- Peptidoglycan

Gram Negative

- Plasma Membrane
- Periplasmic space
- Peptidoglycan
- Outer membrane (lipopolysaccharide and protein)
ENDOTOXIN-ASSOCIATED DISEASES

- **Cognitive impairment** Lee JW et al. J Neuroinflammation 2008; 5: 37
- **Arterio-/Coronary Diseases** Heo SK et al Immunol Lett 2008;120:57-64
- **Diabetes type 1** Nymark M et al Diabetes Care 2009 32(9): 1689–1693
- **Diabetes type 2** Andreasen AS Intensive Care Med. 2010;36:1548-1555
- **ADHD, allergy, ALS, autism, autoimmune diseases, bipolar disease, cataracts, chronic fatigue syndrome, COPD, minimal encephalopathy, fibromyalgia, glaucoma, gulf war syndrome, HIV, iritis, liver cirrhosis, macular degeneration, multiple sclerosis, nephropathies, obesity, osteoporosis, paradontosis, Parkinson, polycystic ovary syndrome, rheumatoid disease, schizophrenia, stress, stroke, uveitis**
ENDOTOXIN & ADHESION FORMATION

Cahill RA et al Surgery 2007;141:403-410

A UPTAKE OF TRANSLOCATED FITC-LPS BY PERITONEAL MACROPHAGES AFTER SURGERY

B UPTAKE OF TRANSLOCATED FITC-LPS BY PERIPHERAL MONOCYTES AFTER SURGERY
INTAKE OF FOOD & INFLAMMATION

Erridge C Brit J Nutr 2011;105:15-23
GLUTEN-CASEIN & LACTOBACILLUS GROWTH

GLUTEN & SURFACE MOLECULE EXPRESSIONS

Class II, CD86, CD40, CD54
An up to 8-fold decrease in cortex tryptophan & serotonin after feeding:

- Zein - most marked
- Casein - moderate
- Gluten - moderate
- Lactalbumin - small
- Soy protein - slight increase
Children with celiac disease (CD) known to have an aberrant gut microflora.

Non-CD relatives have impaired intestinal microbial metabolism;
- significantly lower level of acetic acid and total SCFAs,
- significantly increased level of i-butyric acid and free tryptic activity (FTA)
GLUTEN INTOLERANCE & CHRONIC DISEASES

Ruuskanen A et al. Scand J Gastroenterol. 2010;45:1197-1202

• Associated with risk genotypes: HLA-B8, HLA-DQ2, HLA-DQ8

• Documented increased systemic inflammation

• Observed in 14 % of adult population

• Associated with diseases such as: ADHD, arthritis, Addison’s disease, allergy, autoimmune disorders, autism, bipolar disease, depression, dermatitis herpetiformis, diabetes mellitus, epilepsy, Graves´disease, infections, inflammatory bowel diseases - IBD, irritable bowel syndrome – IBS, lupus erythematosus, myasthenia gravis, osteoporosis and increased risk of fractures, pernicious anemia, polymyalgia rheumatica, psoriasis, schizophrenia, scleroderma, sepsis, Sjögren’s syndrome, thyreotoxicosis, vitiligo
GLUTEN SENSITIVITY (GS)– A NEW ENTITY

Sapone A et al. BMC Medicine 2011, 9:23

Some suffer well-defined chronic diseases incl. therapy-resistant epilepsy and Alzheimer-like symptoms

Others “only” more diffuse distresses; fatigue, lack of energy, mental depression, encephalopathy/‘foggy mind’, diffuse abdominal pain, bloating, diarrhea, eczema and/or rash, undefined headache, numbness in the legs, arms or fingers, joint pain and other manifestations.

Almost all report increased energy, enthusiasm, well-being & demonstrate frequently improved clinical signs

LA-DQ8 present in about half of patients with GS contrast to almost all patients with CD.
Gluten-free diet tried in 15 individuals without gluten intolerance (1st degree relatives)

Insulin sensitivity increased significantly in 12/14 subjects after 6 mo on gluten-free diet ($P \leq 0.04$) & decreased again in 10/13 subjects after 6 mo on “normal” diet ($P=0.07$)
IRRITABLE BOWEL SYNDROME – GLUTEN-FREE DIET

Biesiekierski Jr et al. Am J Gastroenterol 2011;106: 508-514
EXCLUSION DIET IN ADHD

Pelsser LMJ et al Lancet 2011;377:494-503

Switchover study 100 children, aged 4-8 yrs, 9 weeks + 4 weeks
A. Total, B. Inattention, C. Hyperactivity  D. Abbreviated Connor Scale scores (ACS)
Often used supplements in:

- Xanthum gum
- Guar gum
- Corn starch
- Egg

- Buckwheat
- Chickpeas
- Corn
- Potato
- Rice
- Tapioka
- Amaranth
- Arrowroot
- Millet
- Montina
- Lupin
- Quinoa
- Sorghum
- Taro
- Teff
- Chia seed
- Yam
- Bean
- Soybean
- Nuts & almonds
Fig. 4. Antioxidant activity (ABTS) levels of cereal grains. (Adapted from Guajardo-Flores and coworkers [25]).
AGEs/ALEs – AMPLIFIERS OF INFLAMMATION
Bengmark S JPEN 2007;31:430-440

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: Published reports over 5000 papers plus >13,500 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 Alzheimer’s 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)
22 Modified Amino Acid-Based Molecules: Accumulation and Health Implications

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Division of Surgery and Interventional Science, University College London, London, UK

22.1 Abstract

Industrial processing of food has not only improved the management and safety of foods, but also its taste. Unfortunately however, most of these processes — including plant breeding, gene manipulation, fractionation, separation, condensation, drying, freezing, heating, irradiation, roasting, microwaving, toasting, smoking, emulsification and homogenization — appear to be negative, as they reduce the nutritional quality of the food and also contribute significantly to increased vulnerability to development of diseases, especially those referred to as endemic and chronic.

This chapter deals especially with the negative consequences of heating and mainly with the impact of heat-produced glycated and lipoxidated molecules, often referred to as Maillard products. These products are more specifically referred to as advanced glycation end-products (AGE) and advanced lipoxidation end-products (ALE). The negative effects on health of other heat-produced compounds, such as heterocyclic aromatic amines, are outside the scope of this review.

Modern molecular biology has made it possible to explore the impact of these and other process-induced molecules on the body and its functions. The detection in 1992 of a specific receptor in the body for such products provided the opportunity for a better understanding of their effects in health and disease. This receptor for advanced glycation end products (RAGE) is recognized as a key member of the immunoglobulin superfamily of cell surface molecules. It functions as a master switch, induces sustained activation of NF-κB, suppresses a series of endogenous autoregulatory functions, and converts long-lasting pro-inflammatory signals into sustained cellular dysfunction and disease. Its activation is associated with much increased levels of dysfunctioning proteins in body fluids and tissues, and is strongly associated with a series of diseases from allergy and Alzheimer’s disease to rheumatoid arthritis and urogenital disorders. It is important to observe that heat treatment and other forms of processing of foods will dramatically increase the content of these dysfunctional molecules, and thereby, with time, significantly contribute to the epidemic of chronic diseases seen around the world. An increased
AGES/ALES IN TISSUES

Heat-induced glycated proteins induce about 50 times more free radicals than non-glycated proteins - AGEs and ALEs, which:

- accumulate in tissues (amyloid) &
- make the body auto-fluorescing
- impair DNA repair mechanisms
- induce tissue accumulation of toxins
- reduce antioxidant defense

induce inflammation & infection
weaken immune system &
accelerate development of various diseases

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

<table>
<thead>
<tr>
<th>Cytokine/Event</th>
<th>Cell Type/Location</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 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

• SEPSIS
AGEs IN STENOSES

hypochemistry

**Spinal canal stenosis**

*Nokura K et al J Neurol Sci 2000;178 114–123 (x60)*

**Carotid artery stenosis**

*Baumann M et al Cardiovasc Diabetol 2009;8:45 (x400)*
Accumulation of AGEs studied > six years in 302 renal transplant patients during Stronger predictor of graft loss than proteinuria & creatinine clearance

Hartog JWL et al Transplantation
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 (rich in ice cream, baby & clinical nutrition formulas) & cheese, espec. hard cheeses

HEATED GRAIN PRODUCTS: Toasted bread, bread crusts & crisp breads

HEATED MEAT (espec. bacon, sausages), POULTRY, FISH: content increases with exposure to temperature: boiling (1000 kU/serving) frying (9000 kU/serving) Goldberg T et al. J Am Diet Assoc 2004;104:1287-1291

HEATED VEGETABLE OILS: olive oil ca 8000 kU

OTHERS: 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 IN VARIOUS MILK PRODUCTS

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

![Graph showing furosine mg/g of protein for various milk products]

- Powder Milk (a)
- Powder Milk (b)
- UHT Milk
- Evapor. Milk
- Pasteur. Milk
- DIF (c)
- DIF (d)
- Powder Milk (e)
- DIF (d)
- Powder Milk (e)
- UHT lact. Free
- Powder Milk (f)
- UHT Homog.
- DIF with Milk
- DIF lact. Free
- Soya Milk
- Milk (g)
“SMOKING WITH THE STOMACH”

Eating cured meats: (bacon, cured hams, sausage) induces inflammation & reduces FEV1

- 3 - 4 X/mo – 12 ml
- 5 - 13 X/mo – 42 ml
- ≥ 14 X/mo – 110 ml

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

Intake of solid fruits & esp. catechin (tea & apple) reduces inflammation and increases FEV1 + 130 ml

&

Reduces main COPD symptoms: chronic cough, phlegm, breathlessness (p < 0.001)

Tabak C et al Am J Respir Crit Care Med 2001;164:61–64
Detection of acrylamide in carbohydrate-rich foods made as late as 2002

Acrylamide produce adverse effects in the body, the major being CARCINOGENICITY & NEUROTOXICITY

Table 1. Acrylamide data of heat-treated foods.

<table>
<thead>
<tr>
<th>Product group</th>
<th>Typical range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potato crisps</td>
<td>600-2000</td>
</tr>
<tr>
<td>French fries</td>
<td>300-700</td>
</tr>
<tr>
<td>Pan fries potatoes</td>
<td>250-300</td>
</tr>
<tr>
<td>Biscuits and crackers</td>
<td>100-600</td>
</tr>
<tr>
<td>Popcorn</td>
<td>400</td>
</tr>
<tr>
<td>Crisp breads</td>
<td>50-400</td>
</tr>
<tr>
<td>Coffee (powder)</td>
<td>200</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>50-250</td>
</tr>
<tr>
<td>Corn crisps</td>
<td>100-600</td>
</tr>
<tr>
<td>Soft breads</td>
<td>&lt;30-50</td>
</tr>
<tr>
<td>Meat and fish products</td>
<td>&lt;30-50</td>
</tr>
<tr>
<td>Pizza, pancakes, waffles</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Scramble egg</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Raw, boiled or mashed</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Potatoes</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Pasta</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Wheat and rye flour</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Rice, oat flakes</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Vegetarian schnitzel</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Cauliflower gratin</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Dried fruit</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>
ACRYLAMIDE IN BREAD

Granby K et al Food Additiv Contamin 2008; 25:921–929

Toasted bread contains many-fold more acrylamide than untoasted

Wheat: 11–161 vs < 5 mg/kg
Rye: 27–205 vs 7–23 mg/kg
Metabolic effects of diets based on mild steam-cooking vs. high-temperature cooking studied – 62 volunteers, 4 weeks

The steamed-cooked diet induced:
- Significantly improved insulin sensitivity (mean 7.63 => 6.52 mU/L)
- Reduced cholesterol/pl (5%, p= 0.01)
- Reduced triglycerides/pl (9%, p= 0.01)
- Increased Omega-3 fatty acids/pl (217%, p = 0.002)
- Increased Vitamin C/pl (213%, p =0.0001)
- Increased Vitamin E/pl (28%, p=0.01)
Fig. 1 Relation between national per capita fat intake and breast cancer mortality rate (from Carroll, 1975, reproduced with permission).
DAIRY-INDUCED INFLAMMATION
Dietary proteins of cow’s milk
induce inflammation:
• release inflammatory mediators
• increase intestinal permeability
• induce leakage of large molecules; albumin, hyaluronan etc

BOVINE MILK & CHRONIC DISEASES

- **Colorectal cancer** Manousos O et al. Int J Cancer 1999;83:15-17, Ma et al. J Nat Cancer Inst;2001;93:1330-1336
- **Parkinson disease** Park M et al. Neurology 2005;64:1047-1051
The dramatic increase in testicular, breast, prostate, ovarian, corpus uteri & large bowel cancers.

60-80% of the intake of oestrogens originates from dairy foods.

The daily intake of total oestrogens through milk is 372 ng, “dramatically more than currently recognized.”

The content is twice as high in 3.5% fat milk than in non-fat milk & extremely high in butter!
<table>
<thead>
<tr>
<th></th>
<th>PG/G</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>
<td></td>
</tr>
<tr>
<td>Skimmed milk</td>
<td>20.2</td>
<td>3.4</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Whey</td>
<td>3.6</td>
<td>1.5</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Cottage cheese</td>
<td>34.9</td>
<td>10.8</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Butter</td>
<td>539.4</td>
<td>82.3</td>
<td>86.8</td>
<td></td>
</tr>
</tbody>
</table>

*Wolford ST, Argoudelis CJ J Dairy Science 1979;62:1458-1463*
DAIRY CONSUMPTION & IGF-1

Positive correlation between IGF-1 & cancer (and other chronic diseases)

Positive association between consumption of dairy products or milk and IGF-1

Increased IGF-1 in response to a higher intake of milk and dairy products

IGF-1 concentrations significantly lower in vegans cp. lacto-ovo-vegetarians & omnivores
Primary Metabolic Syndrome in Cows

Modern feeds of dairy cows; less forage-based and rich in starch & carbohydrates (corn, maize grains, barley, molasses and dextrose) induces “Western diseases” – also in cows

Insulin resistance observed in calves fed on intensive milk- and lactose diet

Supplementing barley grains associated with:

- increased milk production (27.2 => 31.0 ± 1.2 kg/d)
- reduced feed intake (32.6 => 25.18 kg/d ± 1.30),
- reduced ruminal pH (6.8 => 6.5 ± 0.03)

- increased levels of ruminal endotoxin (5,021 => 8,870) &
- increased plasma concentrations of serum amyloid A, lipopolysaccharide-binding protein & C-reactive protein
isothiocyanates in cruciferous vegetables, anthocyanins and hydroxycinnamic acids in cherries, epigallocatechin-3-gallate (EGCG) in green tea, chlorogenic acid and caffeic acid in fresh coffee beans and also fresh tobacco leaves, capsaicin in hot chili peppers, chalcones in apples, eugenol in cloves, gallic acid in rhubarb, hisperitin in citrus fruits, naringenin in citrus fruits, kaempferol in white cabbage, myricetin in berries, rutin and quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine and virgin peanuts, various curcumenoids, the main yellow pigments in turmeric curry foods, and daidzein and genistein from the soy bean
Review

Curcumin, An Atoxic Antioxidant and Natural NFκB,
Cyclooxygenase-2, Lipoxygenase, 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), lipoxygenase (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)
12
Control of Systemic Inflammation and Chronic Diseases—The Use of Turmeric and Curcuminoids
Stig Bengmark

ABSTRACT
The world suffers an epidemic of both critical illness (CI) and chronic diseases (ChDs), and both groups of diseases increase from year to year, and have done so for several decades. It is strongly associated to the modern, so-called Western, lifestyle: stress, lack of exercise, abuse of tobacco and alcohol, and the transition from natural unprocessed foods to processed, calorie-condensed, and heat-treated foods. There is a strong association between reduced intake of plant fibers and plant antioxidants and increased consumption of industrially produced and processed products especially dairy, refined sugars, and starch products and ChDs. Heating up foods such as milk (pasteurization) and production and storage of milk powder produce large amounts of advanced glycation end products (AGEs) and advanced lipid oxidation end products (ALEs), known as potent inducers of inflammation (see further Chapter 20).

Numerous plant-derived, but also microbe-derived, substances, often referred to as chemopreventive agents, have documented anti-inflammatory

AN EPIDEMIC OF CHRONIC DISEASES AND CRITICAL ILLNESS
Modern medicine has to a large extent failed in its ambition to control both acute and chronic diseases. The world suffers an epidemic of chronic diseases of a dimension never seen before, and these diseases are like a prairie fire also spreading to the so-called developing countries. As an example, there are more cases of diabetes reported in China (24 million) and India (44 million) than in the United States (17 million), and the increase in incidence is faster in these countries than in Western societies. Today, chronic diseases—for example, diseases such as cardiovascular and neurodegenerative conditions, diabetes, stroke, cancers, and chronic respiratory diseases—constitute 46% of the global disease burden and 59% of the global deaths; each year approximately 35 million individuals die in conditions related to chronic diseases, and the numbers are fast increasing and have done so for several years (World Health Organization 2003).
CURCUMIN – MOLECULAR FUNCTIONS

KUNNUMAKKARA AB ET AL CURRENT COLORECTAL CANCER REPORTS 2009, 5:5–14
STABILISING CELL MEMBRANES

Curcumin attenuates endotoxin-induced coagulopathy & prevents disseminated intravascular coagulation


Curcumin pretreatment for 3 d before CLP
- 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
The Utilization of Magnesium by Certain Gram-Positive and Gram-negative Bacteria

By M. Webb

Strangeways Research Laboratory, Cambridge

INTRODUCTION

Although the magnesium requirements for maximal growth in simple chemically defined media are some ten times greater for Gram-positive bacteria than for Gram-negative bacteria (Webb, 1949a) the magnesium contents of these organisms do not differ greatly (Webb, 1949b; Rouf, 1964), and it is probable that the intracellular concentrations of free cation are similar. De Ley’s (1964) observations, for example, on the unity of ribosomes from widely divergent Gram-positive and Gram-negative bacteria, coupled with the known dependence of the structure of polysomes from mammalian, plant and microbial cells on similar concentrations of Mg$^{2+}$, indicate that the intracellular content of the free cation probably must be maintained within certain critical limits. The present study concerns the utilization of magnesium in bacteria growing in simple media. It is shown that the previously observed variations in the requirements of the Gram-positive and Gram-negative species are due to differences in assimilatory efficiency.
MAGNESIUM, INFLAMMATION & SEPSIS

• Hypomagnesemia associated with increased release of endothelin and pro-inflammatory cytokines

• Supply of magnesium down-regulates release of TNF-alpha & IL-6
HYPOMAGNESEMI A & SEPSIS

• Hypo-magnesemia is strongly associated with increased mortality in exp sepsis

• Magnesium replacement provides significant protection against endotoxin

• Administration of Mg to animals with sepsis improves organ function and survival time
52% of patients show Mg-deficiency on admission to MICU & suffer increased:

- **Mortality rate** (57.7% vs 31.7%)
- **Need for ventilatory support** (73% vs 53%)
- **Duration of mechanical ventilation** (4.27 vs 2.15 days),
- **Rate of sepsis** (38% vs 19%)
- **Hypocalcemia** (69% vs 50%)
- **Hypoalbuminemia** (80.76% vs 70.8%)
THE 1986 EXPERIENCE

Review of 81 major liver resections

Morbidity: 33% (17 % major)

No antibiotics, by clinical error, to 24/81 patients

Prophylactic antibiotic (ampicillin, cephalosporin, tetracyclines) given to 57/81 patients

All infections were in antibiotic-treated patients

No infections observed in non-antibiotic-treated patients

Ekberg, PhD thesis, Lund University 1986
Synbiotics in Human Medicine

Thirty years have passed since Gilliland and Speck reported that patients with inflammatory bowel disease (IBD) had a significantly different microbiota from that of healthy individuals (Gilliland and Speck, 1977). Finegold and Sutter reported in the following year an altered microbiota in 75% of healthy omnivorous and 35% of vegetarian Americans (Finegold and Sutter, 1978). Similar observations were later made for European populations (Ahrne et al., 1998).

Numerous attempts during the last 30 years to reconstitute or remodel the microbiota in order to prevent or treat diseases were repeatedly made. However, these often produced dissatisfying results. One obvious explanation suggested by recent reviews (Sartor, 2004; Marteau, 2006) is that the majority of clinical studies thus far have been underpowered.

REGENERATIVE CAPACITY
The spontaneous regenerative capacity of the gastrointestinal tract is much greater in young experimental animals and in animals with induced disease. Regenerative capacity is greater in humans with acute disease than in humans with chronic disease.

DIFFERENCES IN DAILY DOSES
The daily dose related to body weight or to the gastrointestinal mucosal surface is generally much larger in experimental animals and in pediatric cases. In the majority of studies, the daily dose used in humans has been 1 billion lactic acid bacteria (LAB) once or twice per day, up to 10 billion organisms/day. Larger doses delivered more impressive results. Large-scale doses in liver transplantation (Rayes et al., 2005) and trauma (Spindler-Vesel et al., 2007) with Synbiont 2000 and Synbiont 2000 Forte (see below) included 40 and 400 billion LAB per day. In IBD, VSL#3 was administered at a dosage of 1,200 billion LAB per day (Venturi et al., 1999). A total of 80 billion LAB of Synbiont 2000 per day were administered to patients with chronic liver disease, according
LOCATION OF IG-PRODUCING IMMUNOCYTES

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

20-30%

Bone marrow

70-80%

Small intestine

6-7 m

Large intestine

~1.5 m

Lymph nodes

(N=500-1000)

Spleen

Response to LAB not different from what is observed after supply of certain pharmaceuticals, although weaker & without adverse effects;

*L. acidophilus* - antagonists of α-receptor activity, guanine antagonists, synthetic corticosteroids and flavonoids,

*L. casei* - modulators of GABA receptors, cholinergic blocking agents, antagonists of β-adrenergic receptors,

*L. rhamnosus* - glycoside steroids, alkaloids, protein synthesis inhibitors and protein kinase C inhibitors.
FLORA IN WESTERNERS

- *Lb plantarum*, a dominating LAB, in only 25% of omnivorous Americans & in 65% of vegetarian Americans
  

- Common colonic LAB species present only in

- about 50% or less of healthy Scandinavians:

  *Lb plantarum* 52%,
  *Lb rhamnosus* 26%,
  *Lb paracasei ssp paracasei* 17%

| L. plantarum | 0 (0%) | 8 (18.2%) | 0.0004 |
| L. paracasei | 10 (14.7%) | 17 (38.6%) | 0.004 |
| L. reuteri | 6 (8.8%) | 1 (2.3%) | 0.16 |
| L. rhamnosus | 3 (4.4%) | 4 (9.1%) | 0.27 |
| L. ruminis | 3 (4.4%) | 4 (9.1%) | 0.27 |
| L. salivarius | 5 (7.4%) | 2 (4.5%) | 0.43 |
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

SYNBIOTIC 2000
Synbiotic AB, Sweden, contact; synbiotic@gmail.com

400 billion Lactic acid bacteria:
$10^{10}$ 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

10 gram bioactive fibers:
2.5 g of betaglucan
2.5 g of inulin
2.5 g of pectin
2.5 g of resistant starch
SYNBIOTIC 2000 IN LUNG INJURY


- Placebo
- Only fibres
- Synbiotic 2000
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
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 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
SYNBIOTIC 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 %

<table>
<thead>
<tr>
<th>Isolated bacteria</th>
<th>Synbiotic</th>
<th>Fibres only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>(total 1)</strong></td>
<td><strong>(total 18)</strong></td>
<td></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>1</td>
<td>2</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></td>
<td></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></td>
<td></td>
<td></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)
STRESS-INDUCED INFECTIONS

• Luminal release of noradrenaline is a strong inducer of virulence of luminal bacteria
  Kinney KS Life Science 2000;67:3075-3085

• Potentially pathogenic microorganisms (PPMs) change under stress their phenotype and become life-threatening pathogens
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*
## Table 1—Effect of Injecting 1/8000 Adrenaline with Washed Cl. welchii

<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.*
Survival of *B. anthracis* after infusions of English Breakfast tea with and without addition of 20% whole milk
MECHANICALLY INDUCED INFLAMMATION

Aggravated inflammation (neutrophil infiltration of tissues, increased expressions of molecules such as NF-κB, COX-2, LOX and iNOS) & immune deterioration induced by:

• Forceful treatment of tissues; “tooth-brushing” “skin-scrubbing” etc.

• Handling of the bowels during operation
  Kalff C et al Gastroenterology 1999;117:378-387

• Ventilation of the lungs
Parenteral nutrition increases mortality significantly (63% vs 26%) in patients with burns


Enteral nutrition induces loss of mucosal protein content, intestinal microbial overgrowth & translocation; Vivonex (53%), Criticare (67%), or Ensure (60%) (p < .05)


Enteral nutrition with Nutrison induces 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)

*Slotwinski R et al. JOP. J Pancreas 2007; 8:759-769*
DRUGS & RESISTANCE TO DISEASE

• Chemicals incl. pharmaceutical drugs suppress innate immune functions.

• Antibiotics suppress:
  - Lymphocyte proliferation
  - Macrophage functions; chemiluminescence response, chemotactic motility, bactericidal & cytostatic ability

Roszkowski K et al. Zeitschr Bakteriol Hyg 1988;270:270-279
Antibiotics destroys microbiota incl. almost 90 % of its functions; bile acid metabolism, eicosanoid and steroid hormone synthesis etc


Chemotherapeutics reduces microbiota 100-fold; decrease anaerobic bacteria up to 10,000-fold and 100-fold increase in PPMs


Mothers consuming *proton pump inhibitors* during pregnancy increases the risk of offspring getting asthma

*Andersen AB et al. Aliment Pharmacol Ther 2012;35:1190-1198*

Anti-hypertensives reduce mucosa protection espec mucus production and induce gastrointestinal dysbiosis

INFLAMMATION INVOLVES ABOUT 1200 GENES affecting a wide range of effector molecules; pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α and IL-18, chemokines such as IL-8, IP-10, MCP-1, MIP-1 and RANTES, MMPs such as MMP-1, -3, -9 and -13 and metabolic proteins such as Cox-1, Cox-2 and iNOS etc

- **Biologicals aimed to target single genes**: anti-TNF-α, anti-IL-1β, anti-HER2, IL-12/IL-23, IFN-γ, IL-17A, IL-2 and IL-6, and inhibitor of NF-KB

- **Uni-targetting**
- Immediate powerful effects
- Limited by toxicity
- Negative to microbiota
- Sometimes short-lasting effects
- Substantial adverse effects
- Indicated - aggressive diseases

- **Eco-biologicals**: utilizes the anti-inflammatory effects of microbes and plants; Greens, vegetables, fruits & spices to support microbiota

- **Multi-targetting**
- Slower and weaker effects
- GRAS – e.g. no toxicity
- Support microbiota
- For-ever lasting effects
- No adverse effects
- Indicated - prevention and early disease
1. Minimize intake of insulinogenic foods absorbed high in the small intestine and of minimal benefit to microbiota.

2. Reduce intake of highly pro-inflammatory fructose to below 25 gram a day.

3. Minimize intake of dairy products especially butter, cheese and milk powder-detrimental to microbiota.

4. Increase the intake of fresh and raw greens, fresh spices and vegetables - important for diversity, replication, growth and functions of the microbiota.

5. Minimize intake of foods, heated above 100° to avoid proinflammatory molecules AGEs and ALEs, acrylamide and heterocyclic amines.


7. Eliminate/Minimize intake of foods rich in proteotoxins such as casein, gluten and zein.

8. Consume ancient anti-oxidant-rich, high fiber, low-calorie containing grains; as buckwheat, amaranth, chia, lupin, millet, quinoa, sorghum, taro, teff etc, but also beans, peas, chickpeas, lentils, nuts and almonds - most likely of importance for maintenance of a rich microbiota.

9. Restrict exposure to chemicals including pharmaceutical drugs - detrimental to microbiota.

10. Supplement vitamin D and omega fatty acids in large doses – important for function of microbiota.
• Concentrated milk fats abundant in processed and confectionary foods, alter dramatically the composition of bacteria in the intestines.

• Milk-derived-fat-promoted taurine conjugation of hepatic bile acids increases the availability of organic sulphur used by sulphite-reducing microorganisms like B. wadsworthia.

• The levels of Bilophila wadsworthia, are almost undetectable when on a low-fat or unsaturated-fat diet, but the bacteria make up about 6 percent of all gut bacteria when fed a high milk-fat diet

Devkota, S, Chang E et al. Nature E-pub 20120615
The B-team – ”The Bach, Beethoven and Brahms of Hepatic Surgery” (after Michael Trede, Mannheim)

Leslie Blumgart (1931)  Stig Bengmark (1929)  Henri Blumgart (1934)
Roland Andersson Lund (b 1955)

Bengt Jeppsson Malmö   (b 1946)
The danger of wallowing in the past

www.bengmark.com  stig@bengmark.se