

Diets Could Prevent Many Diseases

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ABSTRACT: The 2002 ISSFAL Meeting arranged a special evening discussion with professional dietitians about diet-tissue-disease relationships involving essential fatty acids and eicosanoids. The balance of eicosanoid precursors in human tissues differs widely, reflecting voluntary dietary choices among different groups worldwide. An empirical quantitative diet-tissue relationship fits these diverse values as well as other research reports on essential fatty acid metabolism. Information for dietitians and nutritionists about essential fatty acids and eicosanoids is also given in two distance learning web sites, <http://ods.od.nih.gov/eicosanoids/> and <http://efaeducation.nih.gov/>, which facilitate dietitian education and diet counseling. These sites also have an innovative, interactive diet planning software program with the empirical equation embedded in it to help evaluate personal food choices in the context of the diet-tissue-disease relationship and other widely recommended dietary advice.

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BENEFITS FROM DECREASING EXCESSIVE AUTACOID SIGNALING

Non-steroidal anti-inflammatory drugs (NSAID) are some of the most widely used medications worldwide. The >70–100 million NSAID prescriptions written annually offer a huge profitability potential with annual sales of \$13 billion. The 24.5 million Celebrex® prescriptions in 2001 in the United States were closely matched by 23.7 million prescriptions for Vioxx®; these two alone had worldwide sales of \$5.7 billion. The drugs are taken to decrease an overactive self-healing response by the body's autacoids (auto = self, akos = healing), the n-6 eicosanoids derived from essential fatty acids obtained from the diet (1). This review examines ways in which less costly dietary approaches might also beneficially decrease those overactive responses. The NSAID produce their beneficial anti-inflammatory, analgesic, antipyretic, antithrombotic effects by inhibiting the cyclooxygenase enzyme that converts highly unsaturated fatty acid (HUFA) precursors into active eicosanoids. The worldwide

success of NSAID provides ample “proof of principle” for the desirability of preventing excessive n-6 eicosanoid formation in many disorders such as thrombosis, the arrhythmia of heart attacks, and inflammatory/immune problems in atherosclerosis, arthritis, asthma, and tumor angiogenesis. Moderating those excesses brings an improved quality of life to millions of people. Unfortunately, nearly all of the drugs have some undesired side effects or limitations that are much discussed in assessing benefits and risks of medical treatments.

Ironically, the self-healing eicosanoids that are so important in the body's normal adaptive processes are sometimes overly mobilized, causing people to seek various self-administered medication to decrease the “friendly fire” of those overresponses. The n-6 eicosanoid is formed more rapidly in the case of prostaglandin derivatives (2,3), and acts more intensely in receptor signaling (4) compared with its competing n-3 eicosanoid analog (esp. leukotriene B chemotaxis). These differences produce less intense actions when the mixture of released HUFA precursors has a lower proportion of the n-6 analog to compete for the eicosanoid-forming enzymes. Physiologic benefits depend on moderate transient actions of these autacoids formed from local precursors present in nearly all tissues of the body (1). Once formed, eicosanoids are rapidly inactivated so that active autacoid usually appears only in small amounts at nearby tissue receptors and travels little distance from its site of synthesis. As a result, a small increase or decrease in the rate of synthesis causes a very important difference in the intensity of an autacoid's action at local receptors (1). Inhibitory drugs are voluntarily used by people to moderate an overresponse when eicosanoid action is more intense or for a longer time than desired. However, the difference in potency between the n-3 and n-6 eicosanoids gives another opportunity to decrease chronic excessive formation and action of n-6 eicosanoids by increased dietary intakes of naturally occurring competitive n-3 analogs rather than with pharmaceutical antagonists.

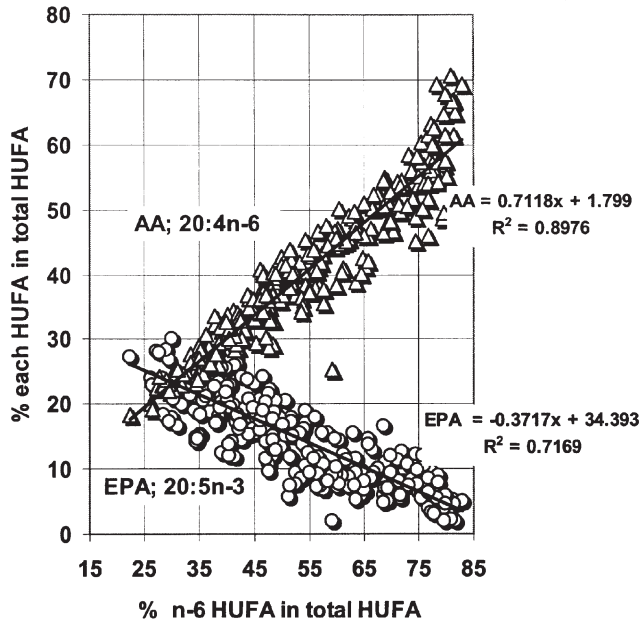
PROPORTIONS OF PRECURSORS RELATE TO INDIVIDUAL HUFA AND TO CORONARY HEART DISEASE (CHD) DEATH RATES

Dietary intake is the only route of entry for eicosanoid precursors, and food choices have an important effect on tissue HUFA levels and tissue autacoid responses. Dietary 18-carbon essen-

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Abbreviations: AA, arachidonic acid; CHD, coronary heart disease; DGLA, di-homo- γ -linolenic acid; HUFA, highly unsaturated fatty acids; MRFIT, multiple risk factor intervention trial; NSAID, non-steroidal anti-inflammatory drugs.

A. Different tissue HUFA proportions



B. Different tissue HUFA proportions

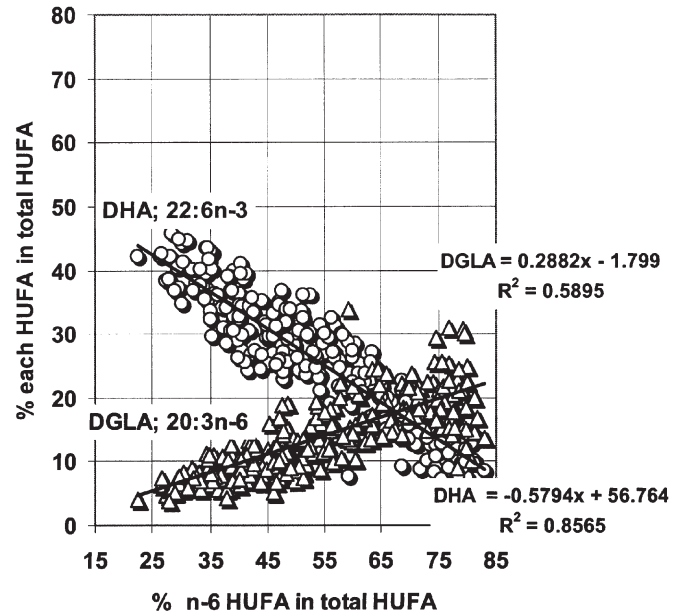


FIG. 1. Different tissue highly unsaturated fatty acid (HUFA) proportions among humans. The phospholipid fatty acids from 380 different plasma samples described in other studies from the United States [$n = 293$ (8)] and Japan [$n = 87$ (9)] were analyzed by gas chromatography. The proportions of individual n-3 HUFA decrease (A: EPA, 20:5n-3, O; B: DHA, 22:6n-3, O) as the n-6 HUFA increase [A: arachidonic acid (AA), 20:4n-6, Δ ; B: di-homo- γ -linolenic acid (DGLA), 20:3n-6, Δ].

tial fatty acids are metabolized to different chain lengths [such as the 20-carbon arachidonic acid, AA (20:4n-6), and EPA (20:5n-3)] and stored as HUFA precursors esterified to tissue phospholipids from which they are mobilized by phospholipase-catalyzed hydrolysis (5). The closely related n-3 and n-6 essential fatty acids compete with each other for accumulation in tissue phospholipids, a process long recognized since the description of competitive hyperbolic interactions for these two types of nutrient by Mohrhauer and Holman (6,7). The voluntary food choices that people make day by day provide diverse proportions of n-6 and n-3 essential fatty acids associated with very different proportions of n-6 HUFA among the total HUFA of plasma phospholipids, which vary from 25 to 85% (Fig. 1). Competition between the n-6 and n-3 fatty acids is clearly evident in the decreased proportions of n-3 HUFA (DHA and EPA) associated with increased proportions of n-6 HUFA [AA and di-homo- γ -linolenic acid (DGLA)] that are stored in the tissue phospholipid HUFA.

High proportions of the n-6 precursor in the tissue HUFA that will be released during a stimulus will give high rates of formation of n-6 eicosanoids, whereas low proportions will give low rates of formation. In this way, the balance of n-3 and n-6 acids in the diet influences the balance of n-3 and n-6 HUFA in tissues and therefore the eventual balance of n-3 and n-6 eicosanoid actions in self-healing processes. CHD involves excessive n-6 eicosanoid actions in chronic and acute inflammatory processes in vascular walls that predispose people to fatal heart attacks as well as in the thrombosis and arrhythmia of the acute event. Because CHD is a major cause of death, many drug treatments are marketed vigorously to meet the need to treat people and reduce

an imminent risk. Figure 2 shows that the age-adjusted risk of CHD mortality is less when the proportion of n-6 eicosanoid precursors in people's tissue HUFA is lower. The wide diversity in abscissa values for Figures 1 and 2 raises the question, "What proportion of n-6 eicosanoid precursor is stored on the shelves of your body's medicine chest?" It also prompts a closer, more quantitative look at the association between tissue HUFA and CHD mortality.

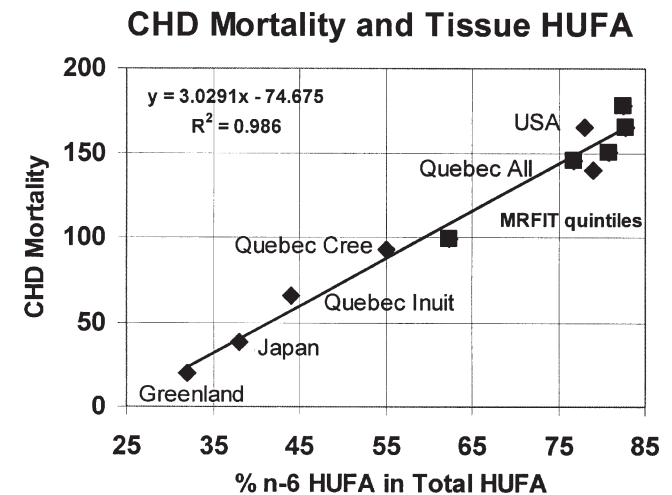


FIG. 2. Coronary heart disease (CHD) mortality rates associated with tissue HUFA proportions. Results from the United States, Japan, and Greenland were discussed earlier (10,11,12) as were quintile results from the Multiple Risk Factor Intervention Trial (MRFIT) study (13) and those from Quebec Inuit (14), Quebec Cree (15), and Quebec over-all (16). For abbreviation see Figure 1.

The Multiple Risk Factor Intervention Trial (MRFIT) was a multimillion-dollar clinical trial in which the "Usual Care" cohort provided prospective longitudinal evidence that people consuming greater levels of n-3 HUFA had a lower relative risk of CHD than those eating less (13). The voluntary intake of n-3 HUFA for 6258 men (expressed as percentage of food energy, en%) had quintile means of 0.001, 0.004, 0.019, 0.063, and 0.272 en%. These relatively low intakes corresponded to proportions of 83, 82, 81, 77, and 62% n-6 HUFA in overall tissue HUFA, respectively. The 1251 men with the most n-3 HUFA intake had a significantly lower relative risk of CHD, 0.6 compared with 1.0, 1.08, 0.91, 0.88. However, Table 1 shows that the limited diversity among Americans in voluntary intake of n-3 HUFA causes this significant effect to be less apparent when all five quintiles are combined together. Predicting the likely proportion of n-6 HUFA in tissue HUFA for each of the quintiles (in column 6) and combining them with the known fraction of deaths in each quintile (column 7) predicts values of 78% for cases and 75% for surviving controls (column 8). Direct gas chromatographic analysis of the HUFA in plasma phospholipids gave good agreement with the values predicted from the dietary data, with an average of 79% n-6 HUFA in tissue HUFA for 94 cases and 76% for 94 controls (17). The clear benefit seen for one quintile and emphasized by Dolecek and Grandits (13) seems less visible when combining all quintiles together as reported by Simon *et al.* (17). Nevertheless, the latter authors concluded that a 1 SD increase in n-6 DGLA (20:3n-6) was associated with an increase in CHD risk of 40%, whereas a 1 SD increase in DHA (22:6n-3) was associated with a decrease in CHD risk of 33% (17). They concluded that the decreased CHD incidence may reflect decreased platelet aggregability after increased dietary intake of n-3 polyunsaturated fatty acids.

Recent results from Quebec (see Fig. 2) fit closely to the relationship observed for the MRFIT cohort as well as for the United States, Japan, and Greenland populations:

$$\text{CHD mortality} = 3 \times (\% \text{ n-6 HUFA in tissue HUFA}) - 75 \quad [1]$$

Although cross-national analyses have been regarded with caution, the Quebec population of groups from the same province

of the same country (14–16) follows the same trend for tissue HUFA influence on the likelihood of fatal CHD events. Knowledge of the molecular mechanisms for n-6 eicosanoid actions in the disease processes of inflammation, thrombosis, and arrhythmia and the success of many NSAID in moderating those processes leads inevitably to considering dietary steps to prevent excessive n-6 eicosanoid actions before they occur rather than relying only on treatment after disease processes become evident. The strong correlation coefficient of 0.99 ($r^2 = 0.986$) for the results in Figure 2 suggests that making dietary choices that decrease the proportion of tissue HUFA that is n-6 HUFA can be an effective primary prevention strategy to decrease the risk of fatal CHD events in a population. Figure 1 shows that many people already do. There are undoubtedly other eicosanoid-mediated diseases for which better nutrition may prevent what must otherwise be treated with drugs.

FOOD CHOICES AFFECT PROPORTIONS OF PRECURSORS IN TISSUE HUFA

Diet choices influence the composition of HUFA in tissue phospholipids, whose composition affects the likelihood of phospholipase releasing n-6 eicosanoid precursors; that in turn affects the probable intensity of n-6 eicosanoid synthesis and action in tissues. In maintaining health and preventing chronic diseases, the tissue is the issue. Extending the work of Mohrhauer and Holman, we examined quantitative metabolic relationships between dietary supply and the proportions of n-6 and n-3 eicosanoid precursors stored in the HUFA of tissue phospholipids. The proportion of n-6 in tissue HUFA can be estimated by an empirical relationship (12) for the quantitative metabolic competitions among four separate types of essential fatty acids in the diet:

1. 18-carbon n-3 PUFA; 18:3n-3
2. 18-carbon n-6 PUFA; 18:2n-6
3. 20- and 22-carbon n-3 HUFA; 20:5; 22:5; 22:6n-3
4. 20- and 22-carbon n-6 HUFA; 20:3; 20:4; 22:4; 22:5n-6

Each of the four types contributes differently to the overall tissue balance. Discussing the four types combined into a single

TABLE 1
Combined Quintile Results from the MRFIT Study^{a,b}

1 Quintile of n-3 HUFA	2 <i>n</i>	3 Deaths	4 RR	5 Dietary en%	6 Estimated % n-6 HUFA	7 3 × 6 Cases	8 (2–3) × 6 Controls
MRFIT #5	1251	24	0.6	0.272	62.3	1495	76,434
MRFIT #4	1252	35	0.88	0.063	76.8	2687	93,428
MRFIT #3	1251	35	0.91	0.019	80.9	2830	98,335
MRFIT #2	1197	39	1.08	0.004	82.4	3215	95,447
MRFIT #1	1307	42	1	0.001	82.8	3476	104,692
Total	6258	175					
					Dolecek data predict	78.3	74.8
						Cases	Controls
					Simon data observed	78.7	76.5

^aResults in the first five columns are from Dolecek and Grandits (13), and the proportion of n-6 HUFA in total HUFA was estimated by an empirical quantitative metabolic relationship (12). Column 7 combines columns 3 and 6 to obtain the average estimated value for coronary heart disease cases, whereas column 8 gives the average estimated value for survivors. Analytical results of Simon *et al.* (17) are also in columns 7 and 8.

^bAbbreviations: MRFIT, Multiple Risk Factor Intervention Trial; HUFA, highly unsaturated fatty acids; RR, relative risk; en%, percentage of food energy.

ratio of total dietary n-6/total dietary n-3, the ratio has no clear meaning because tissue proportions of n-6 HUFA in total HUFA result from the four separate contributions expressed as a percentage of total food energy (en%). To make estimates with all four variables, a simple calculator is accessible at <http://efaeducation.nih.gov/sig/dietbalance.html> to help design general features of dietary intervention protocols.

To facilitate estimates of how different combinations of specific foods can give very different proportions in body tissues, we developed an interactive personalized computer program that manages U.S. Department of Agriculture information about the essential fatty acids in 9214 different servings of food. The software combines information concerning a person's daily food choices and predicts the resulting tissue HUFA proportions, which are biomarkers for essential fatty acid intake (as noted in Ref. 12) as well as surrogate clinical markers (as seen in Fig. 2) that are also metabolically related to the probable intensity of an eicosanoid response as noted above. It can be downloaded without cost from <http://ods.od.nih.gov/eicosanoids/>. Some ethnic food choices achieve healthy tissue proportions and moderate eicosanoid responses by containing large amounts of n-3 HUFA (Japanese or Greenlanders), whereas some populations eat lower amounts of the n-6 18-carbon fatty acids (Mediterranean people). Although intake of linoleate is similar in the United States and Japan (quintile means from 3 to 9 en%), the mean intake for the lowest quintile of dietary n-3 HUFA in Japan (0.31, 0.46, 0.56, 0.71, 0.92 en%) is greater than the highest for the United States (0.001, 0.003, 0.017, 0.057, 0.249), making tissue eicosanoid responses appreciably different for the two populations.

To help clinical investigators design diets that produce the desired tissue HUFA balance, a simple spreadsheet was arranged to combine the four separate dietary influences with the empirical relationship described earlier (12) to predict the likely long-term outcome. Illustrations of three typical ethnic dietary combinations of essential fatty acid intakes (expressed as en%) are in the columns at the right of Table 2. In a 2400 kcal/d diet, 266 mg of fat is 0.10 en%, and a standard 1-g fish oil supplement is equivalent to 180 mg 22:6 + 120 mg 20:5, i.e., ~0.11 en% n-3 HUFA per capsule.

Dietitians who know the importance of voluntary food choices can use their familiarity with nutrient tables and the new interactive software on essential fatty acids to help people choose healthy combinations of palatable foods that will fit their personal tastes and meet their personal target for the balance of tissue HUFA. The interactive software combines

the selected foods into daily meal plans, tracking the calories and estimating the probable proportions of n-6 HUFA in the total tissue HUFA, which can vary from 25 to 85%. The American Heart Association has recommended at least two meals per week of fatty fish to help provide better tissue balance. Careful attention to raising the relative amount of n-3 to n-6 contents of salad and cooking oils is another easy step in shifting tissue HUFA to a healthier balance. Also, discovering and eating the vegetables and legumes with relatively higher proportions of n-3 acids is made easier with a computerized "sort" command. All of the above aspects open the way for dietitians to lead in developing primary prevention strategies that decrease the frequency and severity of eicosanoid-mediated disorders for the whole population.

ACKNOWLEDGMENTS

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REFERENCES

1. Lands, W.E.M. (1979) The Biosynthesis and Metabolism of Prostaglandins, *Annu. Rev. Physiol.* 41, 633–652.
2. Kulmacz, R.J., Pendleton, R.B., and Lands, W.E.M. (1994) Interaction Between Peroxidase and Cyclooxygenase Activities in Prostaglandin-Endoperoxide Synthase, *J. Biol. Chem.* 269, 5527–5536.
3. Malkowski, M.G., Thuresson, E.D., Lakkides, K.M., Rieke, C.J., Micielli, R., Smith, W.L., and Garavito, R.M. (2001) Structure of Eicosapentaenoic and Linoleic Acids in the Cyclooxygenase Site of Prostaglandin Endoperoxide H Synthase-1, *J. Biol. Chem.* 276, 37547–37555.
4. Needleman, P., Raz, A., Minkes, M.S., Ferrendelli, J.A., and Sprecher, H. (1979) Triene Prostaglandins: Prostacyclin and Thromboxane Biosynthesis and Unique Biological Properties, *Proc. Natl. Acad. Sci. USA* 76, 944–948.
5. Lands, W.E.M., and Samuelsson, B. (1968) Phospholipid Precursors of Prostaglandin, *Biochim. Biophys. Acta* 164, 426–429.
6. Mohrhauser, H., and Holman, R.T. (1963) Effect of Linolenic Acid upon the Metabolism of Linoleic Acid, *J. Nutr.* 81, 67–74.
7. Mohrhauser, H., and Holman, R.T. (1963) The Effect of Dose Level of Essential Fatty Acids upon Fatty Acid Composition of the Rat Liver, *J. Lipid Res.* 4, 151–159.
8. Harris, W.S., Ginsberg, H., Arunakul, N., Shachter, N.S., Windsor, S.L., Adams, M., Berglund, L., and Osmundsen, K. (1997) Safety and Efficacy of Omacor in Severe Hypertriglyceridemia, *J. Cardiovasc. Risk* 4, 385–391.
9. Kobayashi, M., Sasaki, S., Kawabata, T., Hasegawa, K., Akabane, M., and Tsugane, S. (2001) Single Measurement of Serum Phospholipid Fatty Acid as a Biomarker of Specific Fatty Acid Intake in Middle-Aged Japanese Men, *Eur. J. Clin. Nutr.* 55, 643–650.
10. Lands, W.E.M., Hamazaki, T., Yamazaki, K., Okuyama, H., Sakai, K., Goto, Y., and Hubbard, V.S. (1990) Changing Dietary Patterns, *Am. J. Clin. Nutr.* 51, 991–993.
11. Lands, W.E.M. (1991) Biosynthesis of Prostaglandins, *Annu. Rev. Nutr.* 11, 41–60.

TABLE 2
Daily Dietary Intakes Affect Tissue HUFA^a

Type of essential fatty acid in the diet	Trial diet	Typical diets		
		U.S.	Mediterranean	Japan
1 en% 18:3n-3	1.00	0.85	0.50	0.83
2 en% 18:2n-6	6.00	6.82	2.30	5.41
3 en% n-3 HUFA	0.10	0.03	0.09	0.71
4 en% n-6 HUFA	0.10	0.08	0.08	0.09
% n-6 in total HUFA	75	80	63	48

^aFor abbreviations see Table 1.10

12. Lands, W.E.M., Libelt, B., Morris, A., Kramer, N.C., Prewitt, T.E., Bowen, P., Schmeisser, D., Davidson, M.H., and Burns, J.H. (1992) Maintenance of Lower Proportions of n-6 Eicosanoid Precursors in Phospholipids of Human Plasma in Response to Added Dietary n-3 Fatty Acids, *Biochim. Biophys. Acta* 1180, 147–162.
13. Dolecek, T.A., and Granditis, G. (1991) Dietary Polyunsaturated Fatty Acids and Mortality in the Multiple Risk Factor Intervention Trial (MRFIT), *World Rev. Nutr. Diet.* 66, 205–216.
14. Dewailly, E., Blanchet, C., Lemieux, S., Sauve, L., Gingras, S., Ayotte, P., and Holub, B.J. (2002) n-3 Fatty Acids and Cardiovascular Disease Risk Factors Among the Inuit of Nunavik, *Am. J. Clin. Nutr.* 76, 85–92.
15. Dewailly, E., Blanchet, C., Gingras, S., Lemieux, S., and Holub, B.J. (2002) Cardiovascular Disease Risk Factors and n-3 Fatty Acid Status in the Adult Population of James Bay Cree, *Am. J. Clin. Nutr.* 76, 85–92.
16. Dewailly, E.E., Blanchet, C., Gingras, S., Lemieux, S., Sauve, L., Bergeron, J., and Holub, B.J. (2001) Relations Between n-3 Fatty Acid Status and Cardiovascular Disease Risk Factors Among Quebecers, *Am. J. Clin. Nutr.* 74, 603–611.
17. Simon, J.A., Hodgkins, M.L., Browner, W.S., Neuhaus, J.M., Bernert, J.T., and Hulley, S.B. (1995) Serum Fatty Acids and the Risk of Coronary Heart Disease, *Am. J. Epidemiol.* 142, 469–476.

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