The Science of Anti-Inflammatory Nutrition
Overview of Anti-Inflammatory Nutrition
Unique Roles For Each

• Zone Diet
  – Reduction of insulin resistance

• Omega-3 Fatty Acids
  – Acceleration of resolution

• Polyphenols
  – Slowing of the aging process
What Is The Zone?

• Maintaining a balance of initiation and resolution of inflammation

• Modulation of gene transcription factors

• Diet-based gene therapy
Benefits of Being in The Zone

• Permanent weight loss
• Treating chronic disease
• Performing better
• Thinking faster
• Better emotional control
• Slowing down the rate of aging
Clinical Markers of the Zone

• Balance of initiation and resolution of inflammation
  – Marker: AA/EPA ratio
  – Goal: Between 1.5 and 3

• Development of insulin resistance in the liver
  – Marker: TG/HDL ratio
  – Goal: <1 (mg/dl) or < 0.4 (mmol/l)

• Long-term glycemic control
  – Marker: HbA₁c
  – Goal: 5%
Your Goal:

Change Your Future By Changing the Expression of Your Inflammatory Genes
How?

• Improved hormonal control

• Gene transcription factors

• Resolution of inflammation

• Epigenetic changes
THE SECRET KILLER

The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER’S and other diseases

What you can do to fight it
Cellular Inflammation Made Simple

Toll-Like Receptors (TLR) and AGE Receptors (RAGE)

AA

NF-κB

PPARγ

Inflammatory Enzymes (COX-2) And Cytokines (IL-1, IL-6, TNF)

DNA

Cytokine Receptors
Dietary Controls on NF-κB Activity

Omega-6 Fatty Acids, Saturated Fatty Acids, Excess Carbs, and Excess Calories

Zone Diet, Omega-3 Fatty Acids, and Polyphenols
The Zone Diet

• 40% low glycemic load carbohydrates
• 30% low-fat protein
• 30% monounsaturated fat
• 1,200 to 1,500 calories per day
### Per Cent Calories Can Be Deceiving

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>1,200 calories/day</th>
<th>1,500 calories/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>120 g/day</td>
<td>150 g/day</td>
</tr>
<tr>
<td>Protein</td>
<td>90 g/day</td>
<td>112 g/day</td>
</tr>
<tr>
<td>Fat</td>
<td>40 g/day</td>
<td>50 g/day</td>
</tr>
</tbody>
</table>
Controlling Insulin Depends on The Protein-to-Glycemic Load Ratio

<table>
<thead>
<tr>
<th>Protein-to-Glycemic Load Ratio</th>
<th>High-Carbohydrate Diets</th>
<th>Zone</th>
<th>Low-Carbohydrate/High Protein Diets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess Insulin Production</td>
<td>Fat Accumulation</td>
<td>Insulin Balance</td>
<td>Excess Glucagon Production</td>
</tr>
<tr>
<td>Loss of Inflammatory Fat</td>
<td>Cortisol Increase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2007 Dietary Guidelines From The Joslin Diabetes Research Center At Harvard

- 40% low glycemic load carbohydrates
- 20-30% low-fat protein
- 30-40% monounsaturated fat
- 1,200 to 1,500 calories per day
Zone Diet and Hormonal Balance
Zone Diet Induces Rapid Changes in Hormonal Responses

Serum Insulin (change)

Plasma Glucagon (change)

Reducing Insulin Resistance Is the Key Benefit of the Zone Diet
What Is Insulin Resistance?
Insulin Resistance is Highly Organ Dependent
Hypothalamus

- Balances of energy intake and expenditure
  - Satiety signals from gut matched to hormonal signals (leptin and insulin) from the blood

- Sensitive to excess calories and saturated fats
  - ER stress and inflammation
Hypothalamic Inflammation is Rapid

• Within 24 hours of HFD

• Precedes any weight gain

• Fatty acid sensors
  – Palmitic acid and TLR-4 receptors
  – Omega-3 and oleic acids
Adipose Tissue

• Rich in stem cells for new fat cell formation
  – PPARγ

• Hypoxia of expanded fat cells
  – Activation of HIF-1 gene
  – Increased JNK and IKK expression
  – Development of insulin resistance
Liver

• Can start earlier than adipose tissue
  – 3 days after HFD
  – Connection to hypothalamus via vagus nerve

• Increase in cholesterol levels

• Development of fatty liver
  – 25% of all Americans
  – 90% of type 2 diabetics
Muscle IR

• Primary site for glucose uptake

• Inflammatory cytokines from adipose tissue and liver disrupt glucose uptake
The Zone Diet is Easy To Follow For A Lifetime
Balance With:

- Fruits & Vegetables
- Low Fat Protein
Zone Diet Is Based on Balance, Not Philosophy

- **Paleo Zone**
  - No legumes, no dairy protein
- **Vegan Zone**
  - No animal protein, no dairy protein
- **Lacto-ovo Vegetarian Zone**
  - No animal protein
- **Omnivore Zone**
  - No restrictions on protein sources
The Zone Diet Is the Evolution of the Mediterranean Diet

• It’s Mediterranean ingredients with a Zone blueprint for hormonal balance

• The more white you put on the plate, the more inflammation you create
Effect of Diet on NF-κB Activity in Humans

• High glycemic load diet increases NF-κB activity
Omega-3 Fatty Acids: Resolution of Inflammation
Inflammation Doesn’t Burn Out On Its Own
Phases of Inflammation

- Initiating Event
- Pro-inflammatory Initiation Response
  - Cellular Destruction
- Anti-Inflammatory Resolution Response
  - Cellular Rejuvenation
What Happens When Inflammation Is Not Resolved?

- Acute Inflammation
  - Resolution
- Acute Inflammation
  - X
  - Resolution
- Chronic Cellular Inflammation
  - X
Are We Missing The Real Cause Of Chronic Inflammation?
Long-Chain Omega 6 Fatty Acid–Arachidonic Acid (AA)

Long-Chain Omega 3 Fatty Acid–Eicosapentaenoic Acid (EPA)
Benefits of a Low AA/EPA Ratio

• Reduction of initiation of inflammation

• Acceleration of resolution of inflammation
First Use of High-Dose Fish Oil To Lower The AA/EPA Ratio

The New England Journal of Medicine

©Copyright, 1989, by the Massachusetts Medical Society

Volume 320 FEBRUARY 2, 1989 Number 5

THE EFFECT OF DIETARY SUPPLEMENTATION WITH n–3 POLYUNSATURATED FATTY ACIDS ON THE SYNTHESIS OF INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR BY MONONUCLEAR CELLS

Stefan Endres, M.D., Reza Ghorbani, B.S., Vicki E. Kelley, Ph.D., Kostis Georgilis, M.D., Gerhard Lonnemann, M.D., Jos W. M. van der Meer, M.D., Joseph G. Cannon, Ph.D., Tina S. Rogers, Ph.D., Mark S. Klempner, M.D., Peter C. Weber, M.D., Ernst J. Schaefer, M.D., Sheldon M. Wolff, M.D., and Charles A. Dinarello, M.D.
Table 1. Fatty Acid Composition of Mononuclear-Cell Membranes as a Percentage of Total Fatty Acid Content.*

<table>
<thead>
<tr>
<th>FATTY ACID</th>
<th>BEFORE n-3 SUPPLEMENT</th>
<th>AFTER n-3 SUPPLEMENT</th>
<th>TIME AFTER END OF n-3 SUPPLEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 WEEKS</td>
<td>20 WEEKS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean percentage ±SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA (n-6)</td>
<td>13.8±1.3</td>
<td>8.6±0.7†</td>
<td>9.5±1.8‡</td>
</tr>
<tr>
<td>EPA (n-3)</td>
<td>0.7±0.1</td>
<td>3.8±0.7§</td>
<td>1.0±0.3‡</td>
</tr>
<tr>
<td>DHA (n-3)</td>
<td>2.3±0.2</td>
<td>3.3±0.4‡</td>
<td>2.0±0.4‡</td>
</tr>
<tr>
<td>AA/EPA ratio</td>
<td>20.9±2.2</td>
<td>2.4±0.2¶</td>
<td>12.0±2.1</td>
</tr>
</tbody>
</table>

*Mononuclear cells were obtained from five subjects receiving dietary supplementation of n-3 fatty acids. AA denotes arachidonic acid, EPA eicosapentaenoic acid, and DHA docosahexaenoic acid.

†Decreased from presupplement levels (P<0.04).
‡No significant change from presupplement levels.
§Increased from presupplement levels (P<0.03).
¶Decreased from presupplement levels (P<0.003).
||Decreased from presupplement levels (P<0.03).
Effect On Cytokines

Figure 2. Synthesis of IL-1β (Solid Bars), IL-1α (Hatched Bars), and Tumor Necrosis Factor (TNF; Open Bars) by Mononuclear Cells Stimulated with 1 ng of Endotoxin per Milliliter (Panel A) or 3 μg of Phytohemagglutinin per Milliliter (Panel B).
High-Dose Omega-3 Fatty Acids Are Both Anti-Inflammatory and Pro-resolution Mediators
Resolvins: Agents of Resolution

How Much Omega-3 Fats Do You Need For Resolution?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain Wellness</td>
<td>2.5 g/day</td>
</tr>
<tr>
<td>Treat Obesity, Diabetes, and CHD</td>
<td>5 g/day</td>
</tr>
<tr>
<td>Treat Chronic Pain</td>
<td>7.5 g/day</td>
</tr>
<tr>
<td>Treat Neurological Disease</td>
<td>&gt;10 g/day</td>
</tr>
</tbody>
</table>
Types of Fish Oil

- Fish
  - Contamination with PCBs and Hg
- Crude fish oil
  - Very high contamination with PCBs
- Health food grade
  - Still contaminated with PCBs
- Ultra-refined EPA/DHA Concentrates
  - “Weapons-grade” fish oil
  - Lower levels of PCBs
  - Can be used in high-dose, long-term applications
Polyphenols: Slowing Down the Aging Process
Different Effects At Different Levels

Low (0.5 g/day): Anti-oxidants
- Reduction of oxidative stress
- Reduction of oxidized LDL

Intermediate (1.0 g/day): Anti-inflammatory
- Activation of PPARγ
- Cardiovascular benefits

High (1.5 g/day): Anti-aging
- Activation of SIRT-1 and AMP kinase
- Cognitive improvement
Potential Sources of Polyphenols

• Vegetables: 0.1% of weight

• Fruits: 0.2% of weight

• Spices: 1% of weight

• Cocoa: 3% of weight

• Refined polyphenol extracts: Up to 40% of weight
Typical Sources Providing 1 gram of Polyphenols

• 1 kg of vegetables or 500 g of berries

• 12 glasses of red wine or 120 glasses of white wine

• 500 ml of extra virgin olive oil
Polyphenols Have To Be Absorbed To Increase Longevity

Polyphenol Pharmacokinetics

Bioavailability of cocoa flavanols from cocoa and chocolate

- 5 people
- 96 g chocolate or 35 g cocoa powder
- On average, 300 mg epicatechines consumed
AMP Kinase: The Enzyme of Life

- Calorie Restriction
- SIRT1
- Polyphenols
Actions of AMP kinase

Targets for AMPK.

Target proteins and processes activated by AMPK activation are shown in green, and those inhibited by AMPK activation are shown in red.
A New Powerful Message

• Diet can *turn on* inflammatory genes

• Diet can *turn off* inflammatory genes
Anti-Inflammatory Nutrition As Advanced Gene Therapy

- Polyphenols
- Omega-3 Fatty Acids
- Zone Diet

INFLAMMATORY GENES