Anti-Inflammatory Supplements
Why Anti-Inflammatory Supplements?
High-Dose Omega-3 Fatty Acids
High-dose Fish Oil Means Exactly That
Phases Of Inflammation

Initiating Event

Pro-inflammatory Initiation Response
Cellular Destruction

Anti-Inflammatory Resolution Response
Cellular Rejuvenation
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
# AA/EPA Ratio Indicates Extent Of Cellular Inflammation

<table>
<thead>
<tr>
<th>AA/EPA Ratio</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>Potential bleeding increase</td>
</tr>
<tr>
<td>1-3</td>
<td>Ideal for resolution of inflammation</td>
</tr>
<tr>
<td>3-6</td>
<td>Good for reducing the initiation of cellular inflation</td>
</tr>
<tr>
<td>6-10</td>
<td>Beginning to move out of range</td>
</tr>
<tr>
<td>10-15</td>
<td>Cellular inflammation beginning to rise</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>Cellular inflammation is systemic</td>
</tr>
</tbody>
</table>
Changes In The AA/EPA Ratio In Italians

First Use of High-Dose Fish Oil To Lower The AA/EPA Ratio

The New England Journal of Medicine

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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 Lonemann, M.D., Jos W. M. van der Meer, M.D., Joseph G. Cannon, Ph.D., Tina S. Rogers, Ph.D., Mark S. Klemperner, M.D., Peter C. Weber, M.D., Ernst J. Schaefer, M.D., Sheldon M. Wolff, M.D., and Charles A. Dinarello, M.D.
## Effect On Fatty Acid Composition

### 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></td>
<td></td>
<td>10 Weeks</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).
# How Much Omega-3 Fats Do You Need For Resolution?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></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>
Why Not Just Eat More Fish?

- Lobster: 6 lbs. per day
- Tuna: 2 lbs. per day
- Salmon: 5 oz. per day
History of Fish Oil Production

- B.C. Garum
- 1780 Cod liver oil fermentation
- 1850 Heating of cod livers in vats
- 1980 Use of fish body oil
- 1990 Fish oil concentrates
- 2000 “Weapons-grade” fish oil
# Requirements for Weapons-Grade Fish Oil

<table>
<thead>
<tr>
<th></th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Long-Chain Omega-3</td>
<td>&gt; 60%</td>
</tr>
<tr>
<td>Dioxins</td>
<td>&lt; 1 ppt</td>
</tr>
<tr>
<td>Mercury</td>
<td>&lt; 10 ppb</td>
</tr>
<tr>
<td>PCB’s</td>
<td>&lt; 5 ppb</td>
</tr>
</tbody>
</table>
What Are PCBs?

- Insulators for electronic transformers
- First production in 1930
- Peaked in 1960
- Banned since 1977
- Neurotoxins, carcinogens, endocrine disruptors
Fish Oil Buyers Beware

• *Consumers Report* (January 2012)

• High in PCBs (1 or 2 capsules >90 ng)
  – CVS
  – Sundown
  – Nature’s Bounty
  – GNC

• Spoilage (Totox >26)
  – Nordic Naturals
PCBs Increase CHD

• 58% increase in CHD at 286 ng/day compared to 100 ng/day

• Overwhelms protective effects of EPA and DHA on CHD

New York Times:
Fish Oil Supplements Don’t Work
Rising The Dead And Curing The Blind:

Clinical Uses of High-Dose Fish Oil To Treat Neurological Disease
Raising The Dead:

Treating Severe Brain Trauma
Miracle Or High-Dose Fish Oil?
# Results To Date

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Location</th>
<th>Occupation/Event</th>
<th>Condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 M</td>
<td>M</td>
<td>WV</td>
<td>Coal miner</td>
<td>CO</td>
<td>Coma</td>
</tr>
<tr>
<td>40 M</td>
<td>M</td>
<td>TX</td>
<td>Firefighter</td>
<td>CO</td>
<td>Coma</td>
</tr>
<tr>
<td>12 M</td>
<td>M</td>
<td>NY</td>
<td>Baseball player</td>
<td>Commotio cordis</td>
<td>Coma Cardiac arrest</td>
</tr>
<tr>
<td>40 M</td>
<td>M</td>
<td>KY</td>
<td>Firefighter</td>
<td>CO</td>
<td>Coma</td>
</tr>
<tr>
<td>29 M</td>
<td>M</td>
<td>WV</td>
<td>Logger</td>
<td>CHI</td>
<td>Coma</td>
</tr>
<tr>
<td>43 F</td>
<td>F</td>
<td>NY</td>
<td>Childbirth</td>
<td>Anoxia</td>
<td>Coma</td>
</tr>
<tr>
<td>55 F</td>
<td>F</td>
<td>FL</td>
<td>Stroke</td>
<td>Ischemia</td>
<td>Coma</td>
</tr>
</tbody>
</table>
Curing The Blind:

Reversing Age-Related Macular Degeneration (AMD)
Normal Vision
What The AMD Patient Sees
Clinical Outcomes Are Easy To Measure
Vision Improvement Depends On The Final AA/EPA Ratio

Letters Improvement

Final AA/EPA Ratio
New York Times: 
Fish Oil Supplements Don’t Work

Supplements Don’t Fight Cognitive Decline, N.I.H. Study Says
By RONI CARYN RABIN     AUGUST 31, 2015 3:15 PM     57 Comments
Is Potential Bleeding With High-Dose Omega-3 Fatty Acids To Increase Resolution A Problem?
### No Bleeding Increase In Six-Month Dose Response Toxicity Study

<table>
<thead>
<tr>
<th>Dose (g EPA and DHA per day)</th>
<th>Final AA/EPA Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>4.7</td>
</tr>
<tr>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>5.0</td>
<td>1.3</td>
</tr>
<tr>
<td>7.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>

3.5 Year Cardiovascular Intervention Study

• 18,000 patients (JELIS)
  – Statins plus EPA or olive oil
• Starting AA/EPA ratio = 1.6
• Ending AA/EPA ratio 0.8
• 20% reduction in cardiovascular events
• Slight increase in bleeding

Other Studies

  – 14 gram fish oil per day for one week

  – No bleeding at 4 grams per day + 300 mg aspirin

  – No relation of bleeding with omega-3 levels
Is Bleeding A Problem?

• Not supported by the data
  – Epidemiological studies
  – Intervention studies
    • With or without anti-coagulants

• Maintaining AA/EPA ratio > 1 prevents potential bleeding
High-Dose Polyphenols:

The Color of Anti-Inflammation Nutrition
Polyphenols

- Provide plants with color
- Little known before 1995
- 8,000 known polyphenols
Polyphenols Modify Gene Transcription

• Anti-oxidants
  – Activation of Nrf2

• Anti-inflammatory
  – Inhibition of NF-κB

• Anti-aging
  – Activation of SIRT-1
Anti-Aging Actions

• Activation of AMP kinase

• Master switch for metabolism

• Mechanism of calorie restriction
AMP Kinase: The Enzyme of Life

- Calorie Restriction
- SIRT1
- Polyphenols

AMP Kinase
Actions of AMP kinase

Target proteins and processes activated by AMPK activation are shown in green, and those inhibited by AMPK activation are shown in red.
Problems with Polyphenols

• Low concentration
  – 0.2% in fruits
  – 0.1% in vegetables

• Poor absorption
  – 2-20%

• Limited lifetime in the blood
  – Half life is about 2 hours
## How Many Polyphenols Do You Need?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce oxidation</td>
<td>0.5 g/day</td>
</tr>
<tr>
<td>Reduce cellular inflammation</td>
<td>1 g/day</td>
</tr>
<tr>
<td>Reduce the rate of aging</td>
<td>1.5 g/day</td>
</tr>
</tbody>
</table>
Polyphenol Purification

- Whole plant
- Juice
- Powder
- Alcoholic extract
- Chromatographic extract
## Polyphenol Concentrations

<table>
<thead>
<tr>
<th>Polyphenol Source</th>
<th>Polyphenol content (g)/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyphenol Extracts</td>
<td>40-50</td>
</tr>
<tr>
<td>Cocoa powder</td>
<td>5.6</td>
</tr>
<tr>
<td>Blueberries</td>
<td>0.5</td>
</tr>
<tr>
<td>Red wine</td>
<td>0.09</td>
</tr>
<tr>
<td>Spinach</td>
<td>0.07</td>
</tr>
<tr>
<td>Extra virgin olive oil</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Refined Is Sometimes Better Than Natural With Cocoa
Cadmium Contamination

• Single serving violates CA Prop 65 for cadmium intake per day

• Makers of dark chocolate bars are being sued in CA for high cadmium levels

• New EFSA standards for cocoa and chocolate products in 2019
Thinking Faster with Purified Cocoa Polyphenols

- Increased activity in hippocampus and improved cognition in 3 months

- 25% increase in cognitive speed in 3 months
Is There A “Best Of The Best” For Polyphenols?
Wild Maqui Berry
Domestication Of Wild Maqui Berries Is A Dirty Business
Indiana Jones Without His Bullwhip In Patagonia
Polyphenols Have To Be Absorbed To Increase Longevity

FIGURE 1 Kaplan-Meier plots of all-cause mortality for 12 y of follow-up in the InCHIANTI study by tertiles of TUPs (log-rank = 29.44; \( P < 0.001 \) by log-rank test between extreme tertiles) (A) and TDPs (log-rank = 3.30; \( P = 0.19 \)) (B). GAE, gallic acid equivalent; InCHIANTI, Invecchiare in Chianti; TDP, total dietary polyphenol; TUP, total urinary polyphenol.

Absorption Depends on Water Solubility
Maqui Activation Of Nrf2

Maq 25 µM

(Nrf2 D.U.)

Rev 25µM

(Nrf2 D.U.)

Maq 25µM

0 1h 3h 6h 12h
0 1h 3h 6h 12h
0 1h 3h 6h 12h
Maqui Reduction Of Cytokines.

- Control
- LPS
- LPS + Res
- LPS + Rev
- LPS + Maq

IL-1β (pg/ml)

IL-6 (pg/ml)

TNF-α (pg/ml)
Effect Of Maqui Extracts On Oxidized LDL

Effect Of Maqui Extracts On Isoprostanes

Reaching The Zone

• Zone Diet
  – Promotes hormonal balance
  – Reduces insulin resistance
  – Increases satiety

• Omega-3 fatty acids
  – Decreases initiation of cellular inflammation
  – Increases resolution at therapeutic levels

• Polyphenols
  – Anti-oxidant at low levels
  – Anti-inflammatory at moderate levels
  – Activates AMP kinase at therapeutic levels
Summary

• Zone Diet remains your foundation for anti-inflammatory nutrition
• Supplements can make the Zone Diet work more effectively
• Supplements have to be taken at a therapeutic level to have an effect
• Purity and potency count
21st Century Anti-Inflammatory Nutrition

• Reduction of cellular inflammation
• Hormonal control
• Diet will be the primary drug
• High-dose fish oil and high-dose polyphenols will be key supplements
• Return to Hippocrates
  – “Let food be your medicine and let medicine be your food”