The Resolution Zone

Causes of Inflammation

- Infection
- Injury
- Diet
- Aging

Inflammation Does Not Burn Out On Its Own

Resolution Is An Active Process

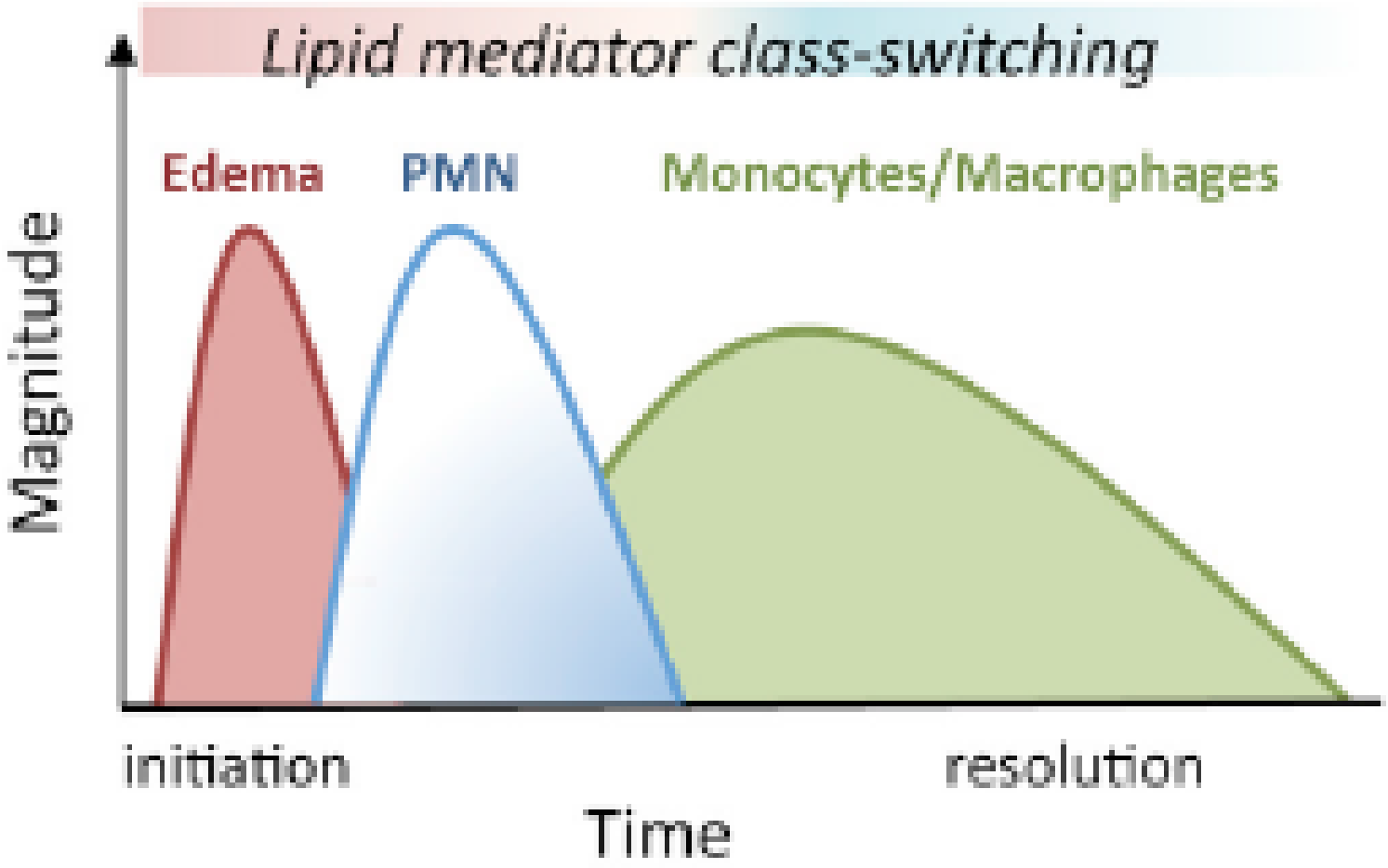
- Final journey back to inflammatory equilibrium
- Does not cause immunosuppression as do steroids

Cutting-Edge Science Today Is An Old Concept

- First used in 11th century in the Canon of Medicine

- Taken 1,000 years to understand the science of resolution

Time Course of Inflammation

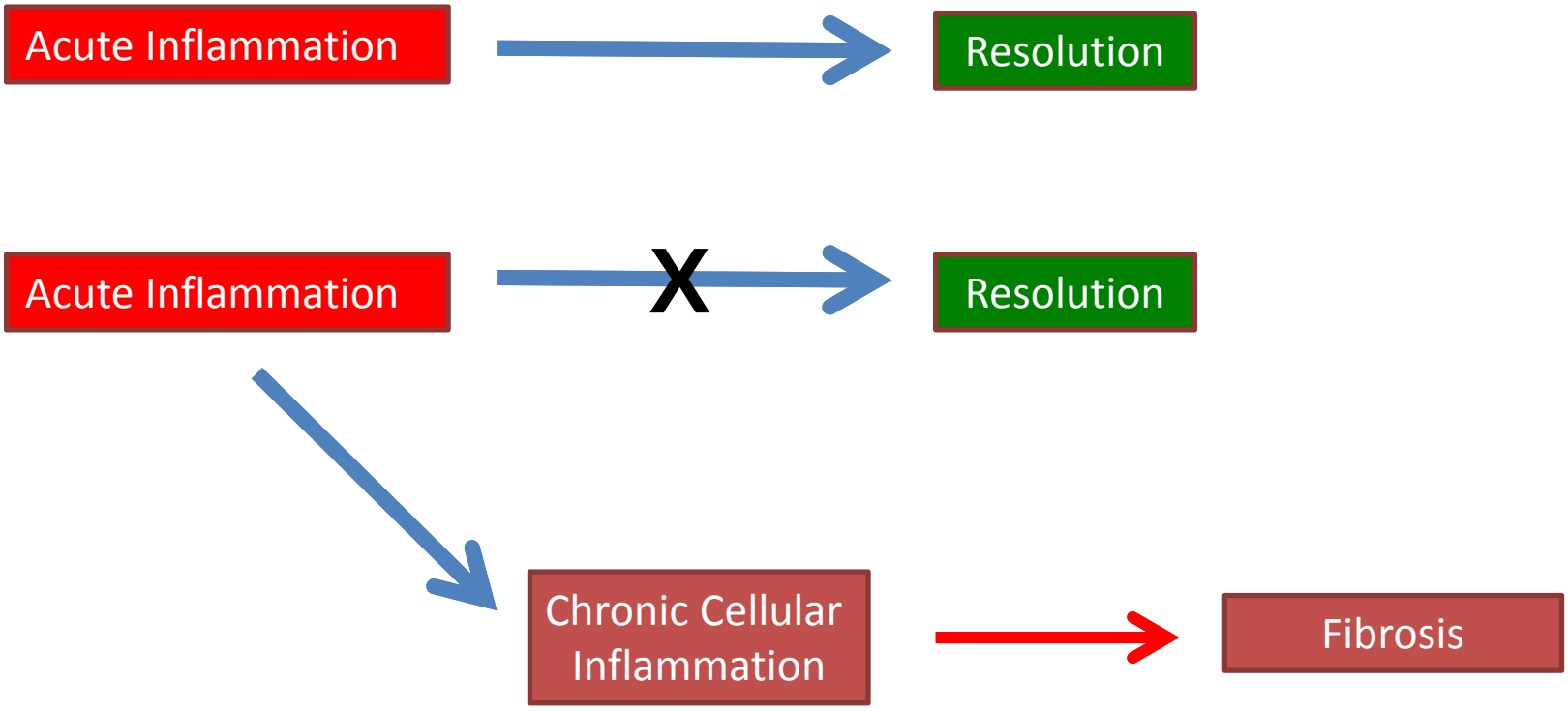


Spite et al Cell Metabol 19:21 (2014)

Resolution Terminology

- *Anti-inflammation*
  - Leukotrienes attract neutrophils
  - Acting as molecular flares
  - Steroids are most powerful anti-leukotriene drugs
- *Pro-resolution*
  - Increased clearing of the macrophages
  - Macrophage switch from M1 to M2
  - Reducing cytokine formation
  - Final removal debris

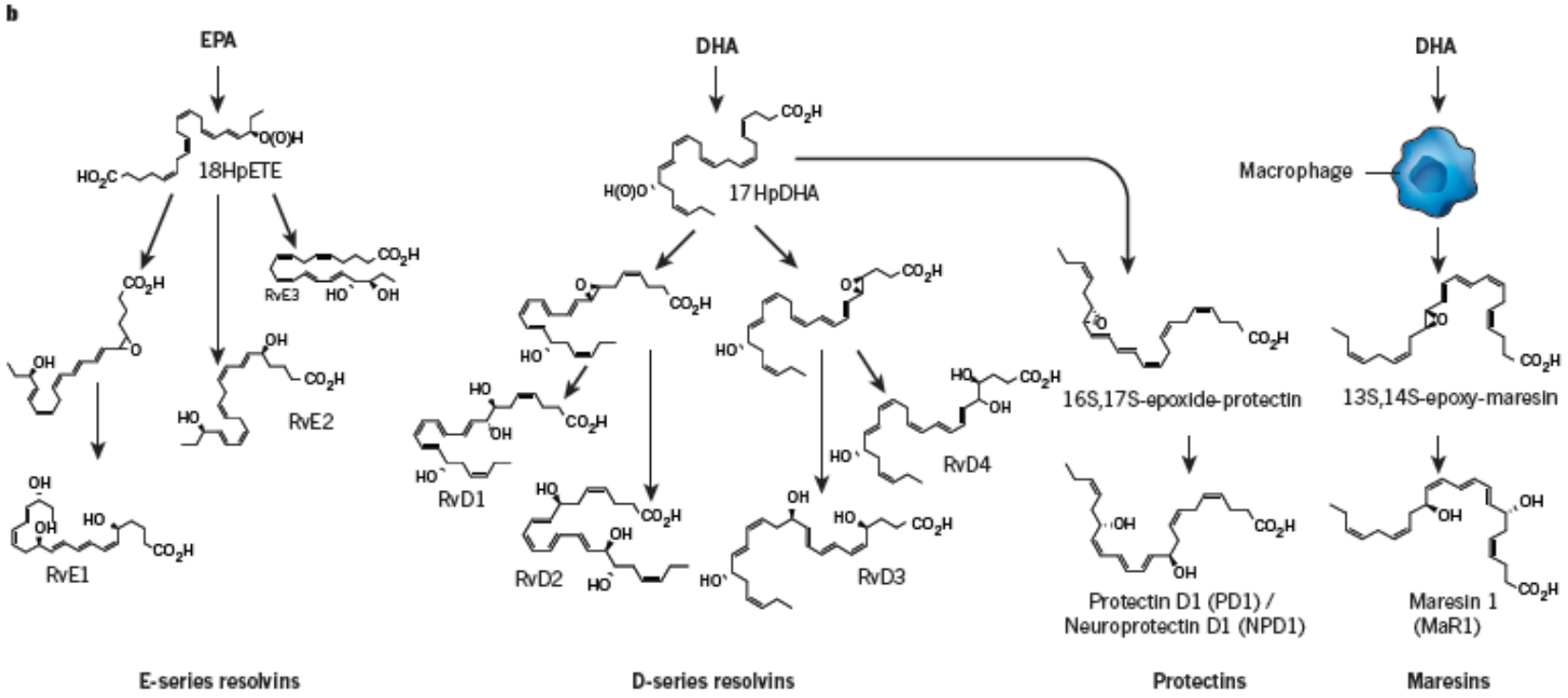
What Happens When Inflammation Is Not Resolved?



Chronic Diseases Characterized By Fibrosis

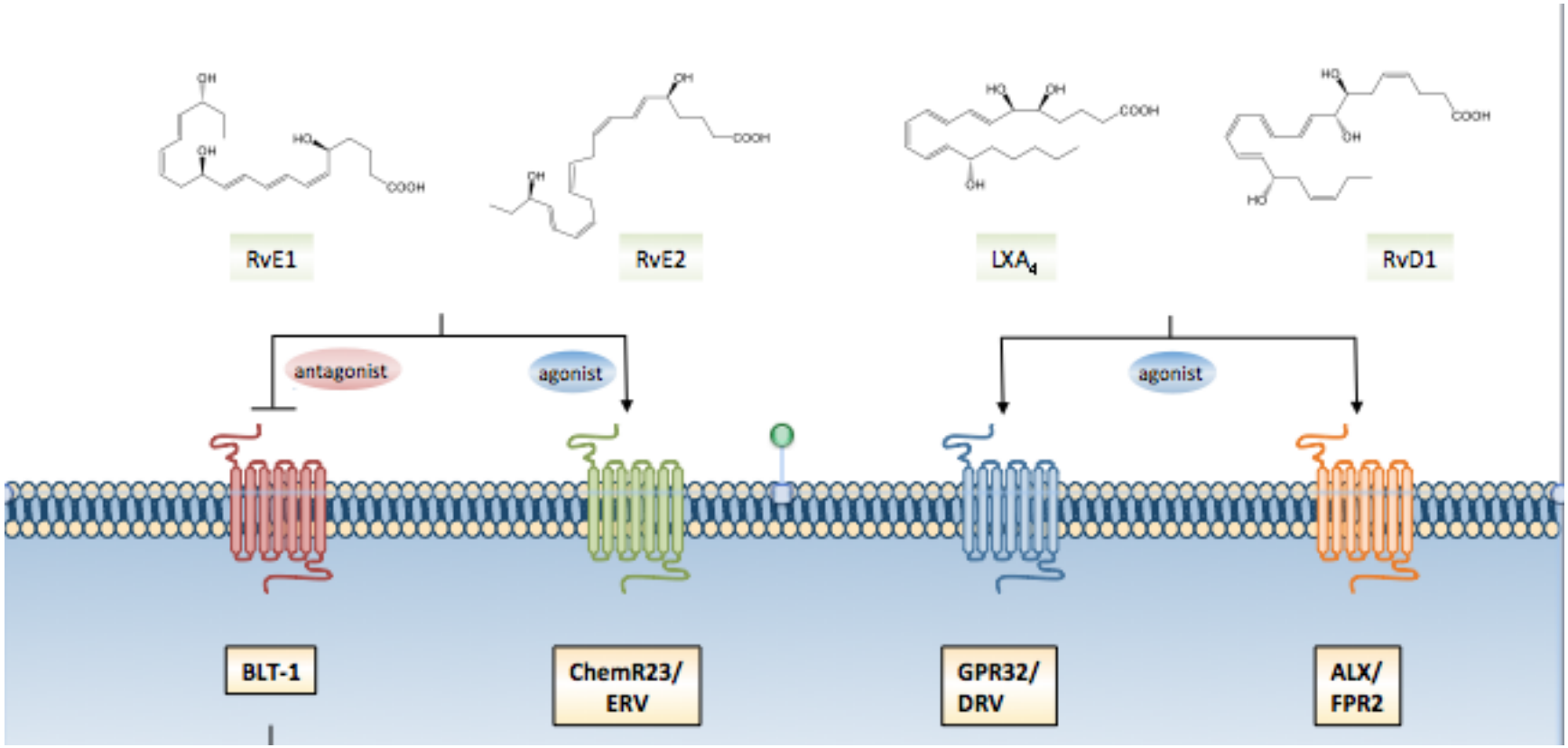
- Heart disease
- Kidney disease
- Lung disease
- Liver disease

Resolvins: Agents of Resolution



Serhan Nature 510:92 (2014)

Receptors for Resolvins



Spite et al. Cell Metabolism 19:21 (2014)

Anti-Inflammatory Drugs Can Also Be Anti-Resolution Drugs

- PGE2 and PGD2 required to initiate resolution
- Aspirin can either enhance or inhibit resolution
  - Low-dose enhances
  - High-dose inhibits

Resolvin Facts

- 1,000 times more powerful than EPA and DHA
- Million times more expensive
- Not immunosuppressive
- Must be injected
- Short life time in the body
- Regulated by microRNA
- Cause tissue regeneration

Resolvins and CHD

- Inhibit adhesion formation
  - 30-50% vascular scarring as consequence of surgery
- Resolvins decrease MMP activity
  - Collagen cap stability increases

Resolvins and Alzheimer's

- Can be viewed as auto-immune disorder
- First indication of plaques appears in retina

Resolvins and Cancer

- Most tumors are dormant
- Cancer as loss of resolution
- Tumor debris from radiation and chemotherapy stimulates cancer growth
  - Awakens dormant tumors
  - Chemotherapy doesn't work on these debris-activated tumors

FAT-1 Transgenetic Mice

Fat-1 Mice Studies

- Obesity
  - Li et al. Mol Endocrinol 28:1316 (2014)
- Fatty liver
  - Kim et al Biochem Pharmcol 84: 1359 (2012)
- Diabetes
  - Smith et al. Appl Physiol Nutr Metab 35: 699 (2010)
  - Wei et al. Diabetes 59: 471 (2010)
  - Bellenger et al. Diabetes 60: 1090 (2011)
  - Rommanatto et al. Biochim Biophys Acta 1842: 186 (2014)

Fat-1 Mice Studies

- Osteoporosis
  - Rahman et al. J Cell Mol Med 13:1833 (2009)
- Ocular
  - Connor et al. Nature Med 7: 868 (2007)
- Alzheimer's
  - Lebbadi et al. J Alzheimers Dis 20: 854 (2011)
- Cancer
  - Lu et al. Mol Cancer Ther 7: 3203 (2008)
  - Taguchi et al. PLoS One 9:e89605

Fat-1 Mice Studies

- Heart Disease
  - Wan et al. Arterioscler Thromb Vasc Biol 30: 2487 (2010)
- Colitis
  - Monk et al. J Nutr 142: 117 (2012)
- Asthma
  - Bilai et al. Biochim Biophys Acta 1812: 1164 (2011)
- Aging
  - Rahman et al. Oxid Med Cell 2: 307 (2009)

You Can Achieve Same Levels of Omega-3 Fatty Acids in Fat-1 Mice With High-dose Fish Oil

Auto-Immune Diseases That Respond to High-Dose Fish Oil

- Rheumatoid arthritis
- Lupus
- Type 1 Diabetes
- Multiple Sclerosis

Rheumatoid Arthritis

- *Royal Transactions of the Philosophical Society* (1786)
  - About 15 grams EPA and DHA per day
- Kremer. *Del Med J* 60:679 (1988)
- Kremer et al. *Arthritis and Rheum* 33:810 (1990)
  - 3 to 6 grams EPA and DHA per day
- Lee et al. *Arch Med Res* 43:356 (2012)
  - > 2.7 grams of EPA and DHA is effective

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

The New England
Journal of Medicine

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.

Effect On Fatty Acid Composition

Table 1. Fatty Acid Composition of Mononuclear-Cell Membranes as a Percentage of Total Fatty Acid Content.*

Fatty Acid	Before n−3 Supplement	After n−3 Supplement	Time after End of n−3 Supplement	
			10 weeks	20 weeks
		mean percentage ±SEM		
AA (n−6)	13.8±1.3	8.6±0.7†	9.5±1.8‡	13.8±2.6‡
EPA (n−3)	0.7±0.1	3.8±0.7§	1.0±0.3‡	0.6±0.1‡
DHA (n−3)	2.3±0.2	3.3±0.4‡	2.0±0.4‡	2.5±0.7‡
AA/EPA ratio	20.9±2.2	2.4±0.2¶	12.0±2.1‖	23.9±4.3‡

*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

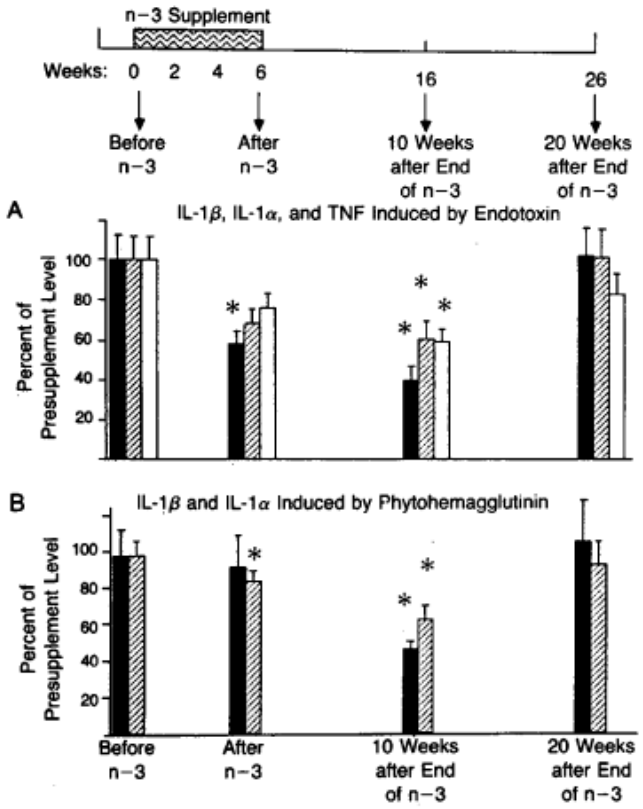


Figure 2. Synthesis of IL-1β (Solid Bars), IL-1α (Hatched Bars), and Tumor Necrosis Factor (TNF; Open Bars) by Mononuclear Cells Stimulated with 1 ng of Endotoxin per Milliliter (Panel A) or 3 μg of Phytohemagglutinin per Milliliter (Panel B).

2012 Sales of Injectable Drugs To Reduce TNF

- Humira
  - $9.3 B
- Enbrel
  - $7.8 B
- Remicade
  - $6.8 B

These TNF-Reduction Drugs Are 3 Of The Top 10 Selling Drugs Of All-Time

Lupus

- Westberg and Tarkowski. *Scan J Rheum* 19:137 (1990)
  - Short-term benefit
- Wright et al. *Ann Rheum Dis* 67:841 (2008)
  - 3 g EPA and DHA per day
- Halade et al. *Exp Bio Med* 238:610 (2013)
  - Strong dose-response (1 vs. 4%) in NZBxNZF mice

Type 1 Diabetes

- Stene et al. *Am J Clin Nutr* 78:1128 (2003)
  - 1.7 grams of EPA and DHA per day for first year 26% decrease in type 1 in case-controlled studies
- Norris et al. *JAMA* 298:1420 (2007)
  - 27% decrease of appearance of anti-bodies or diabetes in those with higher omega-3 in RBC
- Mayer-Davis et al. *Diabetes Care* 36:1842 (2013)
  - C-peptide preservation in recently diagnosed Type 1 with higher levels of EPA and DHA

Multiple Sclerosis

	Start	2 Year
AA/EPA	6	1.5
Disability Status	2.2	1.6*

* $p < 0.005$

Nordvik et al Acta Neurol Scand 102:143 (2000)

Are We Missing The Real Cause Of Chronic Inflammation?

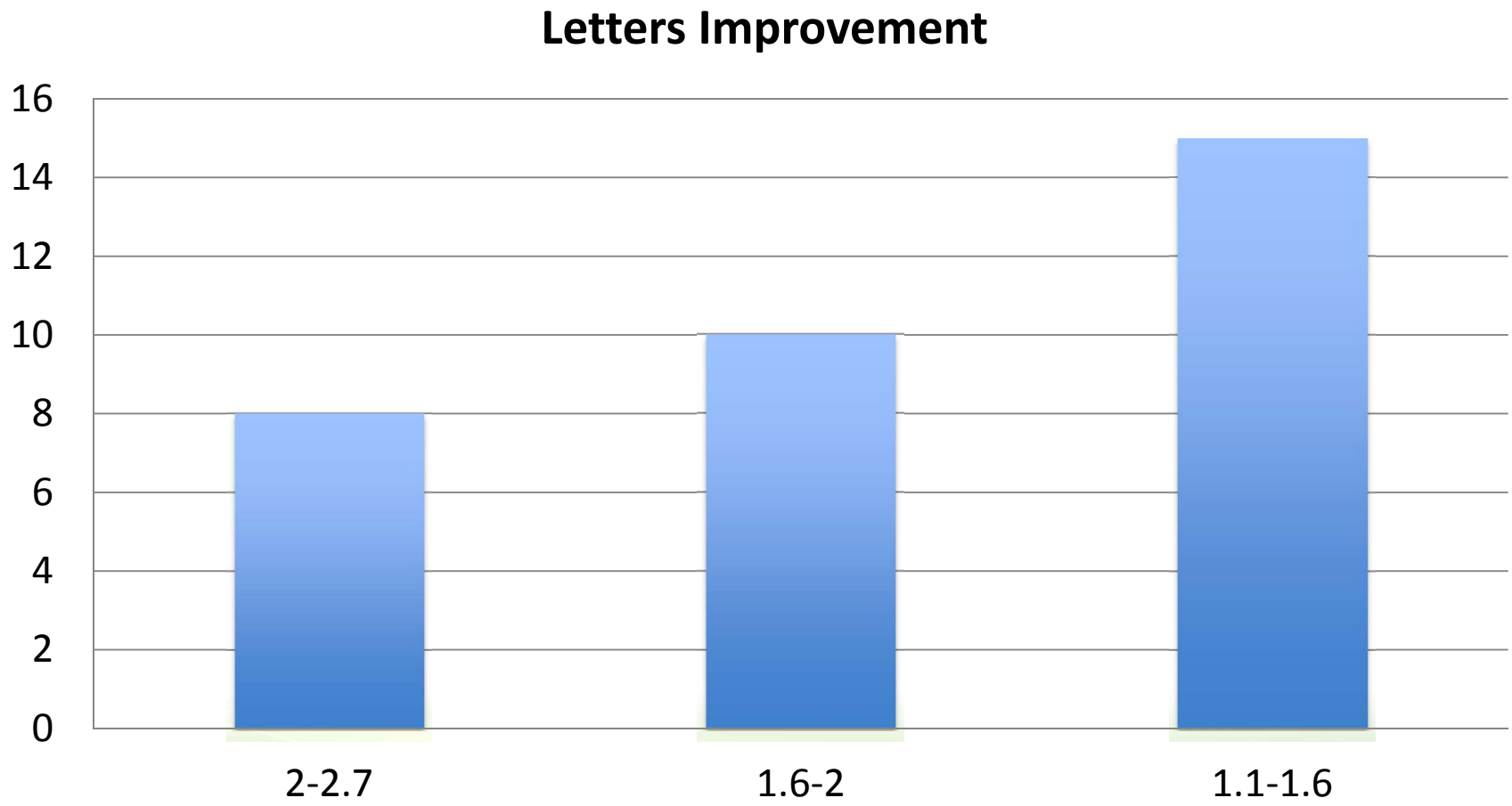
Conditions That May Be Due to Lack of Resolution

- Obesity
- Diabetes
- Cardiovascular disease
- Auto-immune disease
- COPD
- Liver failure
- Kidney failure
- Asthma
- Ocular
- Cancer
- Alzheimer's
- Aging

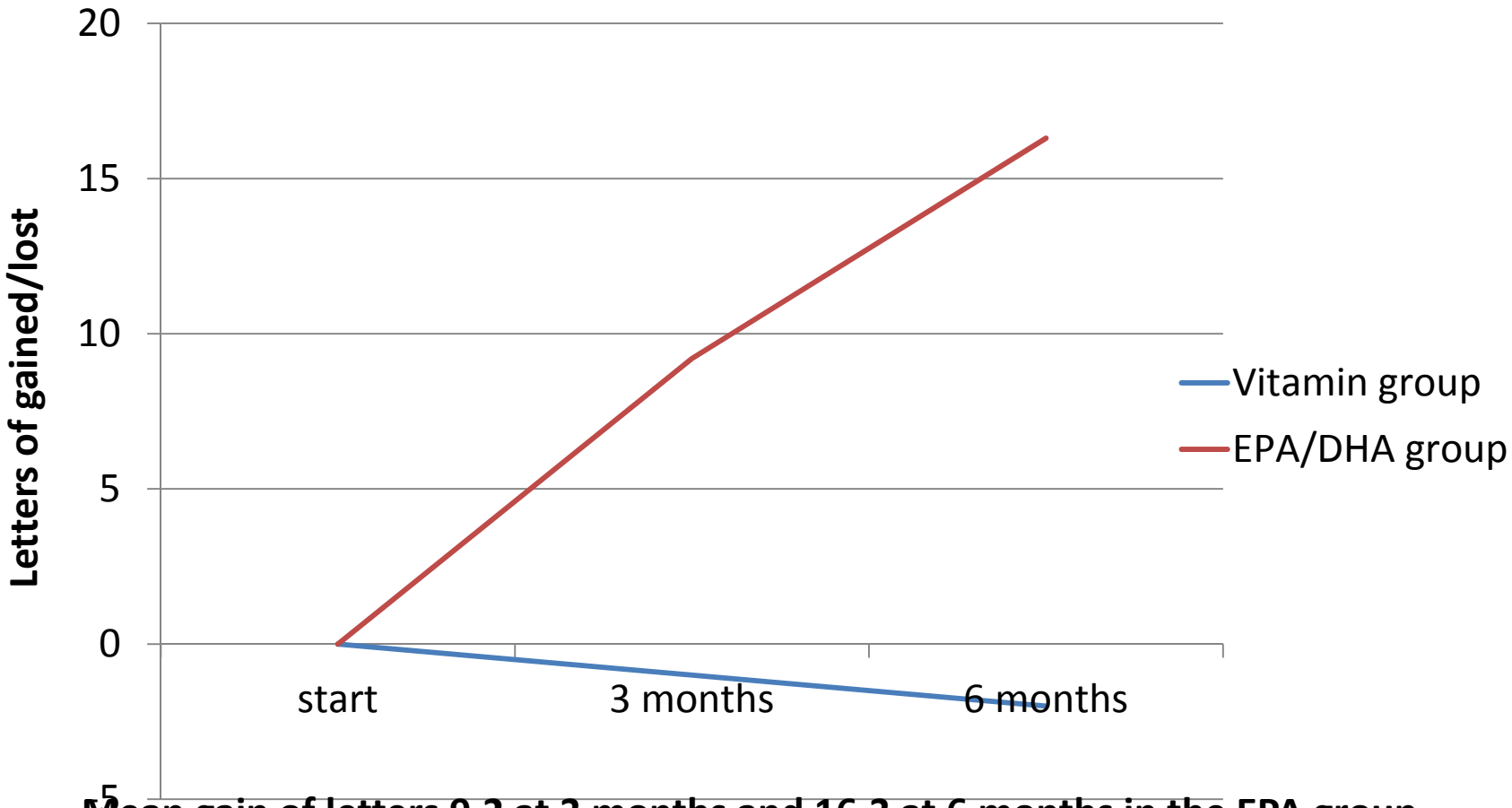
AA/EPA Ratio Can Be A Surrogate Marker For Resolvins

Subject	AA/EPA	% EPA	%DHA	RvD1 (pg/ml)	Low-dose Aspirin
1	1.5	4.8	4.3	44	No
2	2.1	5.1	5.4	74	Yes
3	2.3	3.9	5.4	110	Yes

Sight Improvement Depends on Final AA/EPA Ratio



Dry AMD Results-Moderate Starting Vision Loss



Mean gain of letters 9.2 at 3 months and 16.3 at 6 months in the EPA group

Mean lost of letters 2 at 6 months in the vitamin group

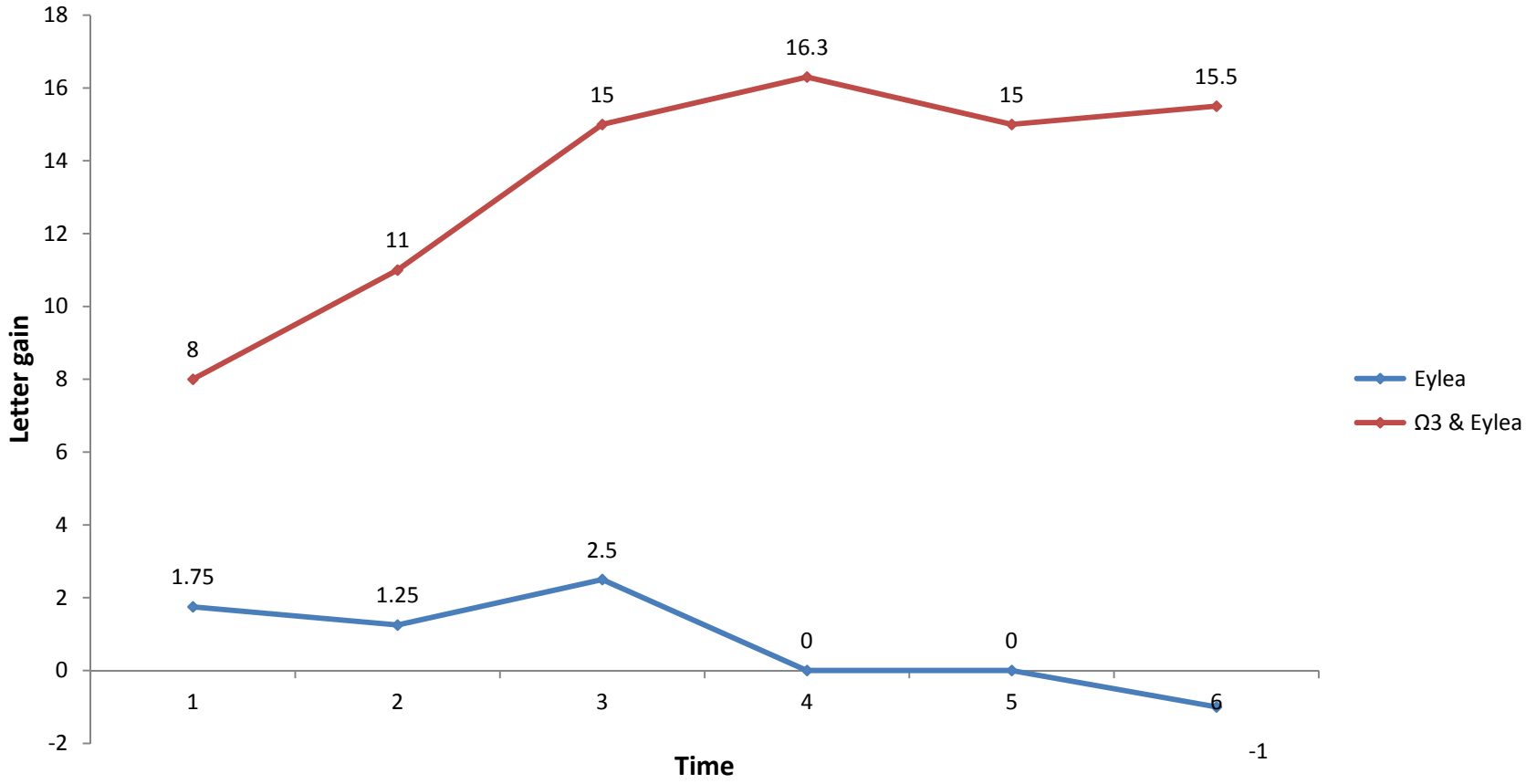
Vision improved from 31% to 44% at 3 months to 65% at 6 months in the EPA group

And the mean AA/EPA ratio was 1.6

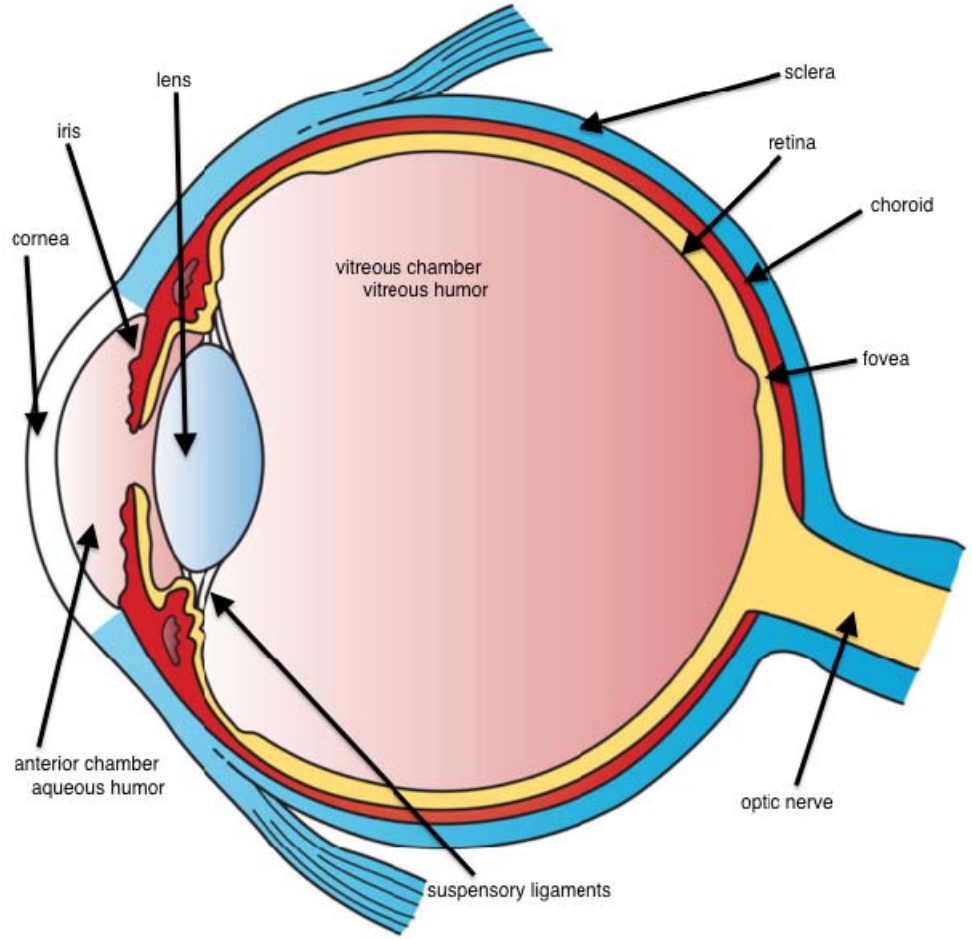
Dry AMD Results-Severe Starting Vision Loss

Time (months)	Vision (% normal)
Start	4
1.5	10
3	16
4.5	20
6	25

Wet AMD Results



Optic Nerve

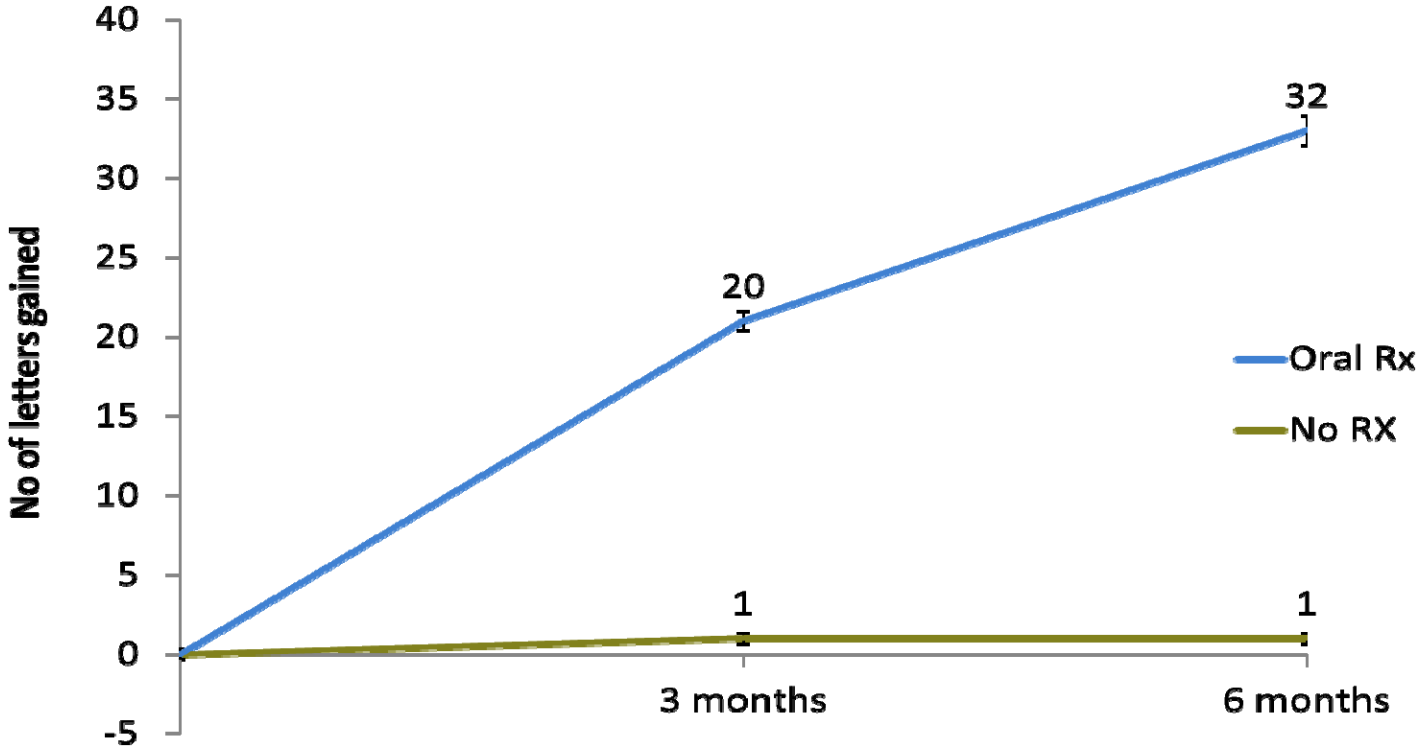

lens
sclera
iris
retina
choroid
cornea
vitreous chamber
vitreous humor
fovea
anterior chamber
aqueous humor
optic nerve
suspensory ligaments

Optical Nerve Atrophy

- Causes
  - Glaucoma
  - Neuritis
  - Multiple sclerosis
- Vision cannot be restored once optic nerve is damaged

Optic Nerve Atrophy Results

- Mean letters gained



Mean VA 18% 42% 74%

Mean vision improved from 18% to 42% at 3 months and to 74% at 6 months in the oral group

Telomeres

- Can be increased by high-dose omega-3 fatty acids
- AA/EPA ratio is best indication of increasing telomere length

Summary

- Resolvins are key to tissue regeneration
- Anti-aging medicine can be best understood as resolution pharmacology
- Without adequate levels of omega-3 fatty acids, resolvins can’t be made