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**Essential Fatty Acids and
Their Interaction with
Other Nutrients and Drugs**

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ESSENTIAL FATTY ACIDS AND THEIR INTERACTION WITH OTHER NUTRIENTS AND DRUGS

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ABSTRACT

Essential fatty acids (EFAs) are nutrients of vital importance that must be obtained in the diet since humans cannot make them. Two groups of fatty acids are essential to the body: the omega-6 (n-6) series derived from linoleic acid (LA; 18:2 n-6) and the omega-3 (n-3) series derived from alpha-linolenic acid (ALA; 18:3 n-3). Both the amount and types of these and other fatty acids in the diet influence the EFA status, and may have profound influences on both health and disease. Dietary components such as vitamins and minerals also influence EFA requirements and are required for optimal activity of EFAs. Evidence is accumulating that EFAs may interact with drugs, leading to possible enhanced or synergistic effects. EFA interactions have been observed in the areas of inflammation, bone formation, cardiovascular disease, and cancer.

INTRODUCTION

Essential fatty acids (EFAs) are nutrients of vital importance that must be obtained in the diet since humans cannot make them. Two groups of fatty acids are essential to the body: the omega-6 (n-6) series derived from linoleic acid (LA; 18:2 n-6) and the omega-3 (n-3) series derived from alpha-linolenic acid (ALA; 18:3 n-3). Both the amount and types of these and other fatty acids in the diet influence the EFA status, and may have profound influences on both health and disease. The requirements, absorption, metabolism, and activity of EFAs may be affected by dietary components such as vitamins and minerals. EFAs may interact with drugs, leading to synergistic effects, and EFA interactions have been observed in the areas of inflammation, bone formation, cardiovascular disease, and cancer. (Table 1 shows the relationships and interactions that various nutrients and drugs have with EFAs.)

ESSENTIAL FATTY ACIDS/NUTRIENT INTERRELATIONSHIPS

Like other essential nutrients, the absorption and activity of EFAs is influenced by various nutrients obtained

in the diet.¹ Likewise, EFAs influence the absorption and activity of certain other essential nutrients.¹ Several dietary components affect EFA requirements because of their interactions with EFA absorption, use, or metabolism.¹ These components include the type and amount of fatty acids in the diet, other macronutrients like protein, and micronutrients such as vitamins and minerals.¹⁻³

ESSENTIAL FATTY ACIDS/MACRONUTRIENT INTERRELATIONSHIPS AND INTERACTIONS

Both the intake of fat and protein in the diet affects the essential fatty acid status of an individual.^{1,3,4} Intake of saturated, monounsaturated, and trans-fatty acids in the diet can influence the metabolism and use of EFAs.¹ High intake of certain saturated fatty acids in the diet may increase EFA requirements by suppressing the metabolism of EFAs and lowering their availability.⁵ As a group, the short-chain and medium-chain saturated fatty acids are mainly used by the body for energy, and are often thought to be problematic in excess. However, it is critical to keep in mind that within the saturated fatty-acid family (indeed within any "group" of fatty acids), there are distinct differences between fats of differing chain length, including differences in physical properties, as well as function and use in the body. As a generality, excess saturated fat may be linked to chronic disease such as cardiovascular disease. However, individual saturated fatty acids may have neutral or beneficial effects towards health and prevention of disease. The medium-chain saturated fatty acid, lauric acid, for instance, possesses antimicrobial and antibacterial properties, has demonstrated no adverse effects on atherosclerosis and cardiovascular disease, and may have significant benefit in immune support and cancer.

Monounsaturated fatty acids, such as oleic acid, can replace EFA in the lipids of cells, possibly leading to essential fatty acid deficiency (EFAD).⁶ Trans-fatty acids found in margarines, shortenings, and baked products increase EFA requirements by influencing the metabolism of unsaturated fatty acids and decreasing the formation of longer-

chain PUFAs.⁷ Thus, high intake of dietary saturated, monounsaturated and trans-fatty acids, common in the North American diet, may increase the need for EFAs. Intake of saturated, monounsaturated, and PUFAs, including the essential PUFAs or EFAs, must be balanced in order to provide fat for energy, meet nutritional needs, ensure optimal health, and help manage disease.

EFAs themselves also interact with each other because of the competitive nature of EFA metabolism.¹ The metabolic pathway for both omega-6 linoleic acid and the omega-3 alpha-linolenic acid proceeds through a series of desaturase and elongase reactions. The rate-limiting step is the conversion of LA to gamma linolenic acid (GLA) and ALA to stearidonic acid via the action of the delta-6-desaturase (D₆D) enzyme. An excess of omega-6 EFAs reduces the metabolism of alpha-linolenic acid, and excess omega-3 EFAs potentially inhibits omega-6 EFA metabolism. However, inhibition of omega-6 metabolism due to excess omega-3 is seldom evident clinically, given the preponderance of omega-6 fatty acids, especially LA, in the diet. The optimal levels of EFAs and the ratio of n-3 and n-6 EFAs that is required in the diet is not yet clear, and may vary depending on factors such as the developmental stage and the presence of longer-chain EFAs, which may be incorporated and used more efficiently in cells. Excessive amounts of omega-6 fatty acids, notably linoleic acid which is high in the Western diet, appears to promote the pathogenesis of many diseases including cardiovascular disease, cancer, inflammation, and auto-immune diseases.⁸ The omega-6 to omega-3 ratio may be 15:1 or higher in the Western diet. Not surprisingly, increasing dietary levels of omega-3 PUFAs exert suppressive effects. However, the optimal omega-6 to omega-3 ratio, as well as the therapeutic dose of omega-3 fatty acids, appears to vary with the specific disease, reinforcing the fact that chronic diseases are multigenic and multifactorial. An omega-6 to omega-3 ratio of 4:1 was found effective in the secondary prevention of cardiovascular disease, resulting in a 70% decrease in mortality; a 2-3:1 ratio suppressed inflammation in rheumatoid arthritis patients; a 5:1 ratio benefited asthmatic patients, but a 10:1 ratio had aversive consequences.⁸ As a general rule, a lower ratio of omega-6:omega-3 fatty acids is desirable in reducing the risk of chronic diseases of high prevalence in Western societies.

In addition to omega-3 supplementation, consideration should also be given to supplementation of GLA, the metabolic product of linoleic acid, since GLA formation in the body is very slow, with the omega-3 fatty acid, alpha-linolenic acid being preferentially metabolized over the omega-6 fatty acid, linoleic acid. GLA formation is dependent on the activity of the D₆D enzyme, which is hindered by numerous factors including aging and lifestyle

factors (smoking and drinking alcohol), as well as certain diseases (such as diabetes and cancer), infections, inflammatory conditions (like arthritis and psoriasis), and certain drugs including corticosteroids.⁹⁻¹² Supplemental GLA, without additional omega-3 fatty acids, has been suggested to be biochemically problematic since the metabolic pathway for omega-6 fatty acids allows for the ultimate generation of desirable 1-series or undesirable 2-series prostaglandins. Unopposed omega-6 supplementation may cause an increase in arachidonic acid and the undesirable 2-series prostaglandins; whereas the combination of ALA (or eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) with GLA may antagonize conversion to arachidonic acid and instead produce desirable anti-inflammatory and anti-thrombotic n-6 eicosanoids, as well as produce less active n-3 eicosanoids. Furthermore, omega-3 PUFAs suppress production of pro-inflammatory cytokines and cartilage-degradative enzymes.¹³

Efficiency of conversion of alpha-LA to long chain n-3 fatty acids in humans depends on a myriad of factors, including the amount of dietary n-6 fatty acids and long chain PUFAs. Studies generally show conversion below 5%, although some research suggests much higher conversion rates.¹⁴ In the absence of lifestyle and disease conditions that inhibit D₆D formation, and in the presence of sufficient nutrient enzyme co-factors, significant amounts of ALA may be converted into EPA and DHA. The conversion of ALA into longer-chain fatty acids may become increasingly important as marine sources of EPA and DHA become more polluted with undesirable environmental toxins. As the parent compound of the omega-3 family, plant-derived ALA is a major component of dietary intake for herbivores on land and in the sea. Furthermore, emerging evidence suggests that ALA has beneficial effects of its own, independent of its conversion to longer chain PUFAs. This has been noted, for example, in the areas of cardiovascular disease, neural function, and cancer.¹⁵

There is a complexity of interactions amongst the EFAs. Plant and marine omega-3 PUFAs and the different omega-6 PUFAs exhibit different physiological effects, and a decrease in omega-6 PUFA intake does not produce the same effects as an increase in omega-3 PUFA intake. In addition to looking at the total ratio of omega-3 to omega-6 in foods or diets, some consideration should also be given to the content of individual fatty acids such as alpha-linolenic acid, marine n-3 PUFA, LA, and GLA when characterizing foods or diets.

Given the complexity of fatty-acid interactions, it is not surprising that different effects are obtained with different combinations of EFA supplementation. GLA, ALA, EPA, and DHA appear to be the most important fatty acids, and different amounts of these may be required based on

current health conditions and drug use.^{1, 4, 12} Consumption of macronutrients such as protein with essential fatty acids may increase the absorption of fatty acids.^{16, 174} By improving the essential fatty acid status, certain health benefits may be realized. This has proven to be the case in one animal study where the anti-inflammatory effect of GLA was increased when protein was consumed along with the GLA-containing borage oil.¹⁷

ESSENTIAL FATTY ACIDS/VITAMIN AND MINERAL INTERACTIONS

Vitamin B₆, zinc, magnesium, ascorbic acid, and calcium are important for optimizing the activity of unsaturated fatty acids including EFAs.¹⁸⁻²⁰ Zinc, ascorbic acid, and vitamin B₆ help regulate D6D activity and aid in the conversion of GLA to alprostadil (PGE₁).²¹ Deficiency of these vitamins and minerals may contribute to low levels of EFAs, and multiple deficiencies (deficiencies of EFAs and other nutrients) are linked to several diseases and disorders. These diseases and disorders include hypertension, arthritis, skin disorders (eczema and psoriasis), premenstrual syndrome, skin rashes associated with cystic fibrosis, multiple sclerosis, attention deficit disorder, cystic fibrosis, kidney disease, osteoporosis, hypertension, diabetes, aging, and cancer.²⁰⁻²⁴

Combination therapy, utilizing EFAs with vitamin and mineral micronutrients, has been suggested as a new protective and therapeutic strategy for some of these diseases.^{19, 24} Supplementation of EFAs in combination with certain vitamins and minerals, including magnesium, selenium, zinc and vitamins B₆, B₂, D and E, on a daily basis, has also been suggested as prevention against developing multiple sclerosis.²⁵ Calcium, magnesium, zinc, and vitamins A, C and E, as well as EFAs, influence blood pressure.²⁴ Low levels of all these nutrients are found in hypertension, and beneficial interactions between these elements could enhance the effectiveness of treatment with these nutrients.²⁴ Evidence is surfacing that these same deficiencies, which are responsible for hypertension, may also be responsible for the development of insulin resistance and diabetes.²⁶ Much of the evidence so far is speculative, suggestive, and preliminary in nature, although human clinical trials have demonstrated some success, most notably in the area of inflammation and bone health.

Recurrent chronic inflammatory injuries such as "tennis elbow" may be helped by a combination of EFAs and antioxidants. One specific treatment comprised of vitamins A, C, and E plus selenium and zinc in combination with fish and borage oil, showed a favorable response for the athletes on Denmark's National Rowing Team.²⁷

Optimal absorption, and thus activity, of vitamin D and calcium are dependent on sufficient fatty acids being supplied in the diet.²⁸⁻³⁰ Supplementation with two essen-

tial fatty acids, GLA and EPA, enhances calcium absorption and activity, with a corresponding decrease or reversal of bone loss.²³¹ This may be due to a multitude of actions since EFAs enhance vitamin D absorption, reduce the excretion of calcium, increase calcium deposition in bone, improve bone strength, and enhance the synthesis of bone collagen. EFAs also improve cell-membrane fluidity and stability, which may also contribute to increased calcium levels. Although most of the research has been done in animals, a placebo-controlled clinical trial in elderly women with senile osteoporosis confirmed an increase in bone density in the women taking GLA and EPA along with their calcium, in comparison to no effect or a decline in bone density in the women consuming calcium alone.³²

High doses of supplemental EFAs may potentially increase the need for vitamin E or other antioxidants since a diet high in polyunsaturated fatty acids may enhance oxidation of lipids, compared to a diet high in monounsaturated or saturated fatty acids.³³ A broad range of tocopherols and their biochemical cousins, the tocotrienols, as well as carotenes are found naturally in some oils, such as palm and coconut oil. These compounds are potential mediators of cellular functions, as well as being powerful antioxidants to help protect against fatty-acid oxidation. In addition, increasing the dietary intake of antioxidant-abundant foods, such as garlic, green tea, carotene-rich red-orange vegetables, and flavonoid-rich berries, will help provide broad-range protection against oxidation of PUFAs in the body. The interaction between fatty acids and antioxidants emphasizes the fact that EFAs are part of the whole diet, and should be viewed in this context, rather than in isolation.

ESSENTIAL FATTY ACIDS/DRUG INTERACTIONS

Since fatty acids can alter the composition of the cell membrane, and therefore its fluidity and permeability, it is not unexpected that fatty acids may modulate the effects of drugs. In fact, evidence is mounting that anomalies in cell-membrane lipid composition may be the defect that links genetic and dietary factors with various disorders and diseases such as inflammatory disease and cancer.³⁴ EFAs may enhance the activity of drugs by improving their absorption and by increasing the entry of the drug into the cell, or by augmenting their pharmacological actions through second messengers or gene regulation. Preliminary research in the area of arthritis and inflammation, infections, immune disorders and cancer suggest that EFAs may increase the effectiveness of drug therapy. EFAs also exhibit activity of their own in these areas.³⁴

INFLAMMATORY DISEASE AND ARTHRITIS

Arthritic patients on standard non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and aspirin, as

TABLE 1
ESSENTIAL FATTY ACIDS INTERACTIONS WITH DRUGS AND NUTRIENTS

Nutrient/Drug	Relationship or Interaction with EFAs
Protein	<ul style="list-style-type: none"> •May increase absorption of fatty acids •May enhance beneficial effects of EFAs
Saturated, monounsaturated, and trans-fatty acids	<ul style="list-style-type: none"> •Decreases formation of long chain EFAs •May increase the need for EFAs
Excess LA in the diet	<ul style="list-style-type: none"> •Decreases formation of GLA due to depression of D₆D activity •Associated with certain disease states (ie, inflammation, dermatitis, diabetes)
Excess omega-3 EFAs	<ul style="list-style-type: none"> •Inhibits omega-6 EFA metabolism
Excess omega-6 EFAs	<ul style="list-style-type: none"> •Inhibits omega-3 EFA metabolism
Corticosteroids	<ul style="list-style-type: none"> •Depresses D₆D activity •Decreases formation of GLA
Vitamin/Mineral Supplements	<ul style="list-style-type: none"> •May be useful, along with EFAs, in the prevention and treatment of certain diseases (ie, multiple sclerosis, hypertension, diabetes) •Zinc, ascorbic acid and vitamin B6 aid in the metabolism of EFAs
Antioxidants	<ul style="list-style-type: none"> •May enhance the anti-inflammatory effect of GLA (borage oil) •Protects against fatty-acid oxidation •Combination with EFAs may prove useful in prevention and treatment of certain diseases
Vitamin D/Calcium	<ul style="list-style-type: none"> •GLA and EPA may enhance calcium absorption and activity of calcium/vitamin D •May enhance the decrease or reversal of bone loss
Fat-soluble vitamins (vitamin A, D, E, K)	<ul style="list-style-type: none"> •Absorption may be increased by increased dietary EFA intake
Vitamin E	<ul style="list-style-type: none"> •Need for vitamin E may be increased with high intakes of unsaturated fatty acids and EFAs
NSAIDs	<ul style="list-style-type: none"> •Supplementation with GLA and EPA may decrease the need for NSAIDs in inflammatory conditions (ie, rheumatoid arthritis, atopic dermatitis)
Steroid drugs	<ul style="list-style-type: none"> •Anti-inflammatory effects of GLA may decrease the need for long-term steroid treatment
Doxorubicin	<ul style="list-style-type: none"> •EPA/DHA may increase the anti-cancer effect of doxorubicin and may decrease the cardiotoxic effects of doxorubicin
Tamoxifen	<ul style="list-style-type: none"> •GLA may enhance the effectiveness of tamoxifen and elicit a faster response
Paclitaxel	<ul style="list-style-type: none"> •GLA may enhance the anti-cancer effect of paclitaxel •ALA, EPA and DHA may also be effective
Anti-cancer drugs	<ul style="list-style-type: none"> •GLA and EPA may be toxic to certain cancer cells which are resistant to other treatment
Anti-thrombotic therapy (ie, aspirin, warfarin)	<ul style="list-style-type: none"> •High dose EPA and DHA may increase bleeding time, decrease clotting time and thin the blood

EFA = essential fatty acids; GLA = gamma-linolenic acid; NSAIDS = non-steroidal anti-inflammatory drugs; EPA = eicosapentaenoic acid; ALA = alpha-linolenic acid; DHA = docosahexaenoic acid

well as those patients on steroids, have been able to decrease the dose of their medication after supplementation with EFAs, notably GLA.³⁵ Some patients have even been able to discontinue the use of their prescription-drug therapy and treat their arthritis using only EFA supplementation.³⁵ The additive or synergistic effects seen when essential fatty acids are combined with anti-inflammatory drug therapy may reduce the dose required, as well as lessen the side effects associated with therapy.

Recent research suggests that treatment of allergies and asthma with GLA, in conjunction with standard steroid treatment, may be able to decrease the risks associated with long-term steroid supplementation.³⁶ This may potentially lower the incidence of side effects, which may occur from potent drug therapy.

In addition, some early research shows that EFAs may positively alter the course of inflammatory disease, indicating the potential of EFAs to actually stop disease progression.³⁷ EFAs have been suggested to act as disease modifying anti-rheumatic drugs (DMARDs). Furthermore, EFAs may be able to directly decrease side effects, such as stomach upset, that may occur with use of anti-inflammatory and steroid medication. PUFAs have been shown to decrease the incidence of drug-induced ulcers, as well as to aid in healing them, in animal and unpublished human studies.^{38, 39} This effect may be related to the ability of PUFAs to inhibit the growth of *Helicobacter pylori* (a bacteria associated with the development of ulcers) in vitro.

INFECTIONS, IMMUNE SYSTEM, AND CANCER

Recent research in the areas of infections, immune system disorders, and cancer suggests that essential fatty acids may enhance the therapeutic effectiveness of drugs used in these conditions. When patients with infections, AIDS, and cancer were given fish oil supplements, they exhibited less weight loss, an increase in weight gain, enhanced immune-system activity, and a decreased number of infections, resulting in fewer hospitalizations.⁴⁰ While this may be due to a variety of factors, EFAs have been shown to be effective in overcoming bacterial resistance by increasing the effectiveness of certain antibiotics on resistant bacteria.^{41,42}

Certain EFAs such as EPA and GLA have been found to increase the effectiveness of certain anti-cancer drugs by increasing their uptake.⁴³ In vitro and in vivo animal studies have shown that fish oil can increase the anti-cancer activity of doxorubicin in various types of cancer, including drug-resistant cancer cells.⁴⁴⁻⁴⁶ The combination of doxorubicin and fish oil resulted in a significant reduction in tumor growth, compared to doxorubicin alone in mice with breast cancer.⁴⁷

Perhaps most promising is the combination of GLA with 2 anti-cancer drugs—tamoxifen and paclitaxel—that

are widely used in the treatment of breast and ovarian cancer. In a human clinical trial, it was found that when GLA was given in combination with tamoxifen, the effectiveness of tamoxifen was enhanced and a faster response was obtained, compared to tamoxifen therapy alone.⁴⁸ In vitro studies demonstrate that various fatty acids can modulate tumor-cell sensitivity to paclitaxel-based therapy.⁴⁹ GLA was the most potent at enhancing the anti-cancer activity of paclitaxel cytotoxicity, followed by ALA, EPA, and DHA. Further research reveals that other standard cancer treatments (employing cisplatin or doxorubicin) may also be enhanced by fatty acid supplementation.^{50, 51} At the same time, EFAs have been shown to reduce the cardiotoxic effects of doxorubicin in cell culture studies.⁵²

As alluded to earlier, supplementation with EFAs may also help overcome tumor cell drug resistance. Tumor cell drug resistance may be due to a lower concentration of the anticancer drug in the tumor cells, due to increased efflux and decreased influx, causing a lower response to the chemotherapy. EPA and GLA have been found to be toxic to certain cancer cells that are resistant to other treatment.⁵⁰ So far, research indicating that EFAs may have the potential to reverse and inhibit tumor cell drug resistance is very encouraging.^{53, 54}

As in other conditions, specific combinations of certain EFAs may be more effective in reducing cancer cells than other combinations. For instance, an in-vitro study on a prostate cell line indicated that the combination of GLA and ALA was more effective in killing cancer cells than ALA alone.⁵⁵

The interaction and synergism between essential fatty acids and certain drugs may make combination therapy that employs both an attractive option. EFAs may potentially be used as an effective adjunctive agent and as replacement therapy for both over-the-counter and prescription drugs. There are no known drug interactions that would limit the use of this therapy, although several cautions have been reported.

In very high doses (such as 10 to 20 grams per day), EPA and DHA thin the blood. An increase in bleeding time and a decrease in clotting time have been noted after supplementation with EPA and DHA.⁵⁶ However, in clinical trials, patients on antithrombotic therapy (aspirin, warfarin) have taken fish oil without experiencing any clinically-significant adverse effects, and with noted improvements in clinical outcome (eg, decreased occlusion after coronary bypass).⁷⁻⁵⁹ Thus, this may be considered a desirable effect that decreases the risk of cardiovascular disease, and which would not normally be of concern. Nonetheless, it may be suggested that patients on anti-coagulant or blood-thinning medications (eg, aspirin, warfarin) should exercise caution when starting EFA supplements containing EPA and DHA,

and should be monitored appropriately when taking these specific supplements. In clinical trials, borage oil (containing GLA) did not affect bleeding or clotting times.

There have been cautions mentioned in the literature regarding supplementation of evening primrose oil in patients suffering from epilepsy. These cautions are based on a report that three patients diagnosed with schizophrenia, but resistant to treatment, were supplemented with evening primrose oil, and subsequently displayed features typical of temporal lobe epilepsy.⁶⁰ GLA and LA have been suggested to be diagnostic aids for differentiating between temporal lobe epilepsy and schizophrenia. Subsequent to this report, evening primrose oil has been given to schizophrenic patients in clinical trials without incident. It has been suggested that the patients discussed in the initial report may have been misdiagnosed, which led to exacerbation of their epilepsy, since no other similar incidents have been reported.

Thus, no concrete contraindications or drug interactions appear to exist with respect to the consumption of EFAs. However, as with any therapy, it is advisable to consult your medical doctor or health care professional before starting supplementation.

SUMMARY

Various dietary factors may affect the absorption and utilization of essential fatty acids, including intake of fatty acids, protein, vitamins and minerals. While the complexity of these nutrient interrelationships make it difficult to ascertain the best diet in which to obtain optimal EFA status, a diet low in saturated and trans-fatty acids, and which provides adequate levels of protein, vitamins and minerals, appears to be prudent. Such a diet may possibly enhance the nutritional status of an individual, especially the essential fatty-acid status, and improve health as well as help prevent and manage disease.

A wide variety of conditions and diseases ranging from arthritis and inflammation to skin disorders and cancer are linked to low levels of EFAs, as well as low levels of other nutrients, in the diet. Many of these disorders have been shown to respond well to combination therapy, employing EFAs with other nutrients as well as drugs. Some of the research is still considered preliminary in nature, such as the anti-cancer research, which requires further confirmation with controlled clinical studies before any firm recommendations can be made. In other areas, such as arthritis and inflammation, the data is much stronger. In these conditions, supplementation with essential fatty acids, either alone or in combination with other nutrient and drug therapy, is a safe and effective option for patients.

EFA supplementation may have synergistic effects, making drug therapy more effective. This supplementa-

tion may allow for dosage reduction and even discontinuation of drug therapy, and may also decrease adverse effects. A major advantage of EFA supplementation, both alone and in combination with other nutrients and drugs, is the long history of use and strong safety profile associated with EFAs. EFAs can be safely used in the majority of patients, along with most other therapies, including vitamins, minerals, and herbs, as well as both over-the-counter and prescription drugs.

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