

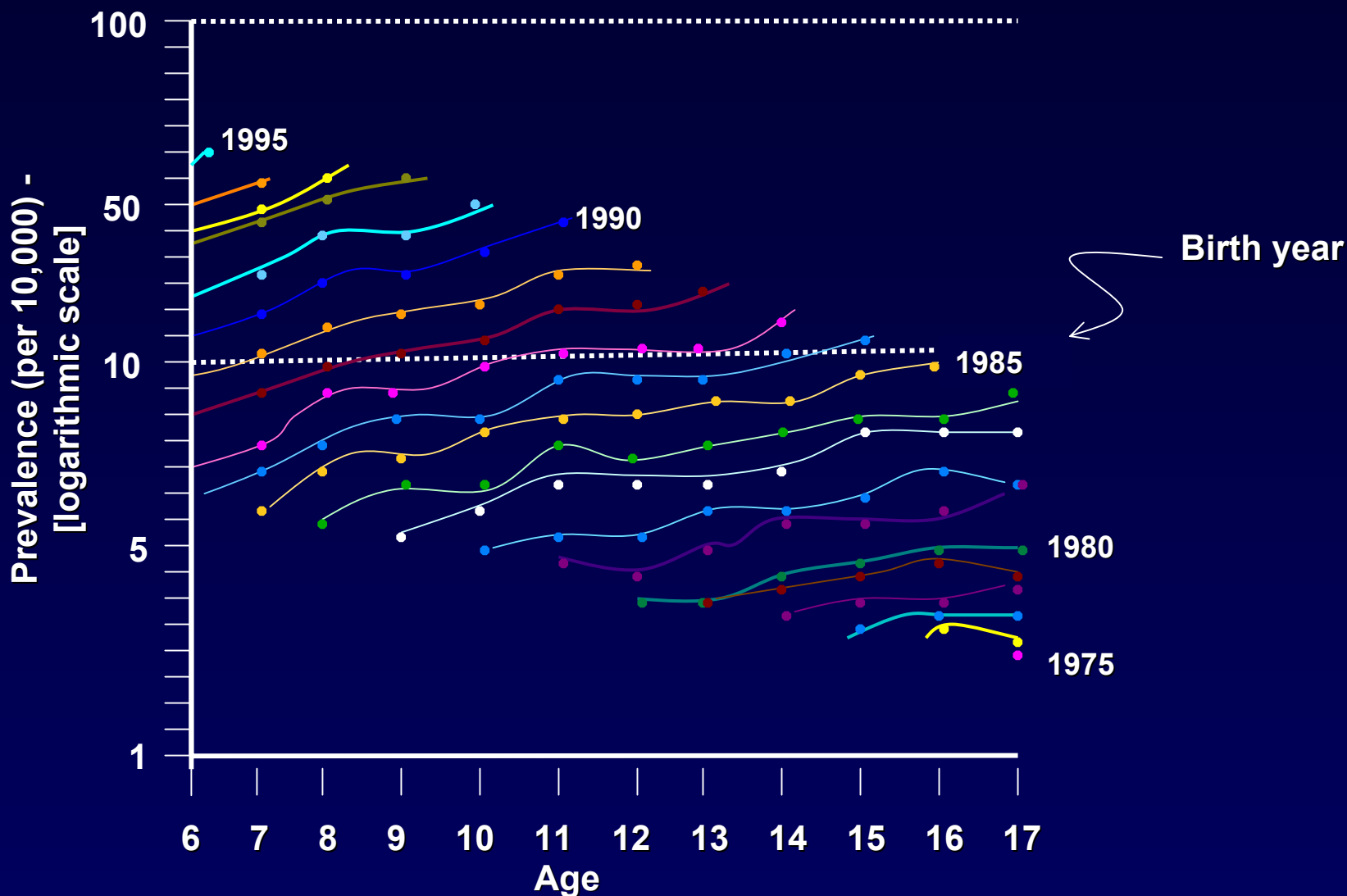
Omega-3 Fatty Acids in Autism and other Neuropsychiatric Disorders

Andrew L. Stoll, M.D. © 2000-05

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The Prevalence of Autism Increased Dramatically during the Last Quarter Century

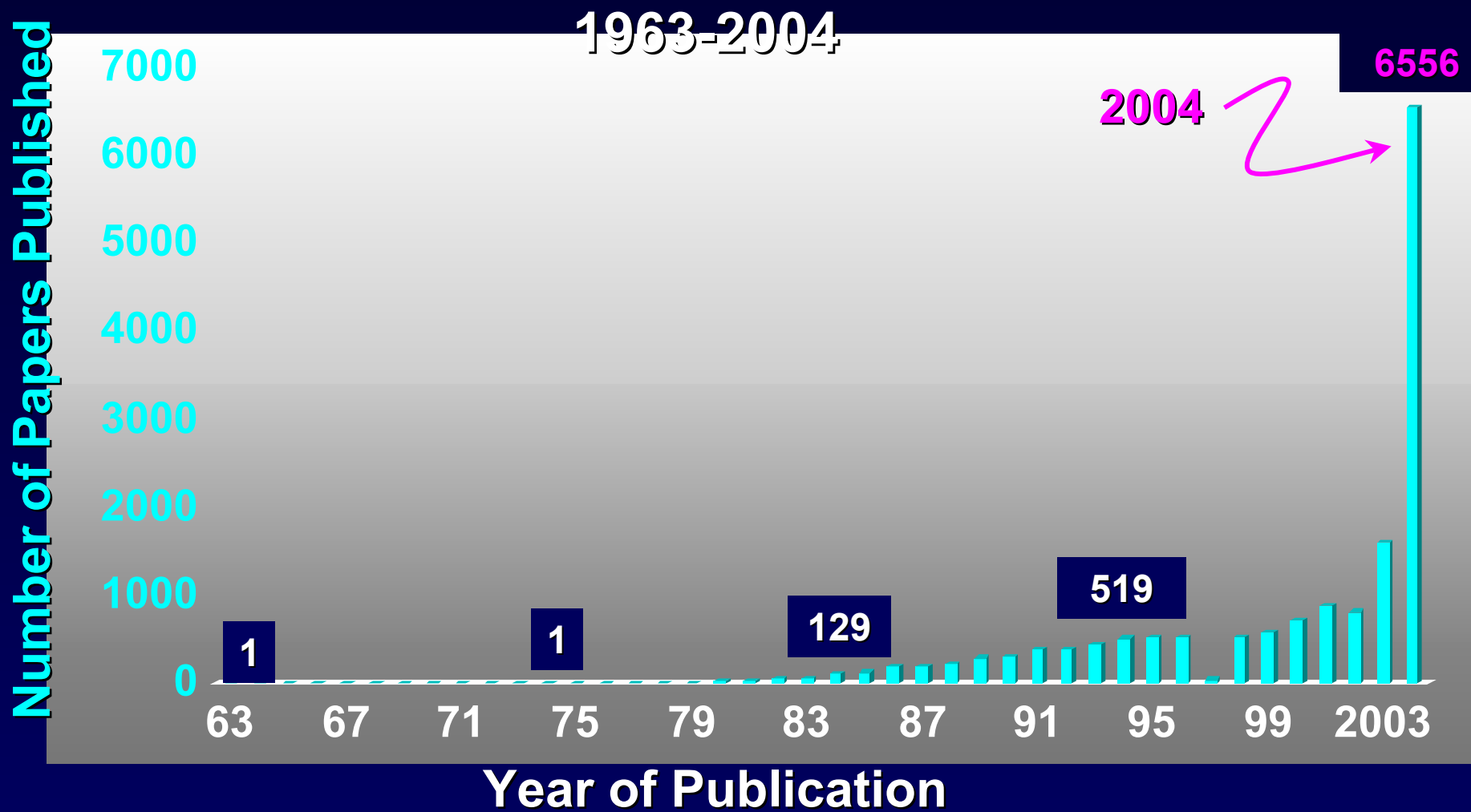




A traditional diet in the Arctic regions of North America provides 15-19 grams/day of EPA + DHA (omega-3 fatty acids).

In the U.S. < 1 gram/day of omega-3 fatty acids are consumed ₃

Number of Scientific/Clinical Papers¹ on Omega-3 Fatty Acids Published per Year



¹Only research papers on Medline are reported.

Nutritional Deficiencies in Developed, Western Nations

- The modern Western diet is profoundly depleted of essential fatty acids (omega-3 >> omega-6).¹
 - A recent study suggests that the modern Western diet is also profoundly depleted of essential trace minerals²
 - Compared the mineral content of 40 different fruits and vegetables from the UK between 1930s and 1980s
 - Marked reductions in Ca⁺⁺, Mg⁺⁺, Cu⁺⁺, Na⁺ in vegetables
 - Marked reductions in Mg⁺⁺, Fe⁺⁺⁺, Cu⁺⁺, K⁺ in fruits
-

¹Stoll AL. *The Omega-3 Connection*. 2001. Simon and Schuster.

²Mayer A-M. Historical changes in the mineral content of fruits and vegetables. *British Food Journal* 1997;99:207-211.

OMEGA-3 FATTY ACIDS IN BIPOLAR DISORDER: Study Design

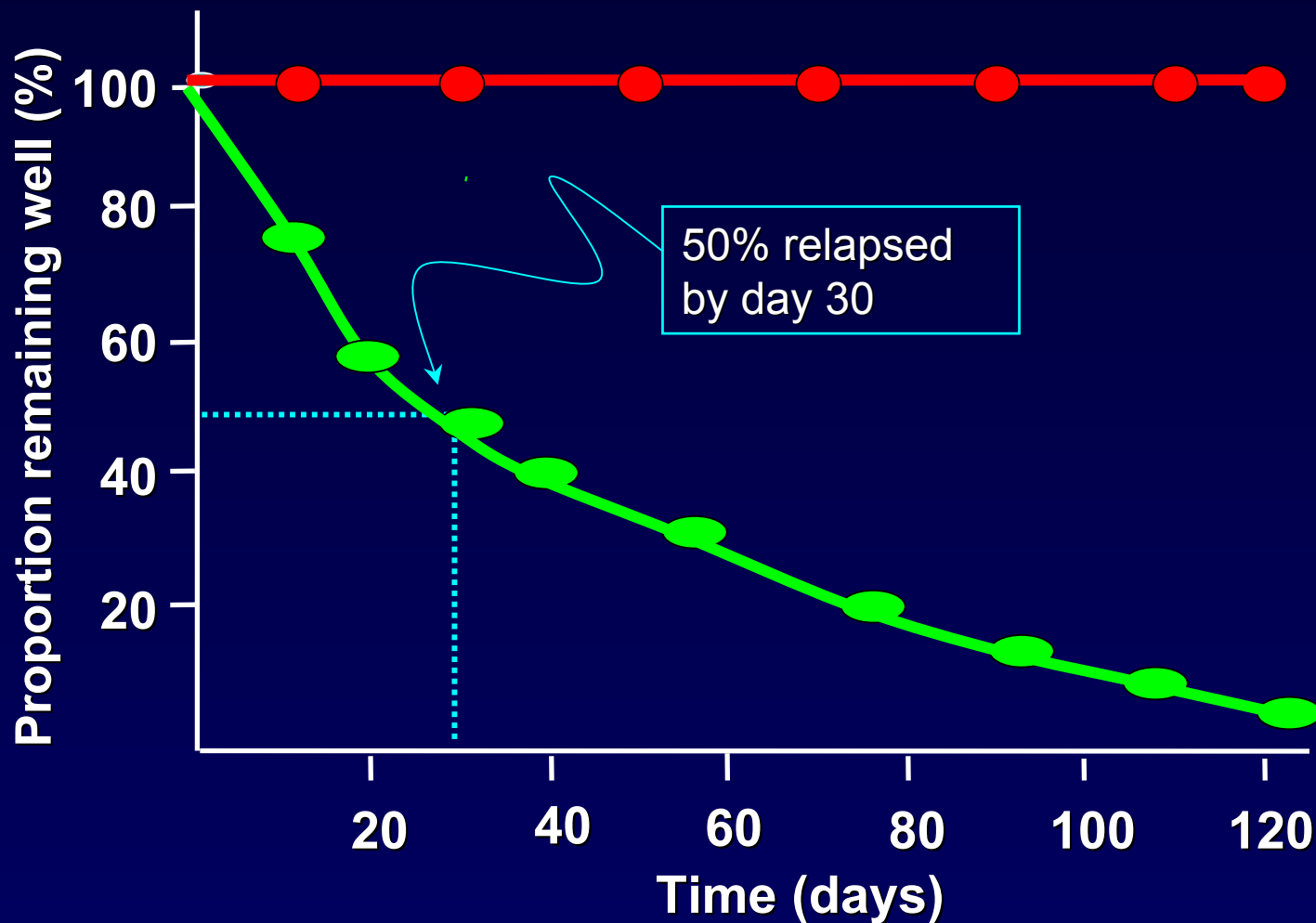
- Double-blind placebo-controlled 4-month trial
- N = 30 bipolar outpatients (mostly Type I)
- All subjects had mania/hypomania within past 1 year
- Randomized to 9.6 g/day omega-3 vs. placebo (olive oil)
- Concomitant meds left unchanged
- 8 entered study on no other drug therapy
- Main outcome measures:

Recurrence or lack of response
SCID Status at end of trial

Investigators

- Andrew L. Stoll, M.D.
Harvard Medical School
- Emanuel Severus, M.D., Ph.D.
Free University of Berlin
- Lauren Marangell, M.D.
Baylor College of Medicine
- Marlene Freeman, M.D.
University of Arizona

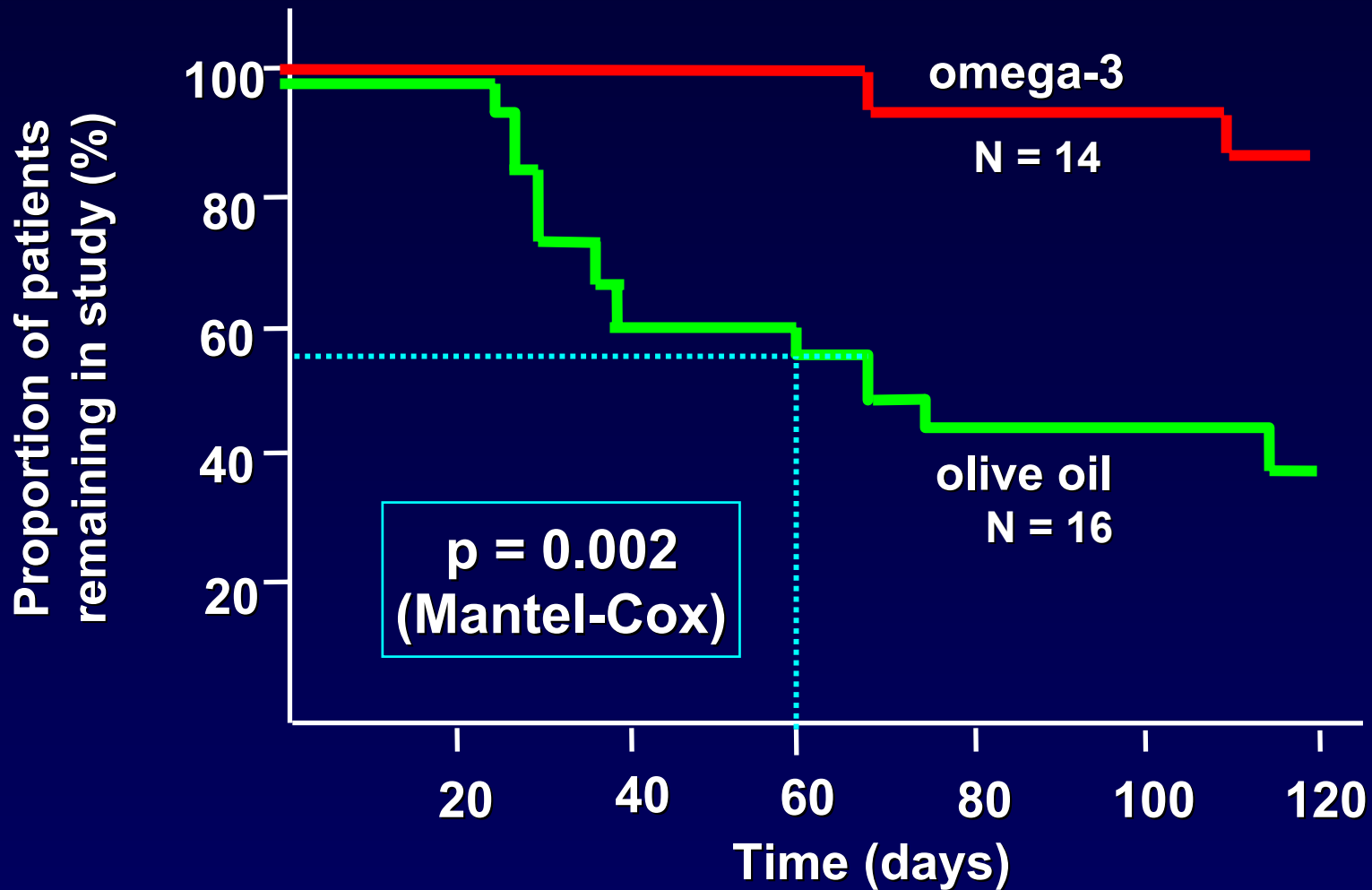
Survival Analysis (hypothetical)



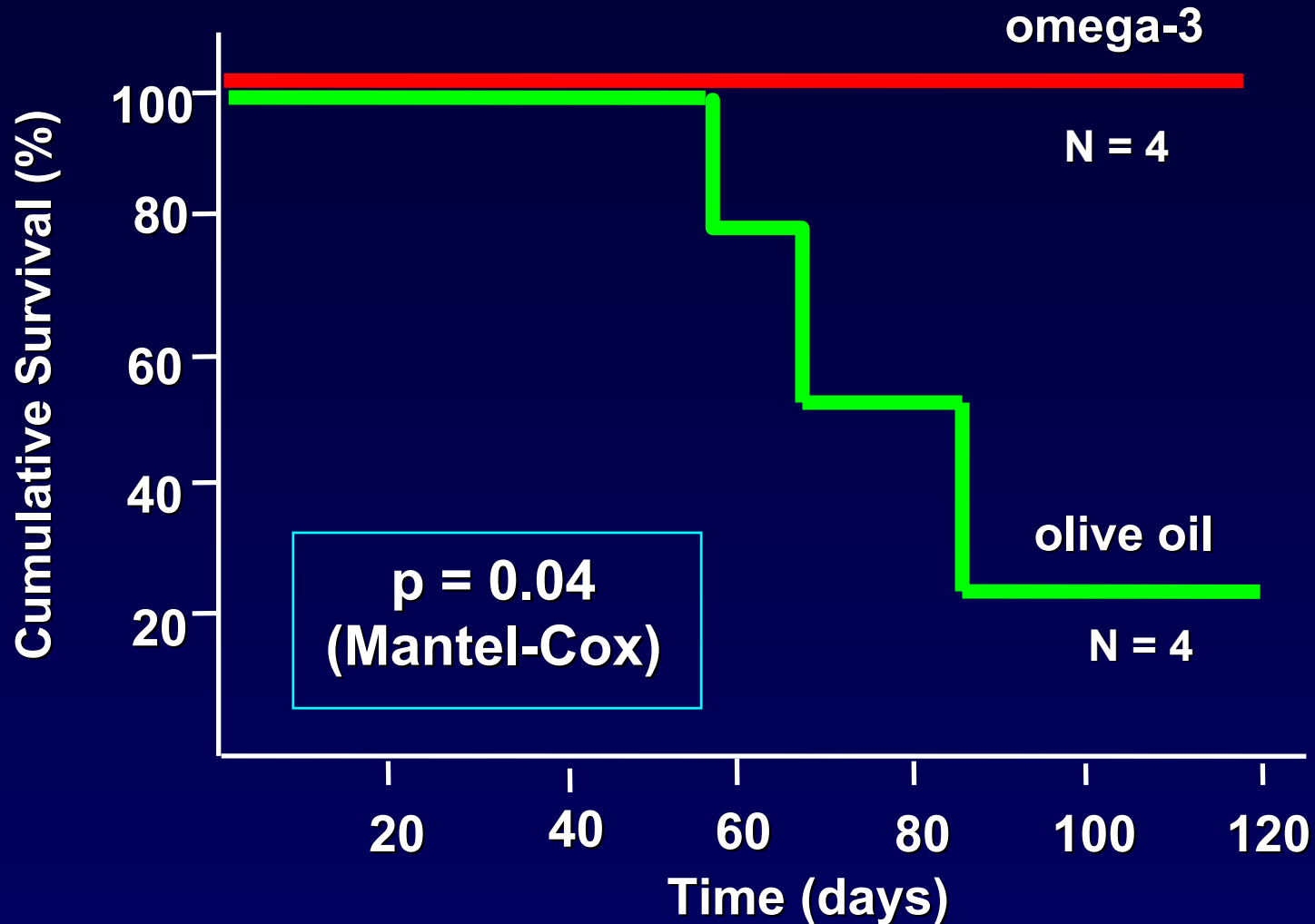
A perfect result:
all patients make it
through the 4 month
study without a
recurrence of
symptoms

A lousy result:
nearly all of the
patients had a
recurrence of
symptoms during
the 4 months of
the study

OMEGA-3 IN BIPOLAR DISORDER: Survival Analysis



OMEGA-3 FATTY ACID MONOTHERAPY: Survival Curve



OMEGA-3s IN SCHIZOPHRENIA

- Evidence for phospholipid abnormalities in schizophrenia¹.
- Open-label data suggest benefits of EPA^{2,3}.
- EPA (n=15) superior to placebo (n=14) & DHA (n=16) in a 3-month, add-on, double-blind trial⁴.
- EPA (n=14) superior to placebo (n=12) in medication-free subjects in a separate 3-month trial⁴.
- Outcome in schizophrenia better in fish consuming nations.⁵

¹Horrobin *Schizophr Res* 1998;30:193-208.

²Rudin *Biol Psychiatry* 1981;16:837-848.

³Mellor et al. *Human Psychopharmacol* 1996;11:39-46.

⁴Peet et al. *Schizophr Res* 2001;49:243-251.

⁵Christensen *Acta Psychiatr Scand* 1998;78:587-591.

OMEGA-3 FATTY ACIDS in UNIPOLAR DEPRESSION

Considerable Indirect Efficacy Data Exists

1. 4 studies reported lower blood omega-3 fatty acids (usually EPA) in patients with major depression.
2. Epidemiological evidence points to lack of omega-3 fatty acids as world-wide risk factor for depression.
3. The neurochemical effects of omega-3 depletion are consistent with models of depression.
4. Abnormalities in the omega-3 dependant eicosanoid and cytokine pathways are present during major depression.
5. Open-label case series reporting antidepressant effects.
6. Double-blind data reporting the antidepressant effects of fish oil in in bipolar disorder.
7. Reduced rates of seasonal mood shifts in Iceland and Japan.

Omega-3s in Unipolar Depression

Direct Evidence of Efficacy

Efficacy of EPA >>> DHA

4 double-blind, placebo-controlled trials

- EPA add-on in unipolar depression¹effective
 - EPA add-on in recurrent unipolar depression²effective
 - EPA + DHA (3:2) add-on in unipolar depression³..... effective
 - DHA monotherapy in unipolar depression⁴ineffective
-

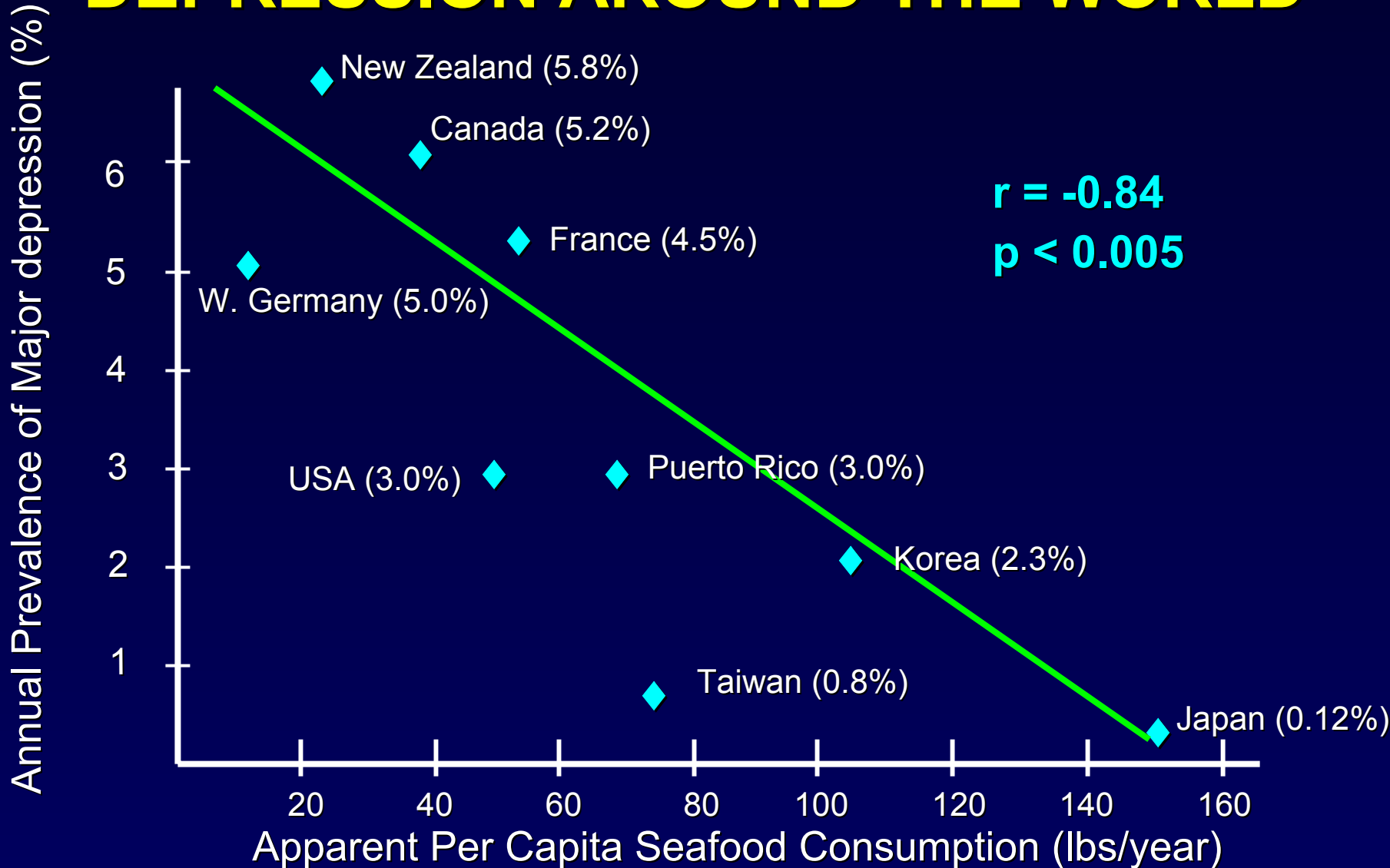
¹Peet et al. EPA for unipolar major depression. *Abstr Biol Psychiatry*. 2001.

²Nemets et al. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*. 2002;159:477-9.

³Su et al. Omega-3 fatty acids in major depressive disorder: a preliminary double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2003;13:267-271.

⁴Marangell et al. A double-blind, placebo-controlled study of the omega-3 fatty acid DHA in the treatment of major depression. *Am J Psychiatry*. 2003;160:996-8. .

FISH CONSUMPTION AND MAJOR DEPRESSION AROUND THE WORLD



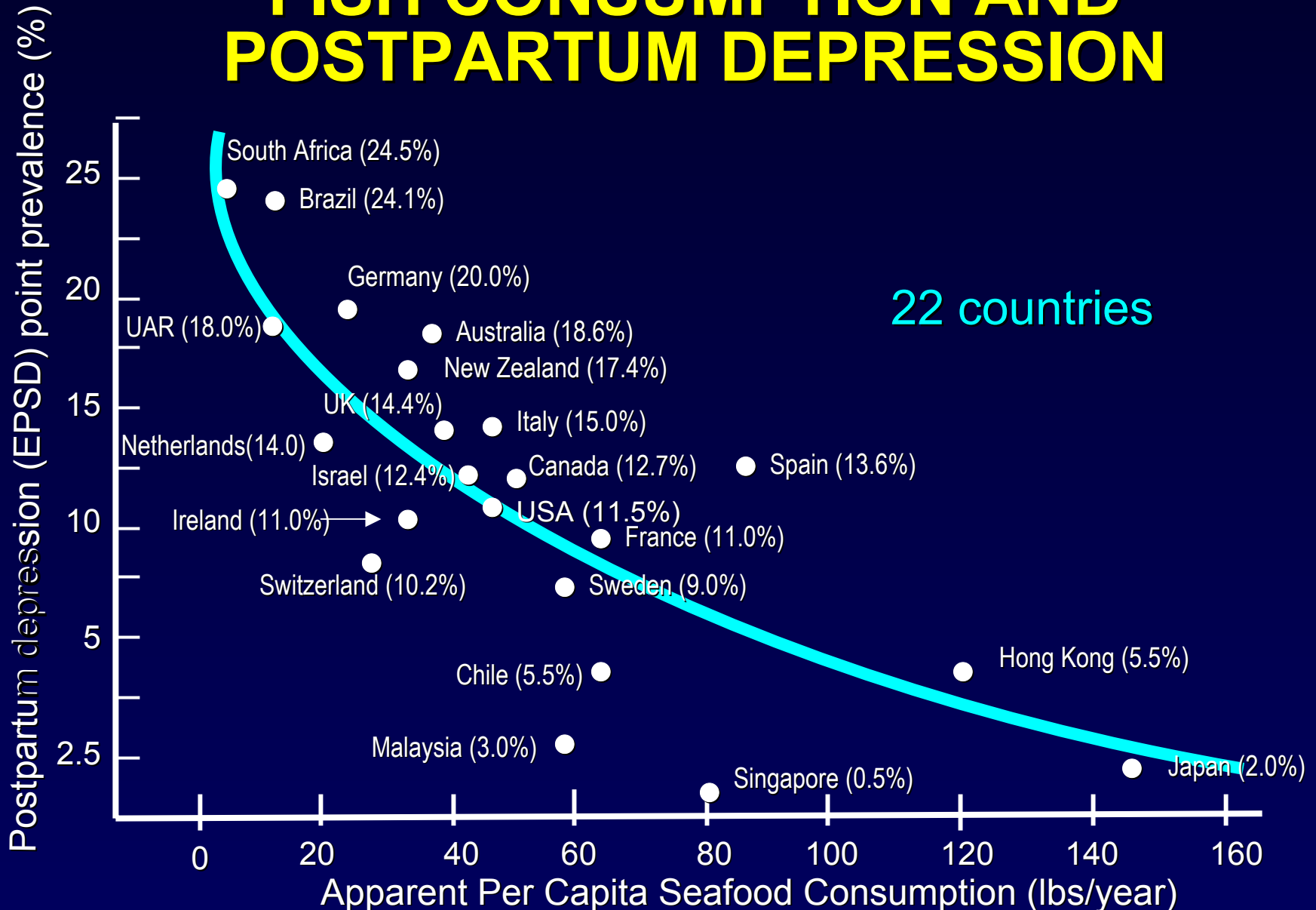
OMEGA-3 FATTY ACIDS: Critical in Brain Development

- Concentrated in breast milk (not in U.S. formula).
- DHA is one of the most abundant lipids in brain.
- DHA crucial for visual system development.
- DHA improves cognitive function in infants.
(explains breast-fed vs. bottle-fed disparity)
- World-wide rates of major depression and schizophrenia outcome inversely correlated with national fish consumption.
- Omega-3 fatty acids are depleted in the U.S. diet.

OMEGA-3 FATTY ACID DEPLETION IN POST-PARTUM WOMEN

- After 1 child: Low DHA
- After 2 children: Lower DHA
- After 3 children: Lowest DHA
- Triplets > twins:
- Triplets:
- Lactation: At 16 weeks, decreased DHA

FISH CONSUMPTION AND POSTPARTUM DEPRESSION

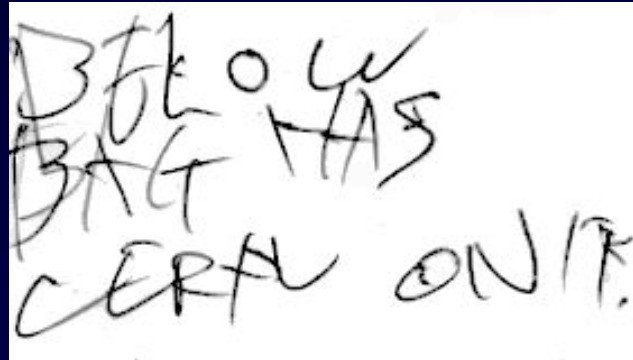


Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect Disord.* 2002;69:15-29.

OmegaBrite™ (EPA:DHA = 7:1) in Huntington's Disease

10-Dec-00:

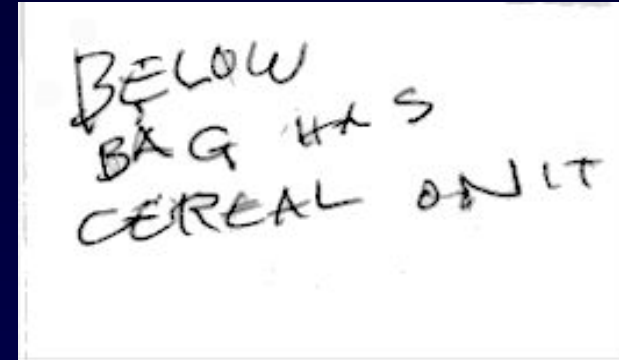
HD patient W, in the EPA Study, began taking OmegaBrite for 2 grams of EPA/day (6 capsules)



BELOW
BAG HAS
CEREAL ON IT.

28-Feb-01:

William wrote this note to his wife.



BELOW
BAG HAS
CEREAL ON IT

27-Apr-01:

William wrote this note for his wife.



<http://hdlighthouse.org/see/index.html>

Also see: Puri et al. MRI and neuropsychological improvement in Huntington disease following ethyl-EPA treatment. *Neuroreport*. 2002;13:123-6.

IDEAL CHARACTERISTICS OF A FISH OIL SUPPLEMENT

- Maximum concentration
 - >90% now available
 - No heavy metal or organic carcinogens
 - Any concentrated fish oil (> 50%) is convincingly safe
 - No fishy aftertaste, smell, or “repeat”
 - Mitigated by encapsulating under nitrogen to minimize oxidation
 - EPA >> DHA
 - The data points to EPA as the active ingredient
-

OmegaBrite

Supplement Facts

Serving Size: 3 capsules

Amount Per Serving

% Daily Value

Calories	15	
Calories from fat	15	
Total fat	1.5 g	2%*
Polyunsaturated fat	1.5 g	☐
Cholesterol	0 g	0%*
Vitamin E (as d-a-tocopherol)	3 IU	11%
EPA (eicosapentanoic acid)	1,125 mg	☐
DHA (docosahexanoic acid)	165 mg	☐
Other omega-3 fatty acids	90 mg	☐
Omega-6 fatty acids	60 mg	☐
Other fatty acids	60 mg	☐

1125 mg
÷ 3

375 mg EPA
(per 500 mg capsule)

*Percent Daily Values are based on a 2,000 calorie diet.

☐ Daily value not established.

Ingredients: fish oil, gelatin, glycerin
and vitamin E (as d-a-tocopherol).

Distributed by Omega Natural Science, Inc.
Waltham, MA 02451 www.omegabrite.com

OMEGA-3 FATTY ACIDS

Usage Guide

- Fish oil preferred to flaxseed oil at this time.
 - Adult starting dosage: 1 g EPA/d (or 1-2 g EPA + DHA/d)
 - Usual dosage range: 1 - 6 g/d of EPA (or EPA + DHA).
 - BID schedule optimal (qd, TID also ok).
 - Food increases omega-3 absorption.
 - Highest content of EPA desirable¹.
 - Antioxidants (vitamins C 250-500 mg/d & E 200-400 IU/d) may prevent in vivo degradation of omega-3s.
 - If GI upset: Divide dose, ginger root, Daikon radish
 - Caution: Xenical; Anticoagulants or high-dose NSAID?
-

¹If pregnant or nursing, higher amounts of DHA are required for optimal brain and visual system development in the baby. The 3rd trimester is crucial, because most brain growth occurs then. A typical EPA:DHA ratio of 3:2 is usually suggested here.

POTENTIAL ADVERSE EFFECTS:

Fish oil

- Fishy aftertaste (the “repeat”)
 - Due to rancidity of fatty acids through oxidation
- Gastrointestinal disturbance
 - Benign and generally only seen at high dosage
- Hypervitamosis A
 - Only if high-dose cod liver oil used
- Impaired platelet function
 - Theoretical risk of bleeding only. Unlike aspirin, EPA binds platelets reversibly and inhibits aggregation only partially
- Exposure to heavy metals or chemical pollutants
 - not an issue with concentrated fish oils due to distillation(s) and other purification steps
 - It is an issue with fish

FLAX OIL

(α -Linolenic acid)

Advantages

- More palatable than fish oil
- Native flax oil more concentrated than native fish oil
- May be used in recipes (but not as a frying oil)

Drawbacks

- Limited conversion of ALA to longer chain omega-3 in humans
- No controlled data in neuropsychiatric disorders
- May cause more manic switch than fish oil

Usage: 1 tablespoon (~7 g of ALA) qd-TID or use capsules. Omega-3 dosage with flax oil should be the same or higher as that used for fish oil, due to the incomplete conversion of ALA to EPA

FLAXSEED BENEFITS

- Oil contains a high concentration of a-linolenic acid (ALA, a short-chain omega-3), and likely has many health benefits.
- Excellent treatment for constipation:
 - Seed husks are a good fiber source.
 - Oil has mild laxative effect.
- Keep dosage below 3-4 tablespoonfuls per day

FLAXSEED TOXICITY!?

- Inexplicable link of ALA to prostate cancer:
 - At least 4 epidemiological studies associated ALA content of blood with elevated rates of prostate cancer.¹⁻⁴
 - In vitro data also suggests ALA promotes prostate cancer.⁵
 - Omega-6 fatty acids also promote tumorigenesis.⁵
 - In contrast, adequate EPA inhibits tumorigenesis.⁵
- The seed husks of flaxseeds (also lima & cassava beans) contain cyanogen, which is converted to thiocyanate. Thiocyanate inhibits iodine uptake by thyroid, possibly leading to goiter. Cyanogen is destroyed during cooking. Flaxseed oil is free of cyanogen.⁶

¹Giovannucci et al. *J Natl Cancer Inst* 1993;85:1571-1579.

²Godley et al. *Cancer Epidemiol Biomarkers Prev* 1996;5:889-895. ³Harvei et al. *Int J Cancer* 1997;71:545-551

⁴De Stefani et al. *Cancer Epidemiol Biomarkers Prev* 2000;9:335-338. ⁵Pandalai et al. *Anticancer Res* 1996;16:815-820.

⁶Simopoulos A. 1999

Dietary Patterns of Early Modern Humans

- 25-50% of dietary protein came from aquatic sources¹
 - Freshwater or Marine: fish, crustaceans, mollusks, waterfowl
- Methodology
 - Direct
 - ¹³C and ¹⁵N isotope measurements of femur collagen¹
 - Paleoarcheological samples: fish & shellfish remains
 - Dental wear patterns
 - Indirect
 - Cave art
 - Artifacts: weapons, nets, fish jewelry
- ~~Inland-dwelling Neandertals relied on large herbivores~~

¹Richards et al. *Proc Nat Acad Sci*. 2001

Why not just eat more fish?

WILD FISH: Classifications

- **Locale**
 - Freshwater fish: No body of water in No. America is safe.
 - Assume all fish are contaminated.
 - Saltwater fish
 - Less predictable contamination
- **Size and place in the food web**
 - Small prey fish: Short-lived, plentiful, and prey to bigger fish (anchovies, sardines, menhaden, etc.): Little or no contamination
 - Large Predators: Long-lived and predatory (tuna, salmon, cod, etc.): Risk of pollutant accumulation
- **Lipid storage**
 - Fish that store lipids in liver (e.g cod, swordfish, etc.):
 - Flesh is relatively clean, but little or no omega-3s.
 - Fish that store lipids in muscles (e.g. salmon, tuna, etc.):
 - Flesh is the omega-3 source, but variable pollution effects.

Isn't Farmed Fish Safe?

- **Aquaculture economics**
 - Improving, but still more expensive than commercial fishing
- **Environmental impact**
 - Improving in developed countries due to regulations & technology.
 - Worsening in developing countries
- **Farmed fish species: Food value**
 - Salmon: Generally good omega-3 source. Salmon require omega-3 fatty acids for growth, but the amount is variable and could be less or more than in wild salmon. Dye is added to farmed salmon to make them pink & appealing. The dye is chemically similar to the pigment that makes wild salmon pink (from a shellfish prey's shell). There is NO current requirement for industry to disclose contamination or omega-3 content.
 - Catfish, Talapia, Shrimp: No omega-3s at present
- **Contamination**
 - Recent reports of high mercury and PCBs in farmed fish due to almost universally contaminated feed¹.

¹ Easton et al. Preliminary examination of contaminant loadings in farmed salmon, wild salmon and commercial salmon feed. *Chemosphere*. 2002;46:1053-74.

TERRESTRIAL SOURCES OF OMEGA-3 FATTY ACIDS

- Flaxmeal or flaxseed oil
- Perilla Oil
- Chia
- Borage seed oil
- Hemp oil: Too much omega-6 (n6:n3 = 4:1)
- Wild game
- Omega-3 enriched eggs^{1,2,3}

¹Lewis et al. Enriched eggs as a source of n-3 polyunsaturated fatty acids for humans. *Poult Sci* 2000;79:971-4.

²Three omega-3 enriched eggs = 1 serving fatty fish.

³The Country Hen. Box 333, Hubbardston, MA

01452 www.countryhen.com

Omega-3s and Autism: State of the Science

- Still no double-blind, placebo-controlled trials of omega-3s in autism.
- However, indirect data continues to mount, indicating that omega-3s may be helpful in autism.
 - The epidemiological evidence of a rapidly rising incidence of autism is consistent with the progressive depletion of omega-3s in the 20th C.
 - Blood levels of omega-3 fatty acids appears to be lower in children with Autism.
 - The biochemical effects of omega-3s are consistent with some of the leading hypotheses regarding the pathophysiology of autism, especially inflammatory mechanisms.
 - Omega-3s, in controlled studies, have been shown to be helpful in every neuropsychiatric disorder tested to date.

INDIRECT EVIDENCE FOR OMEGA-3 DEFICIENCY IN AUTISM

- Reduced frequency and shorter duration of breastfeeding in autistic children compared to their normal siblings^{1,2}.
- Abnormal heart rate variability³.
- High rates of stereotyped behaviors in omega-3 deficient rhesus monkeys⁴.
- High rate of inflammatory bowel disease.

¹Burd et al. *J Dev Behav Pediatr* 1988;9:247-251.

²Tanoue & Oda. *J Autism Development Dis.* 1989;19:425-434.

³Hutt et al. *Acta Psych* 1975;51:361-372.

⁴Reisbick et al. *Physiol Behav* 1994;55:231-239.

Vancassel et al.

Plasma fatty acid levels in autistic children.

Prostaglandins Leukot Essent Fatty Acids. 2001;65:1-7.

- Purpose: To compare the phospholipid fatty acids in the plasma of a population of autistic subjects compared to mentally retarded controls.
- Results:
 - Autistic children had a 23% lower blood level of 22:6n-3 (DHA), when compared to MR controls.
 - Autistic children had a 20% lower blood level of total omega-3 (n-3), without a significant reduction in omega-6 fatty acids (n-6), when compared to MR controls.
 - This led to a 25% increase in the omega-6: omega-3 ratio.

Stevens et al. Omega-3 fatty acids in boys with behavior, learning, and health problems.
Physiol Behav. 1996;59:915-20.

- Purpose: To compare behavior, learning, and health problems in 2 groups of boys ages 6 to 12.
 - #1: Low blood levels of omega-3 or omega-6 fatty acids.
 - #2: High levels of omega-3 or omega-6 fatty acids.
- Results:
 - A greater number of behavior problems, assessed by the Conners' Rating Scale, temper tantrums, & sleep problems were reported in subjects with lower blood omega-3 levels.
 - More learning and health problems were found in subjects with lower blood omega-3 levels.
 - More colds and more antibiotic use were reported by those subjects with lower total omega-6.

Richardson AJ, Ross MA.

Fatty acid metabolism in neurodevelopmental disorders: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum.

Prostaglandins Leukot Essent Fatty Acids. 2000;63:1-9.

- There is increasing evidence that abnormalities of fatty acid and membrane phospholipid metabolism play a part in many neurodevelopmental and psychiatric disorders.
- ADHD, dyslexia, dyspraxia and autism fall within a **phospholipid spectrum of disorders**.
- This proposal could explain:
 - The high degree of co-morbidity between these conditions,
 - Their aggregation within families (through a genetically-linked biochemical abnormality).
 - Effect of our changing diet (↓omega-3s) on a population level

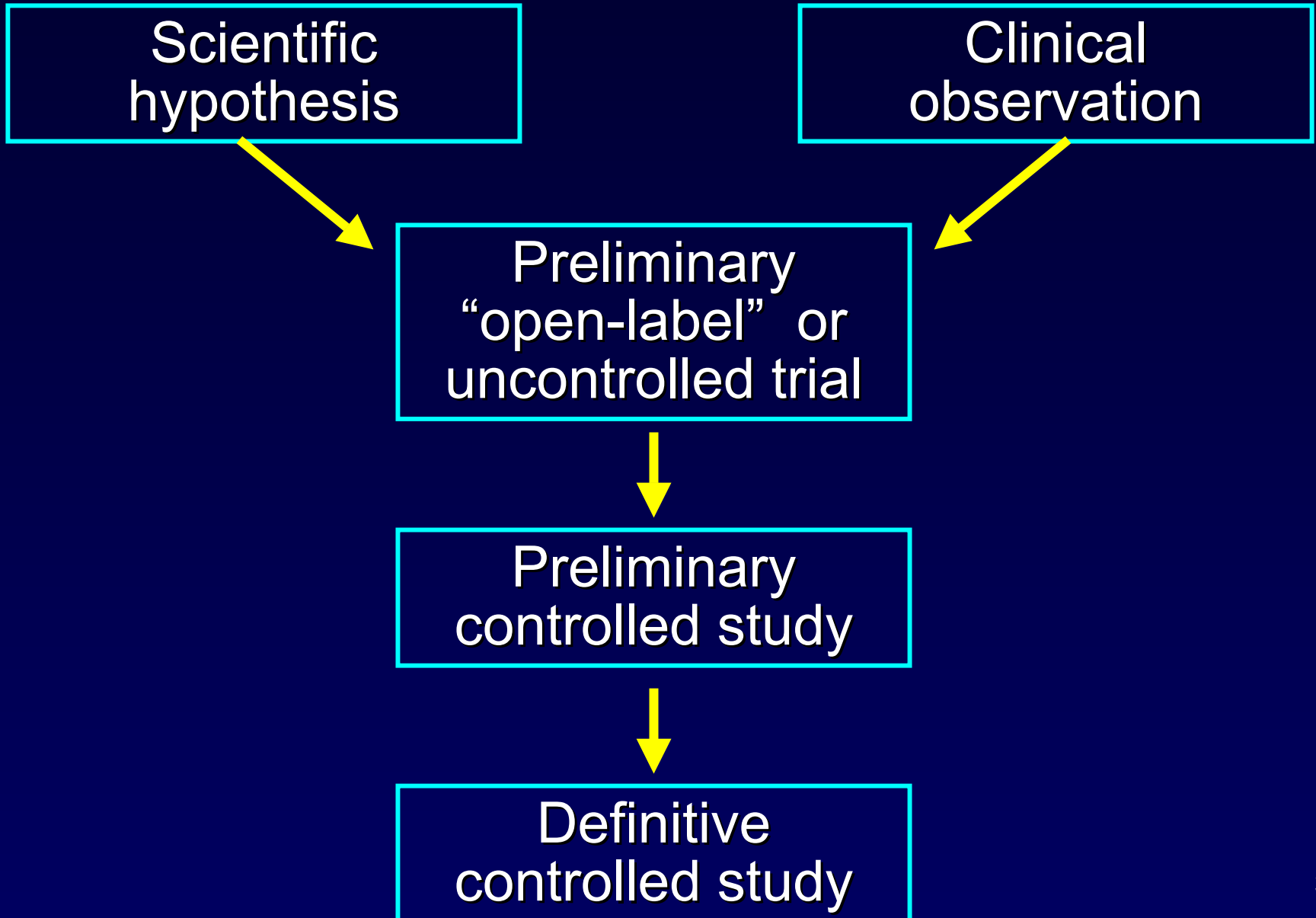
Clinical Experience with Omega-3s in Autism

- Informal surveys of past DAN! audiences.
- Numerous e-mail descriptions and testimonials.
- Dr. Paul Hardy has treated several hundred children with autism and related neurodevelopmental disorders with omega-3 fatty acids¹.
 - He reports a “dramatic response” in ~ 50% of kids.

**WE DESPERATELY NEED
CONTROLLED STUDIES!**

¹Personal communication with Dr. Hardy on 3-21-05

PHASES OF MEDICAL RESEARCH



The Importance of Preliminary “Open-Label” or Uncontrolled Studies

- “Open-label” means both the patient and clinician/researcher know that the patient is receiving the “active” drug.
- This is where major discoveries are made.
- Inexpensive
- Huge, double-blind, placebo-controlled studies are crucial for confirmation of initial findings

The Importance of Scientifically Controlled Research

- Evaluates preliminary uncontrolled findings
- Permits other researchers to replicate methods
- Permits patients, families, and clinicians to evaluate the merits & drawbacks of a new treatment
- Permits insurance companies, the FDA, and other regulatory agencies to evaluate the merits and drawbacks of a new treatment

OMEGA-3 FATTY ACIDS IN AUTISM: Unanswered Questions

- Are omega-3s truly effective in autism?
- If so, which omega-3(s) is the active component (EPA, DHA, ALA) - or are all 3 active?
- What is the proper dosage?
- Oral vs. IV?
- Are there biological markers that will predict omega-3 response?
- Are there subtypes of autism that preferentially respond to omega-3s?

FINANCIAL DISCLOSURE

Andrew L. Stoll, M.D.

**Dir., Psychopharmacology Research Lab., McLean Hospital
Assistant Professor of Psychiatry, Harvard Medical School**

- Current Research Grant support: The Stanley Foundation.
- Past Research Grant support: The Poitras Charitable Fund, and the Hirschhorn Foundation. Abbott Laboratories, Janssen Pharmaceutica, Eli Lilly & Co., Solvay, NIH (NCCAM) and Harvard Medical School,
- Current Speaker's Bureau: Harvard Medical School (Dept. Of Continuing Medical Education), Abbott Laboratories, Bristol-Myers Squibb, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica,
- Past Speaker's Bureau: Astra-Zeneca, Smith-Kline Beecham, Eli Lilly & Co., Organon, Pfizer (Parke-Davis), and Wyeth-Ayerst.
- Current consulting: Omega Natural Science, Inc.
- Past Consultant: Abbott Laboratories, Bristol-Myers Squibb, Glaxo, Eli Lilly & Co., Pfizer (Parke-Davis), and CX Research, Inc.
- Major Stockholder: None.
- Other: Dr. Stoll has published a book on omega-3 fatty acids: "*The Omega-3 Connection*" (Simon and Schuster, 2001). His wife, Carol A. Locke, M.D. creates nutraceutical products for psychiatry and general medicine and is the Founder and CEO of Omega Natural Science, Inc. (OmegaBrite™).