JOSEPH HIBBELN
10/ 6S240
9000 Rockville pike
Behesda, MD 20892

ATTN:
PHONE:301-435-4028
FAX: -
E-MAIL

NIH Fiche to Paper Journal

TITLE: AMERICAN JOURNAL OF CLINICAL NUTRITION
PUBLISHER/PLACE: American Society Of Clinical Nutrition Bethesda Md
VOLUME/ISSUE/PAGES:1995 Jul;62(1):1-9 1-9
DATE: 1995
AUTHOR OF ARTICLE: Hibbeln JR; Salem N
TITLE OF ARTICLE: Dietary polyunsaturated fatty acids and depression
ISSN: 0002-9165
OTHER NOS/LETTERS: LOANSOMEDOC: 0376027
Library reports holding volume or year
7598049
SOURCE: PubMed
CALL NUMBER: W1 AM45J (GENCOLL); W1 AM45J (REFCOLL); Film S0414
REQUESTER INFO: JHIBBELN
DELIVERY: E-mail: jhibbeln@niaaa.nih.gov
REPLY: Mail:

Special Article

Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy[1,2]

Joseph R Hibbeln and Norman Salem Jr

ABSTRACT Recent studies have both offered and contested the proposition that lowering plasma cholesterol by diet and medications increases suicide, homicide, and depression. Significant confounding factors include the quantity and distribution of dietary n−6 and n−3 polyunsaturated essential fatty acids that influence serum lipids and alter the biophysical and biochemical properties of cell membranes. Epidemiological studies in various countries and in the United States in the last century suggest that decreased n−3 fatty acid consumption correlates with increasing rates of depression. This is consistent with a well-established positive correlation between depression and coronary artery disease. Long-chain n−3 polyunsaturate deficiency may also contribute to depressive symptoms in alcoholism, multiple sclerosis, and postpartum depression. We postulate that adequate long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid, may reduce the development of depression just as n−3 polyunsaturated fatty acids may reduce coronary artery disease. *Am J Clin Nutr* 1995;62:1–9.

KEY WORDS Alcoholism, dietary fat, arachidonic acid, docosahexaenoic acid, cholesterol, multiple sclerosis, coronary artery disease, ω-3 fatty acids, depression, postpartum depression

INTRODUCTION

Recent studies have suggested that lowering serum cholesterol reduces death from cardiac causes but may increase overall mortality due to increased suicide, homicide, and accidents (1–3). A similar association between low serum cholesterol and increased depression was reported by Morgan et al (4). In contrast, others have shown no association (5) or opposite results (6, 7). Examination of the differences in the intake of polyunsaturated fatty acids may explain the conflicting reports. In a prospective 5-y study, Weidner et al (6) found that switching patients to a cholesterol-lowering diet was associated with reductions in measures of depression ($r = -0.10$, $P < 0.02$) and aggressive hostility ($r = -0.10$, $P < 0.08$) in the Hopkins Symptom Checklist. In this diet, patients were instructed to increase fish consumption, which increased n−3 polyunsaturate intake (6, 8). Similarly, Pekkanen et al (7) found that lower serum cholesterol was associated with lower mortality due to accidents and violence in coastal Western Finland but no association was found in Eastern Finland, which is inland; thus, the consumption of fish may have been protective. Although Kaplan et al (9) showed increased aggression in primates with a diet that lowered serum cholesterol, the composition of essential fatty acids in the two diets also changed. Ratios of n−6 to n−3 essential fatty acids increased from ≈6:1 on a high-fat diet to ≈33:1 on a low-fat diet. In the serum of violent impulsive offenders, Virkkunen et al (10) noted a similar increase in long-chain n−6 polyunsaturates and a decrease of long-chain n−3 polyunsaturates, when compared with diet-matched control subjects. Both serum cholesterol and dietary polyunsaturated fats play a role in the pathogenesis of atherosclerosis, and both should be examined in studies of depression and aggression.

Dietary polyunsaturated fats and cholesterol are the major determinants of membrane order (or fluidity) in synaptic membranes. Up to 45% of the fatty acids of synaptic membranes are essential fatty acids (11). These long-chain polyunsaturated fatty acids, docosahexaenoic acid (DHA, or 22:6n−3) and arachidonic acid (AA, or 20:4n−6), can be ingested directly or biosynthesized from essential fatty acid precursors (18:3n−3 and 18:2n−6, respectively) (12). Mammals cannot interconvert fatty acids between n−6 and n−3 families. Unsaturated fatty acid composition is a major physiological determinant of the biophysical properties of membranes and 22:6n−3 seems highly specialized for neuronal membrane function (13). 22:6 n−3 is replaced by n−6 fatty acids in n−3 deficiency states but biophysical properties may not be fully compensated (14).

EPIDEMIOLOGY

Increasing rates of depression among cohorts in the last century may be influenced by the consumption of increased amounts of saturated fatty acids and n−6 essential fatty acids and the decreased consumption of n−3 essential fatty acids. Increases in the lifetime prevalence of depression in North America during the last 100 y are dramatic and well documented by the Epidemiological Catchment Area survey (15). Since 1900, every progressive cohort (ie, those born between 1930 and 1940) has had a higher lifetime risk of depression than the previous cohort (ie, those born between 1920 and

[1] From the Laboratory of Membrane Biophysics and Biochemistry, DICBR, National Institute of Alcohol Abuse and Alcoholism, Rockville, MD.

[2] Address reprint requests to JR Hibbeln, Laboratory of Membrane Biophysics and Biochemistry, DICBR, National Institute of Alcohol Abuse and Alcoholism, 12501 Washington Avenue, Rockville, MD 20852.

Received June 8, 1994.

Accepted for publication February 14, 1995.

1930). Many stresses of modern life contribute to this effect, but relative deficiencies in n−3 essential fatty acids may also intensify vulnerability to depression. On the basis of estimates of paleolithic nutrition and modern hunter-gatherer populations, (16) humans evolved on a diet lower in saturated and higher in polyunsaturated fats than the modern diet. Moreover, the proportion of n−6 polyunsaturates in the diet has markedly increased in the last century because of the reliance of agriculture on a few plant species as sources for essential fatty acids for the domestic food chain (17). Wild and free-range animals have significantly more n−3 fatty acids in tissues than currently produced commercial livestock (18). During human evolution, ratios of dietary n−6 to n−3 fatty acids were ≈1:1, but are now estimated to be 10:1 to 25:1 (19, 20). Use of infant formula, which is devoid of 22:6n−3 in contrast with human milk, has also increased in the latter half of this century. Lower concentrations of n−3 fatty acids in formulas compared with breast milk resulted in decreased cortical concentrations of 22:6n−3 in preterm and full-term human infants (21, 22). One physiological outcome may be a decreased intelligence quotient in 7-y olds who were formula-fed as infants (23). Just as increased consumption of saturated fat and the altered ratio of n−6 to n−3 intake is believed to have increased the incidence of atherosclerosis in the last century (24), it is suggested here that decreasing n−3 essential fatty acid intake may also affect the nervous system, in early development or adulthood, to increase vulnerability to depression.

Societies consuming large amounts of fish and n−3 fatty acids appear to have lower rates of major depression. In an intensive cross-national collaborative study of rates of depression, North American and European populations showed cumulative rates of depression 10-fold greater than a Taiwanese population (25). Similarly, in Hong Kong, the prevalence of single episodes in males and females, respectively, was 0.71% and 1.30% and of recurrent episodes was 0.55% and 1.11% (26), described by culturally specific, well-verified, rating scales (27). However, in North America the rates of major depression found in the Epidemiological Catchment Area survey were 4.4% and 8.7% (New Haven, CT), 2.3% and 4.9% (Baltimore), and 2.5% and 8.1% (St Louis) for males and females, respectively (28). As expected in countries where fish is a prominent constituent of the diet, n−3 fatty acid consumption is greater in Chinese and Taiwanese than in North American populations (29). In Japan where fish consumption is high, rates of depression were estimated at 0.35% and 0.46% for males and females, respectively (30, 31). In three elderly Japanese populations, prevalence rates of depressive symptoms have been reported as 1.9% (n = 16; none with major depression requiring treatment), as 0.9% n = 5000; all met ICD-9 criteria), and as 0.0% in a rural fishing village where all elderly inhabitants (n = 708) were interviewed by psychiatrists (32). Establishment of the magnitude of epidemiological relations between n−3 intake and depression will require simultaneous sampling of dietary fatty acid intake and culturally specific measures of depression, because many factors play a role in this complex disease process.

CORONARY ARTERY DISEASE AND DEPRESSION

If low n−3 fatty acid intake contributes to depression, and low n−3 intake contributes to coronary artery disease (33) then this hypothesis predicts that depression and coronary artery disease should be positively correlated. In a meta-analysis of 83 studies, Booth-Kewley and Friedman (34) found a consistent positive association between depression and coronary heart disease (r = 0.205, $P < 0.0000001$) and myocardial infarction (r = 0.259, $P < 0.0000001$). Depression was more strongly associated with coronary artery disease (r = 0.205) than were any other personality variables, including combined measures of type A personality (r = 0.136), Jenkins Activity Scale measures (r = 0.067), or specific measures such as hostility or competitiveness. Fielding (35) reviewed 30 y of research and consistently found that premorbid depression predicts coronary artery disease and poor survival outcome. Depression as a reaction to acute myocardial infarction was considered separately. Felding also suggested that depressive symptoms and acute myocardial infarction have a common etiology. Major depression near the time of myocardial infarction predicted additional adverse cardiac events and cardiac mortality in the following 24 h, and after 6, 12, and 18 mo (36–39). The statistically robust positive correlation between depression and coronary artery disease suggests that if elevated serum cholesterol predicts coronary artery disease, it should also predict increased depression, if serum cholesterol is linked to both illnesses. Therefore, the robust positive correlation between depression and coronary artery disease (34, 35) is in contrast with the previously proposed (2–4) association of low serum cholesterol and increased depression, violence, and serum cholesterol, which would predict a protective effect of depression on coronary artery disease.

ALCOHOLISM

Depression secondary to alcoholism is common, occurring in 16–59% of alcoholic patients (40, 41), who represent 5–10% of the US population. Depression occurs more frequently in alcoholics (58%) than in opiate addicts (32%) or schizophrenics (28%) (42). Schuckit (43) noted serious depression in 70% of patients with prolonged heavy drinking and argued that these depressions were the consequence of the pharmacological effects of alcohol intoxication, withdrawal, and life crises. Severe depressive symptoms remitted within 4–6 wk of abstinence alone. Alcohol is a prooxidant that leads to increased lipid peroxidation (44, 45). A consequence of increased lipid peroxidation may be a decrease in the concentrations of the more highly unsaturated species such as 22:6n−3. Several studies have demonstrated that chronic alcohol intoxication depletes long-chain n−3 polyunsaturated fatty acids from neuronal membranes (46), which we suggest may facilitate development of depressive symptoms. With sobriety, depression may resolve in patients as polyunsaturated fatty acids reaccumulate in the nervous system. This hypothesis predicts that supplementation with dietary long-chain n−3 polyunsaturated fatty acids may speed resolution of depressive symptoms in recovering alcoholics.

MULTIPLE SCLEROSIS

The incidence of depression in multiple sclerosis is high and out of proportion to the incidence found in patients with similar disabilities, as reported in a meta-analysis of six studies (47).

Lesion location also does not explain depressive symptomatology (48). We suggest that depletion of n−3 fatty acids in the central nervous system, outside of the plaques, may contribute to these symptoms. Wilson and Tocher (49) confirmed the early observations (50, 51) that the long-chain polyunsaturates 20:4n−6 and 22:6n−3 are reduced in normal-appearing white matter, compared with control subjects. Marked reductions also occur in plasma (52, 53), and 22:6n−3 was not detected in adipose stores (54). Bernsohn and Stephanides (55) suggested that deficient dietary intake of 22:6n−3 during critical periods of brain development could explain the geographical differences in the incidence of multiple sclerosis. These geographical differences are curiously similar to differences in rates of major depressions (28). Treatment with mixtures of n−3 and n−6 fatty acids generally results in a mild reduction in relapses but a general overall improvement in perception of quality of life (56), which may indicate a reversal of depressive symptoms.

POSTPARTUM DEPRESSION

Pregnancy leads to a depletion of maternal plasma 22:6n−3 (57), presumably because of the increased supply of this critical nutrient to the developing fetal nervous system. A single pregnancy depletes maternal plasma 22:6n−3, and multiple pregnancies cause a progressive decrease in maternal plasma 22:6n−3 concentrations (58). This relative maternal depletion of 22:6n−3 may be one of the complex factors leading to increased risk of depression in women of childbearing age (28) and in postpartum periods (59).

AFFECTIVE DISORDERS

Data on lipid composition in tissues from depressed patients is sparse. However, Sengupta et al (60) documented decreases in total serum phosphatidylserine in patients with unipolar depression. Abnormalities in biophysical measures of membrane order that have been reported in erythrocytes, lymphocytes, and platelets of patients with affective illnesses (61, 62) may be one outcome of alterations in lipid composition. In contrast with the prediction of this hypothesis, Fehily et al (63) and Ellis and Sanders (64) found that the concentrations of 22:6n−3 in plasma phosphatidylcholine increased with severity of depressive symptoms, but these findings are difficult to interpret because of the diagnostic heterogeneity of the patients, lack of dietary assessment, and reported decreases in total serum phosphatidylcholine in patients with unipolar depression (60). In addition, one-third of these patients were taking psychotrophic medications, which may cause phospholipidosis (65). Decreased long-chain n−3 polyunsaturated fatty acids in the blood of depressed patients may reflect several processes: *1*) long-term dietary deficiency of n−3 fatty acids, increasing vulnerability to depression; *2*) insufficient capacity for elongation and desaturation of n−3 precursors or elevated catabolism in depressed patients, leading to a state of long-chain n−3 deficiency; *3*) hyperactivation of the hypothalamic pituitary adrenal stress axis, causing increased degradation of polyunsaturates; *4*) depression, causing changes in dietary fat selection, which excludes n−3 fatty acids; and *5*) other confounding factors that are common to depression, eg, smoking. The clinical studies referenced here do not resolve these possibilities. To our knowledge, no study has controlled or documented dietary polyunsaturate intake, smoking habits, blood or adipose fatty acid composition, metabolism to long-chain fatty acids, and quantified depressive symptoms, which would be required to definitively test this hypothesis.

DIET-INDUCED MEMBRANE DISORDER AND DISRUPTION OF MULTIPLE NEUROTRANSMITTER SYSTEMS: A BIOPHYSICAL HYPOTHESIS

Reduced functioning of adrenergic (66) and serotonergic neurotransmission are central to the pathophysiology of depression as predicted by the biogenic amine hypothesis. Membrane essential fatty acids may influence each step in biogenic amine function, including neurotransmitter production, degradation, release, reuptake, and binding. Data concerning the specific effects of dietary long-chain n−3 polyunsaturates on biogenic amine function are sparse but studies of n−3 and n−6 fatty acids do suggest that dietary polyunsaturates may effect noradrenergic and serotonergic neurotransmission. Phosphatidylserine prepared from brain cortex, therefore rich in 22:6n−3 (12, 13), increased dopamine, norepinephrine, and epinephrine concentrations but phosphatidylserine prepared from soybean, with low concentrations of 22:6n−3, did not effect catecholamines (67). In an animal model of depression, mice supplemented with lard showed resistance to depletion of brain serotonin when challenged with reserpine (68). Brain concentrations of serotonin and 5-hydroxyindolacetic acid were higher after a corn-oil diet than after a tallow diet (69). It is difficult to determine which diet had more total n−3 fatty acids and more long-chain fatty acids. Perhaps the tallow had greater amounts of 22:6n−3. In adrenal medullary cells, 20:4n−6 activates tyrosine hydroxylase, the rate-limiting step of catecholamine synthesis (70). Tryptophan hydroxylase activity, the rate-limiting step of serotonin synthesis, has a nonlinear response to small changes in membrane order (71). Monoamine oxidase activity in brain mitochondria was significantly lower in rats fed a soybean-oil diet compared with lard (72). These data suggest that the balance between n−3 and n−6 fatty acids and other measures of the distribution of fats in the diet, may modulate the metabolism of biogenic amines.

Receptor function in the nervous system can also be modified by dietary polyunsaturates. Rats fed a diet deficient in 18:3n−3 showed decreased tissue concentrations of 22:6n−3 and replacement with 22:5n−6 in frontal cortex and striatum (S Delion, D Chalon, J Jouve, C Couet, G Durand, unpublished observations, 1993; 12, 13) and in human brain (21, 22). However, 22:5n−6 may not mimic the biophysical properties of 22:6n−3 (14). These changes were accompanied by a 55% decrease in dopamine concentrations and a 13% decrease in dopamine D_2 receptor binding (S Delion, et al, unpublished observations, 1993). Diets rich in sunflower oil (high in n−6) increase norepinephrine release and α_2 adrenergic sensitivity (73) as well as β_2 adrenergic binding and coupling to adenylate cyclase (74, 75). Engler (76) suggested that 22:6n−3–induced relaxation of vasculature in vitro was specific to α_2 adrenergic receptors. However, vascular endothelium from n−3–supplemented animals has increased relaxation in response to serotonin, indicating augmented receptor sensitivity (77). Serotonin binding is markedly altered in vitro by changes in membrane

order induced by 18:2n−6 (78) or by cholesterol (79). Serotonin release from platelets is inhibited by *cis*-unsaturated fatty acids and inversely correlated with their melting points (80). Finally, serotonin reuptake, a site of action for many antidepressants, is decreased by cholesterol and increased by 18:1n−9 in vitro (81). Therefore, many aspects of biogenic amine neurotransmission, including its metabolism, release, uptake, and receptor function, appear to be influenced by dietary fatty acyl composition and the resulting changes in membrane lipid composition and biophysical properties. The high concentrations of long-chain n−3 fatty acids in synaptic membranes (12), with their unique but not well-understood biophysical properties (13, 14), indicate that they may have a critical role in synaptic neurotransmission.

SIGNAL TRANSDUCTION

Abnormalities of G protein–mediated signal transduction have been implicated in affective disorders (82, 83). Schreiber et al (84) reported hyperfunctional G proteins in manic patients. Diets enriched with n−3 fatty acids, when compared with those enriched with n−6 fatty acids or cholesterol, greatly enhance G_s coupling to adenylate cyclase stimulated by glucagon (85) as well as G_s number (86). In depressed patients, Pandey et al (87) reported a decrease in β_2 adrenergic–stimulated cyclic AMP concentrations, which is G protein–dependent. Adenylate cyclase is dependent on its lipid environment for optimal functioning (88). Mitchell et al (89) have focused on the critical contribution of fatty acyl chain composition on G protein–mediated signal transduction. They have demonstrated that polyunsaturate composition is the primary component determining the fractional volume of the membrane, which predicts kinetics of G_s protein diffusional search and coupling to rhodopsin. Cholesterol appears to have only a role in fine tuning this classic model of a heptahelical receptor system, which is secondary to the effects of polyunsaturate composition. Thus, small changes in membrane structure induced by alterations in phospholipid molecular species may impair signal transduction, leading to changes in brain function and behavior (71).

INSULIN RESISTANCE IN DEPRESSION

Insulin resistance, presumably due to receptor insensitivity, has repeatedly been observed in patients with major depression (90–92) and in chronic alcoholics after withdrawal, independent of liver disease (93, 94). Peripheral depletion of 22:6n−3 may help to explain these findings. Decreased skeletal muscle concentrations of 22:6n−3 and 22:5n−3 are very highly correlated ($r = 0.97$) with increased insulin receptor insensitivity in rats fed n−3 and n−6 fatty acids in a variety of ratios (95). Human rectus abdominus muscle biopsies show similar effects of 20- and 22-carbon fatty acids and also suggest that elevated 18:2n−6 is associated with increased receptor insensitivity (96). Retinoblastoma cells enriched with 22:6n−3 show an increase in insulin binding because of an increase in receptor number (97).

CALCIUM CHANNELS

Increased intracellular calcium has been documented in depressed patients and is compatible with many clinical observations of depressive effects of hypercalcemia (98). Interestingly, addition of exogenous 22:6n−3 lowers stimulated increases in intracellular calcium by inhibition of L-type calcium channels in cultured cardiac myocytes (99). If 22:6n−3 has similar function in the central nervous system in vivo, then depletion of 22:6n−3 might be expected to increase stimulated calcium flux and intracellular concentrations. Verapamil (Wyeth-Ayherst, Philadelphia), which blocks L-type calcium channels and is useful in treating some affective disorders, may reverse the effects of 22:6n−3 depletion on calcium metabolism.

KINDLING AND LONG-TERM POTENTIATION

One possible mechanism by which decreased brain 22:6n−3 may predispose the developing nervous system to depression is by allowing the development of kindling. Human depression is a cycling recurrent illness that may be modeled in animals with a paradigm known as kindling (100). In humans, periods of severe stresses are often followed by depressions and it is hypothesized that repeated stress may entrain self-propagating cycles of depression in vulnerable individuals. In the kindling paradigm, animals receive electrical or chemical stimulation repeated daily. These stimulations are initially subthreshold but eventually induce stereotypic behaviors and seizures. Provided the environment is held constant, these behaviors become self-propagating and emerge in the absence of any stimulus, which is analogous to human depression (100). Kindling is dependent on NMDA (*N*-methyl-D-aspartate) stimulation of protein kinase C and other membrane-dependent second messengers required for the development of long-term potentiation (101, 102). Many protein kinase C species are critically dependent on the biophysical properties of the membrane determined by both lipid head group and fatty acyl composition (103). Neuronal membranes are rich in 22:6n−3, which may facilitate protein conformational changes and optimal activation of protein kinase C (104). Compared with other dietary fatty acids, 22:6n−3 has unique effects on protein kinase C (105, 106). Of all free fatty acids, only 22:6n−3 was able to stimulate the γ subunit of protein kinase C without diacylglycerol (107). 22:6n−3 has unique biophysical properties simultaneously allowing optimal packing and maximal acyl chain disorder that cannot be duplicated with other polyunsaturates from the n−6 or n−3 family (14). Phosphatidylcholine species with 22:6n−3 stabilize protein kinase C, either potentiating or attenuating its activity (108). Lithium, which clinically dampens affective cycling, also attenuates protein kinase C membrane translocation in response to serotonin (109). Lithium-induced increases in 22:6n−3 and 20:4n−6 in phosphatidylethanolamine and phosphatidylinositol in rat brain synaptosomes may account for this effect (110). Valproic acid, a short-chain fatty acid, may also alter fatty acyl composition. Thus, a small increase of neural 22:6n−3, mediated by either diet or lithium, may lead to a more optimal environment for NMDA-protein kinase C signal transduction and thus may dampen development of depressive cycles in response to stresses.

REPEATED STRESSES MAY INDUCE POLYUNSATURATE DEPLETION

Repeated periods of emotional stress may lead to a reduction of neuronal long-chain polyunsaturates as well as kindling self-propagating periods of depression. Gulyaeva et al (111) noted increased lipid peroxidation in brain tissue during 3 wk of emotional and pain stress in rats. This chronic stress regimen initially induced superoxide dismutase activity (which plateaued and was apparently overwhelmed) leading to increased peroxidation products, decreased neuronal phospholipids, and behavioral changes consistent with depression. Similarly, 2 wk of repeated immobilization stress led to structural and functional (Na^+-K^+ ATPase) biophysical perturbations in synaptosomal membranes of rat cortex (112). In an acute-stress paradigm, 24 h of immobilization doubled concentrations of thiobarbituric acid reactive substances in rat brain (113). Six hours of immobilization markedly reduced concentrations of ascorbic acid in striatum, hypothalamus, and hippocampus (114), which may indicate depletion of protective antioxidants. One hour of immobilization reduced superoxide dismutase in the sensory motor cortex by nearly one-half (115). Hildalgo et al (116) noted an increase in brain metallothionein after 18 h of immobilization but not at 6 h, indicating a time-dependent induction of antioxidant enzymes. Kindling of the amygdala is associated with decreases in membrane order and lipid peroxidation in hippocampus, striatum, and frontal cortex 24 h after the last seizure (117). Collectively these data may suggest that repeated periods of severe stress may lead to a reduction in tissue antioxidants and increase lipid peroxidation in the brain, because the ability of the organism to regulate the antioxidant status is overtaxed.

Chronic stresses are thought to contribute to coronary artery disease by elevating triglycerides and total cholesterol (118). Although norepinephrine stimulation of lipolysis from adipose tissue during psychological stress is well described (118), it is not widely recognized that norepinephrine-activated lipoprotein lipase preferentially releases highly unsaturated fatty acids from adipose tissue (119). Highly unsaturated fatty acids are most vulnerable to peroxidation and depletion when in the form of free fatty acids. In depressed patients, plasma free fatty acids are increased to a higher concentration than can be accounted for by their peripheral catecholamine and cortisol concentrations (120). Medical students had higher ratings of stress, anxiety, and depression, but lower plasma concentrations of 20:4n−6 and 18:2n−6 than control subjects (121). Ratios of 20:4n−6 to 20:5n−3 were not calculated. Isolation stress in rats significantly inhibited the activity of liver Δ5- and Δ6 desaturases, the enzymes necessary for conversion of 18-carbon fatty acid precursors to 22:6n−3 and 20:4n−6 (122). Finally, Reisbeck et al (123) note that n−3 fatty acid deficiency might increase reactivity to stress expressed behaviorally by polydipsia in rhesus monkeys. Thus, in the absence of dietary supplementation, repeated stresses may lead to increases in long-chain polyunsaturate degradation via peroxidation, inadequate replacement by precursors, and eventual depletion of long-chain polyunsaturates, especially 22:6n−3, which may increase the vulnerability to depression.

THERAPEUTIC TRIALS OF POLYUNSATURATED FATTY ACIDS

Although 22:6n−3 has not been directly tested in clinical trials, indirect evidence may suggest that essential fatty acids have therapeutic efficacy in treating depression. In *The Anatomy of Melancholy*, published in 1652, Burton (124) recommended the use of borage oil, high in n−6 polyunsaturates, as well as a low-fat diet including fish. For severe cases, Burton (124) recommended a 2-wk diet of brains, an excellent source of 22:6n−3 and 20:4n−6. More recently, treatment with oral phosphatidylserine, prepared from bovine cortex (BC-PS), markedly improved depressive symptomatology in 11 elderly women (125). Bovine gray matter phosphatidylserine contains 29% of its fatty acids as 22:6n−3 (126). In a multicenter study of 494 elderly patients, treatment with 300 mg BC-PS/d markedly reduced withdrawal and apathy scores compared with a corn-oil placebo (127). Withdrawal and apathy scores, are often difficult to distinguish from depression. Schizophrenics with negative symptoms, characterized by withdrawal and apathy, have less than one-half the concentrations of 22:6n−3 in red blood cells compared with schizophrenics with positive, psychotic symptoms (128). Negative symptoms appear to respond to supplementation with MaxEPA (129). Stockert et al (130) suggested that BC-PS may regulate the serotonin reuptake site, a site of action of fluoxetine (Prozac; Dista Products Co, Division of Eli Lilly, Indianapolis). They noted that BC-PS reduced [^{3}H]imipramine binding sites in rat brain by 23% alone and by 47% when combined with amitryptyline. In humans, mixtures of hypothalamic phospholipids potentiated antidepressant actions (131–133) and increased cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid concentrations as well as somatotrophin release, measures often associated with an improvement in depressive symptoms (134, 135). Similar mixtures reduced immobility of rats in the Porsolt swim test (136). Borage oil and 20:5n−3 reversed psychosocial stress–induced hypertension in humans (137) and rats (138). In case reports, Rudin (139) noted beneficial psychotrophic effects of linseed oil, which is high in 18:3n−3. Taken together, these studies merely hint at a therapeutic role for n−3 essential fatty acids in depression.

CONCLUSION

Dietary long-chain polyunsaturated fatty acids, critical to both nervous system and cardiovascular function, may be an important confounding factor in the recent observations that lowering serum cholesterol may increase the risk of depression, suicide, or violence. If low serum cholesterol concentrations were linked to increased depression as Muldoon et al (140) suggest, then depression might be associated with decreased risk for coronary artery disease. This is in marked contrast with decades of psychological research that indicates that depression is positively associated with coronary artery disease. The endpoint of serum cholesterol may not be specific enough. Dietary advice given in an effort to lower serum cholesterol typically alters polyunsaturated fatty acid intake by substituting n−6 polyunsaturates for saturated fat, which increases the ratios of n−6 to n−3 fatty acids, thereby lowering n−3 fatty acids in tissues and organs (141). Human infant studies suggest that such diets given in early development lead to lowered concen-

trations of 22:6n−3 in neural tissues (21–23). Other conditions associated with 22:6n−3 depletion, including alcoholism, multiple sclerosis, and postpartum states are also associated with curiously high rates of depression. One mechanism may be disruption of the biophysical properties of neuronal membranes, which are critically determined by long-chain polyunsaturated fatty acid composition. Biophysical properties of synaptic membranes directly influence neurotransmitter biosynthesis, signal transduction, uptake of serotonin, binding of β_2 adrenergic and serotonergic receptors, and monoamine oxidase activity, factors that are all implicated in the neurobiology of depression. Previous hypotheses concerning eicosanoids (142, 143) and membrane order (144, 145) are consistent with this biophysical hypothesis. Although we present a case for the association between depression and 22:6n−3 deficiency, the relations between dietary polyunsaturated fats, affective and psychotic (146) disorders, as well as type A personality traits, impulsivity, and violence, may also be important. The core hypothesis presented here, that inadequate 22:6n−3 in the nervous system may increase vulnerability to depression, requires a great deal of future experimental work for confirmation but may suggest a role for dietary supplementation in prevention or therapy for depression.

We acknowledge the late T George Bidder for his contributions to science, education, and this hypothesis.

REFERENCES

1. Fowkes FGR, Leng GC, Donnan PT, Deary IJ, Riemersma RA, Housley E. Serum cholesterol, triglycerides and aggression in the general population. Lancet 1992;340:995–8.
2. Endelberg H. Low cholesterol and suicide. Lancet 1992;339:727–9.
3. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. Br J Med 1990;301:309–14.
4. Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depressive symptoms in older men. Lancet 1993;341: 75–9.
5. Brown LS, Salive ME, Harris TB, Simonsick EM, Guralnik JM, Kohout FJ. Low cholesterol concentrations and severe depressive symptoms in elderly people. Br Med J 1994;308:1328–32.
6. Weidner G, Connor SL, Hollis JF, Connor WE. Improvements in hostility and depression in relation to dietary change and cholesterol lowering. Ann Intern Med 1992;117:820–3.
7. Pekkanen J, Nissinen A, Punsar S, Karvonen MJ. Serum cholesterol and the risk of accidental or violent death in a 25 year follow-up: the Finnish cohorts of the Seven Countries Study. Arch Intern Med 1989;149:1589–91.
8. Connor WE, Connor SL. Dietary treatment of hyperlipidemia. In: Rifkind BM, Levy RI, eds. Hyperlipidemia: diagnosis and therapy. New York: Grune and Stratton, 1977:281–326.
9. Kaplan JR, Manuck SB, Shively C. The effects of fat and cholesterol on social behavior in monkeys. Psychosom Med 1991;53:634–42.
10. Virkkunen ME, Horrobin DF, Jenkins DK, Manku MS. Plasma phospholipids, essential fatty acids and prostaglandins in alcoholic, habitually violent and impulsive offenders. Biol Psychiatry 1987;22: 1087–96.
11. Sun G, Sun C. Effect of chronic ethanol administration on phospholipid acyl groups of synaptic membrane fraction isolated from guinea pig brain. Res Commun Chem Pathol Pharmacol 1979;24:405–8.
12. Salem N Jr. Omega-3 fatty acids: molecular and biochemical aspects. In: Spiller GA, Scala J, eds. New roles for selective nutrients. New York: Alan R Liss Inc, 1989:109–228.
13. Salem N Jr, Kim HY, Yergey JA. Docosahexaenoic acid: membrane function and metabolism. In: Simopoulos A, Kifer RR, Martin R, eds. Health effects of polyunsaturated seafoods. New York: Academic Press, 1986:263–317.
14. Salem N Jr, Niebylski CD. The nervous system has an absolute molecular species requirement for proper function. Mol Membr Biol 1995;12:131–4.
15. Klerman GL, Weisman MM. Increasing rates of depression. JAMA 1989;261:2229–35.
16. Eaton BS, Konner M. Paleolithic nutrition: a consideration of its nature and current implications. N Engl J Med 1985;312:283–9.
17. Simopoulos A. Omega-3 fatty acids in health and disease growth and development. Am J Clin Nutr 1991;54:438–63.
18. Crawford MA, Gale MM, Woodford MH. Linoleic and linolenic acid elongation products in muscle tissue of *Syncerus caffer* and other ruminant species. Biochem J 1969;115:25–7.
19. Hunter JE. Omega-3 fatty acids from vegetable oils. In: Galli C, Simopoulos AP, eds. Dietary ω3 and ω6 fatty acids: biological effect and nutritional essentiality. Series A: life sciences. New York: Plenum Press, 1989;171:43–55.
20. Raper NR, Exler J. Omega-3 fatty acids in the US food supply. In: Simopoulos AP, Kifer RR, Martin, eds. Health effects of ω3 polyunsaturates in seafoods. World Rev Nutr Diet 1991;66:514(abstr).
21. Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Infant cerebral cortex phospholipid fatty-acid composition and diet. Lancet 1992;340:810–3.
22. Makrides M, Simmer K, Goggin M, Gibson RA. Erythrocyte docosahexaenoic acid correlates with visual response of healthy, term infants. Pediatr Res 1993;33:425–7.
23. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. Lancet 1992;339:261–4.
24. Leaf A, Weber PC. A new era for science in nutrition. Am J Clin Nutr 1987;45:1048–53.
25. Cross National Collaborative Group. The changing rate of major depression: cross national comparisons. JAMA 1992;268:3098–105.
26. Chen C, Wong J, Lee N, Chan-Ho M, Lau JT, Fung M. The Shatin community mental health survey in Hong Kong II. Major findings. Arch Gen Psychiatry 1993;50:125–33.
27. Hwu HG, Yeh EK, Chang LY. Prevalence of psychiatric disorders in Taiwan defined by the Chinese Diagnostic Interview Scale. Acta Psychiatr Scand 1989;79:136–47.
28. Robins LN, Regier DA, eds. Psychiatric disorders in America: the epidemiologic catchment area study. New York: The Free Press, 1991.
29. Vartiainen E, Dianjun D, Marks JS, et al. Mortality, cardiovascular risk factors, and diet in China, Finland and the United States. Public Health Rep 1991;106:41–6.
30. Hirayasu A. An epidemiological and sociopsychiatric study on the mental and neurologic disorders in an isolated island in Okinawa. Psychiatry Neurol Jpn 1969;71:466–91.
31. Haruki A. A psychiatric epidemiological and sociopsychiatric survey on mental disorders in Tsuma-mura, Okinoshima island, Shimane prefecture. Psychiatry Neurol Jpn 1972;74:301–11.
32. Hasegawa K. The epidemiological study of depression in later life. J Affect Disord 1985;S1:S3–6.
33. Connor WE. Evaluation of publicly available scientific evidence regarding certain nutrient disease relationships: 7. Omega-3 fatty acids and heart disease. Bethesda, MD: Life Sciences Research Office, 1991. (Task order #9, contract 223–88-2124.)
34. Booth-Kewley S, Friedman HS. Psychological predictors of heart disease: a quantitative review. Psychol Bull 1987;101:343–62.
35. Fielding R. Depression and acute myocardial infarction: a review and reinterpretation. Soc Sci Med 1991;32:1017–28.
36. Silverstone PH. Depression and outcome in myocardial infarction. Br Med J 1987;294:219–20.
37. Frasure-Smith N, Lesperance F, Talajic M. Depression following

myocardial infarction, impact on 6 month survival. JAMA 1993;270: 1819–25.
38. Carney RM, Rich MR, Freedland KE, et al. Major depressive disorder predicts cardiac events in patients with coronary artery disease. Psychosom Med 1988;50:627–33.
39. Kennedy GJ, Hofer MA, Cohen D, Shindledecker R, Fisher JD. Significance of depression and cognitive impairment in patients undergoing programmed stimulation of cardiac arrhythmias. Psychosom Med 1987;49:410–21.
40. Merikangas K, Gelertner G. Comorbidity for alcoholism and depression. Psychiatr Clin North Am 1990;13:613–32.
41. Winokur G. The concept of secondary depression and its relationship to comorbidity. Psychiatr Clin North Am 1990;13:567–83.
42. Weissman MW. The treatment of depressive symptoms secondary to alcoholism, opiate addiction and schizophrenia: evidence for the efficacy of tricyclics. In: Clayton PJ, Barret JE, eds. Treatment of depression: old controversies and new approaches. New York: Raven Press, 1983:207–16.
43. Schuckit MA. Genetic and clinical implications of alcoholism and affective disorders. Am J Psychiatry 1986;143:140–7.
44. Rosenblum ER, Gavaaler JS, VanThiel DH. Lipid peroxidation: a mechanism for alcohol-induced testicular injury. Free Radic Biol Med 1989;7:569–77.
45. Bjorneboe A, Bjorneboe GE. Antioxidant status and alcohol-related diseases. Alcohol Alcohol 1993;28:111–6.
46. Salem N Jr, Ward G. The effects of ethanol on polyunsaturated fatty acid composition. In: Alling C, Diamond I, Leslie SW, Sun GY, Wood WG, eds. Alcohol, cell membranes, and signal transduction in brain. New York: Plenum Press, 1993:33–46.
47. Schubert DSP, Foliart RH. Increased depression in multiple sclerosis patients, a meta-analysis. Psychosomatics 1993;34:124–30.
48. Minden SL, Schiffer RB. Affective disorders in multiple sclerosis. Arch Neurol 1990;47:98–104.
49. Wilson R, Tocher DR. Lipid and fatty acid composition is altered in plaque tissue from multiple sclerosis brain compared with normal white brain matter. Lipids 1991;26:9–12.
50. Kishimoto Y, Radin NS, Tourtellotte WW, Parker JA, Itabashi HH. Gangliosides and glycerphospholipids in multiple sclerosis white matter. Arch Neurol 1967;16:44–56.
51. Gerstl B, Tavaststjerna MG, Hayman RB, Eng LF, Smith JK. Alterations in myelin fatty acids and plasmalogens in multiple sclerosis. Ann N Y Acad Sci 1965;122:405–7.
52. Holman RT, Johnson SB, Kokman E. Deficiencies in polyunsaturated fatty acids and replacement by nonessential fatty acids in plasma lipids in multiple sclerosis. Proc Natl Acad Sci U S A 1989;86: 4720–4.
53. Cunnane SC, Ho SY, Dore-Duffy P, Ells KR, Horrobin DF. Essential fatty acid and lipid profiles in plasma and erythrocytes in patients with multiple sclerosis. Am J Clin Nutr 1989;50:801–6.
54. Nightingale S, Woo E, Smith AD, et al. Red blood cell and adipose tissue fatty acids in mild inactive multiple sclerosis. Acta Neurol Scand 1990;82:43–50.
55. Bernsohn J, Stephanides LM. Aetiology of multiple sclerosis. Nature 1967;215:821–3.
56. Bates D. Dietary lipids and multiple sclerosis. Ups J Med Sci 1990; S48:173–87.
57. Holman RT, Johnson SB, Ogburn PL. Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation. Proc Natl Acad Sci U S A 1991;88:4835–9.
58. Al M, Houwelingen AC, Honstra G. Docosahexaenoic acid, 22:6(n3), cervonic acid (CA), and hypertension in pregnancy: consequences for mother and child. Scientific conference on omega-3 fatty acids in nutrition, vascular biology and medicine. Houston, TX: American Heart Association, 1994:17–9(abstr 56).
59. Gitlin M, Pasnau RO. Psychiatric syndromes linked to reproductive function in women: a review of current knowledge. Am J Psychiatry 1989;146:1413–22.
60. Sengupta N, Datta SC, Sengupta D. Platelet and erythrocyte membrane lipid and phospholipid patterns in different types of mental patients. Biochem Med 1981;25:267–75.
61. Pettegrew JW, Nichols J, Minshew NJ, Rush AJ, Stewart RM. Membrane biophysical studies of lymphocytes and erythrocytes in manic-depressive illness. J Affect Disord 1982;4:237–47.
62. Piletz JE, Sarasua M, Chotani M, Saran A, Halaris A. Relationship between membrane fluidity and adrenoreceptor binding in depression. Psychiatry Res 1991;38:1–2.
63. Fehily AMA, Bowey OAM, Ellis FR, Meade BW, Dickerson JWT. Plasma and erythrocyte membrane long chain fatty acids in endogenous depression. Neurochem Int 1981;3:37–42.
64. Ellis FR, Sanders TAB. Long chain polyunsaturated fatty acids in endogenous depression. J Neurol Neurosurg Psychiatry 1977;40: 168–9.
65. Kodavanti UP, Mehendale HM. Cationic amphiphillic drugs and phospholipid storage disorder. Pharmacol Rev 1990;42:327–54.
66. Bunney WE, Davis JM. Norepinephrine in depressive reactions: a review. Arch Gen Psychiatry 1965;13:483–94.
67. Toffano G, Leon A, Benvegnu D, Boarato E, Azzone GF. Effect of brain cortex phospholipids on the catecholamine content of mouse brain. Pharmacol Res Commun 1976;8:581–90.
68. Jain ML, Curtis B, Forbes J, Krantz J Jr. The effect of fat diet on reserpine-induced depression in mice. Res Commun Chem Pathol Pharmacol 1973;6:1091–3.
69. Mullen BJ, Martin RJ. The effect of dietary fat on diet selection may involve central serotonin. Am J Physiol 1992;263:R559–63.
70. Koda Y, Wada A, Yanagihara N, Uezono Y, Izumi F. *Cis*-unsaturated fatty acids stimulate catecholamine secretion, tyrosine hydroxylase and protein kinase C in adrenal medullary cells. Neuroscience 1989; 29:495–502.
71. Mandell AJ. Non-equilibrium behavior of some brain enzyme and receptor systems. Annu Rev Pharmacol Toxicol 1984;24:237–74.
72. Crane SB, Greenwood CE. Dietary fat source influences neuronal mitochondrial monoamine oxidase activity and macronutrient selection in rats. Pharmacol Biochem Behav 1987;27:1–6.
73. Semafuco WEB, Rutledge CO, Dixon WR. Modulation of adrenergic neurotransmission in the rat tail artery by dietary lipids. J Cardiovasc Pharmacol 1989;13:138–45.
74. Rulka CA, Hamm MW. Dietary fat and the β-adrenergic mediated chronotropic response in the rat. J Nutr 1988;118:1304–10.
75. Nicolas C, Lacasa D, Giudicelli Y, et al. Dietary (n−6) polyunsaturated fatty acids affect β-adrenergic receptor binding and adenylate cyclase activity in pig adipocyte membrane. J Nutr 1991;121:1179–86.
76. Engler MB. Effects of omega-3 fatty acids, docosahexaenoic and eicosapentaenoic, on norepinephrine-induced contractions. Can J Physiol Pharmacol 1992;70:675–9.
77. Shimokawa H, Vanhoutte PM. Dietary ω-3 fatty acids and endothelium-dependent relaxations in porcine coronary arteries. Am J Physiol 1989;256:H968–73.
78. Heron D, Shinitzky M, Hershkowitz M, Samuel D. Lipid fluidity markedly modulates the binding of serotonin to mouse brain membranes. Proc Natl Acad Sci U S A 1980;77:7463–7.
79. Papaphilis A, Deliconstantinos G. Modulation of serotonergic receptors by endogenous cholesterol in dog synaptosomal plasma membranes. Biochem Pharmacol 1980;24:3324–7.
80. MacIntyre DE, Hoover RL, Smith M, et al. Inhibition of platelet function by *cis*-unsaturated fatty acids. Blood 1984;63:848–57.
81. Block E, Edwards D. Effects of plasma membrane fluidity on serotonin transport by endothelial cells. Am J Physiol 1987;253:C672–8.
82. Manji HK. G proteins: implications for psychiatry. Am J Psychiatry 1992;149:746–60.
83. Avissar S, Schreiber G. Ziskind-Somerfeld Research Award. The involvement of guanine nucleotide binding proteins in the pathogenesis and treatment of affective disorders. Biol Psychiatry 1992; 31: 435–59.

84. Schreiber G, Avissar S, Danon A, Belmaker RH. Hyperfunctional G proteins in mononuclear leukocytes of patients with mania. Biol Psychiatry 1991;29:237–80.
85. Lee CR, Hamm MW. Effect of dietary fat and cholesterol supplements on glucagon receptor binding and adenylate cyclase activity of rat liver plasma membrane. J Nutr 1989;119:539–46.
86. Ahmad SN, Alma BS, Alam SQ. Dietary omega-3 fatty acids increase guanine nucleotide binding proteins and adenylate cyclase activity in rat salivary glands. FASEB J 1989;3:A948(abstr 4196).
87. Pandey GN, Janicak P, Davis JM. Studies of beta-adrenergic receptors of leukocytes of patients with affective illness and effects of antidepressant drugs. Psychopharmacol Bull 1984;21:603–9.
88. Housley MD. Regulation of adenylate cyclase by its lipid environment. Proc Nutr Sci 1985;44:157–65.
89. Mitchell DC, Kibelbek J, Litman BJ. Rhodopsin in dimyristoylphosphatidyl-choline-reconstituted bilayers forms metarhodopsin II and activates G_t. Biochem 1991;30:37–42.
90. Mueller PS, Heninger GR, McDonald RK. Insulin tolerance test in depression. Arch Gen Psychiatry 1969;21:587–94.
91. Koslow SH, Stokes PE, Mendels J, Ramsey A, Casper R. Insulin tolerance test: human growth hormone response and insulin resistance in primary unipolar depressed, bipolar depressed and control subjects. Psychol Med 1982;12:45–55.
92. Winokur A, Maislin G, Phillips JL, Amsterdam JD. Insulin resistance after oral glucose tolerance testing in patients with major depression. Am J Psychiatry 1988;145:325–30.
93. Adner N, Nygren A. Insulin sensitivity in alcoholics in a withdrawal state. J Intern Med 1990;228:59–64.
94. Andersen NB, Hagen C, Faber OK, Lindholm J, Boisen P, Worning H. Glucose tolerance and B cell function in chronic alcoholism: its relation to hepatic histology and exocrine pancreatic function. Metabolism 1983;32:1029–32.
95. Storlien L, Jenkins AB, Chishlom DJ, Pascoe WS, Khouri S, Kraegen EW. Influence of dietary fat composition on development of insulin resistance in rats. Diabetes 1991;40:280–9.
96. Borkman M, Storlien LH, Pan DA, Jenkins AB, Chisholm DJ, Cambell LV. The relationship between insulin sensitivity and the fatty acid composition of skeletal muscle phospholipids. N Engl J Med 1993;328:238–44.
97. Yorek M, Leeney E, Dunlap J, Ginsberg B. Effect of fatty acid composition on insulin and IGF-1 binding in retinoblastoma cells. Invest Ophthalmol Vis Sci 1989;30:2087–92.
98. Dubovsky SL, Franks RD. Intracellular calcium ions in affective disorders: a review and hypothesis. Biol Psychiatry 1983;18:781–97.
99. Hallaq H, Smith TW, Leaf A. Modulation of dihydropyridine-sensitive calcium channels in heart cells by fish oil fatty acids. Proc Natl Acad Sci U S A 1992;89:1760–4.
100. Post RM, Weiss SRB. Non-homologus animal models of affective disorders: clinical relevance of sensitization and kindling. In: Koob GF, Ehlers CL, Kupfer DJ, eds. Animal models of depression. Boston: Birkhäuser 1989:30–54.
101. Nishizuka Y. Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. Science 1992;258:604–14.
102. Colley PA, Routtenberg A. Long term potentiation as synaptic dialogue. Brain Res Rev 1993;18:115–22.
103. Zidovetski R, Lester D. The mechanism of action of protein kinase C: a biophysical perspective. Biochim Biophys Acta 1992;1134:261–72.
104. Stubbs CD. The structure and function of docosahexaenoic acid in membranes: In: Sinclair A, Gibson R, eds. Third International Congress on essential fatty acids and eicosanoids, Adelaide, Australia. Champaign, IL: American Oil Chemists Society, 1992:116–21.
105. Speizer LA, Watson MJ, Brunton LL. Differential effects of omega-3 fish oils on protein kinase activities in vitro. Am J Physiol 1991;261: E109–14.
106. Holian O, Nelson R. Action of long chain fatty acids on protein kinase C activity: comparison of omega-6 and omega-3 fatty acids. Anticancer Res 1992;12:975–80.
107. Shinomura T, Asaoka Y, Oka M, Yoshinda K, Nishizuka Y. Synergistic action of diacylglycerol and unsaturated fatty acid for protein kinase C activation: its possible outcome. Proc Natl Acad Sci U S A 1991;88:5149–53.
108. Slater SJ, Kelly MB, Taddeo FJ, Ho C, Rubin E, Stubbs CD. The modulation of protein kinase C activity by membrane lipid bilayer structure. J Biol Chem 1994;269:4866–7.
109. Friedman E, Wang HY, Levinson D, Connell TA, Singh H. Altered platelet protein kinase C in bipolar affective disorder, manic episode. Biol Psychiatry 1993;33:520–5.
110. Lopez-Corcuera B, Gimenez C, Aragon C. Change of synaptic membrane lipid composition and fluidity by chronic administration of lithium. Biochim Biophys Acta 1988;22:467–75.
111. Gulyaeva NV, Levshina IP, Obidin AB. Indices of free-radical oxidation of lipids and antiradical protection of the brain: neurochemical correlates of the development of the general adaptation syndrome. Neurosci Behav Physiol 1989;19:367–82.
112. Avdulov NA, Eremenko AV, Valdman KM, et al. Changes in synaptosomal membranes from cerebral cortex due to psychogenic stress in rats. Ann Ist Super Sanita 1990;26:31–6.
113. Sosnovskii AS, Tsvetlova MA, Uzunova PI, et al. Lipid peroxidation in rats with emotional stress: correlation with open field behavior. Byull Eksp Biol Meditsin 1992;113:19–21.
114. Desole MS, Meile M, Esposito G, Enrico P, De Natale G, Meile E. Analysis of immobilization stress-induced changes of ascorbic acid, noradrenaline and dopamine metabolism in discrete brain areas of the rat. Pharmacol Res 1990;22:S3:43–44.
115. Sosnovskii AS, Balashova TS, Pirogova GV, Kubatiev AA and Pertsov SS. Activity of antioxidant enzymes in the limbic reticular structures of rat brain after short-term immobilization. Byull Eksp Biol Med 1993;115:683–5.
116. Hildalgo J, Borras M, Garvey JS, Armario A. Liver, brain and heart metallothionein induction by stress. J Neurochem 1990;55:651–4.
117. Itoh T, Akiyama K, Hiramatsu M, Otsuki S. Synaptosomal membrane fluidity, lipid peroxidation and superoxide dismutase activity in the brain of amygdala-kindled rats. Jpn J Psychiatry Neurol 1992;46: 957–66.
118. Niaura R, Stoney CM, Herbert PN. Lipids in psychological research: the last decade. Biol Psychol 1993;34:1–43.
119. Gavino VC, Gavino G. Adipose hormone sensitive lipase preferentially releases polyunsaturates from triglycerides. Lipids 1992; 27:1–954.
120. Mueller PS, Davis JM, Bunney WE Jr, Weil-Malherbe H, Cardon PV Jr. Plasma free fatty acids concentrations in depressive illness. Arch Gen Psychiatry 1970;22:216–21.
121. Williams LL, Kiecolt-Glaser JK, Horrocks LA, Hillhouse JT, Glaser R. Quantitative relationship between altered plasma esterified omega-6 fatty acid proportions and psychological stress. Prostaglandins Leukot Essent Fatty Acids 1992;47:165–70.
122. Mills DE, Huang Y-S, Nance M, Poisson J-P. Psychosocial stress, catecholamines, and essential fatty acid metabolism in rats. Soc Exp Biol Med 1994;205:56–61.
123. Reisbeck S, Neuringer M, Hasmain R, Connor W. Polydipsia in rhesus monkeys deficient in omega-3 fatty acids. Physiol Behav 1990;47:315–23.
124. Burton R. The anatomy of melancholy. The classics of psychiatry and behavioral sciences library. Birmingham, AL: Division of Gryphon Editions, Inc, 1988.
125. Maggioni M, Picotti GB, Bondiolotti GP, et al. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. Acta Psychiatr Scand 1990;81:265–70.
126. Salem N Jr, Serpentino P, Puskin JS, Abood LG. Preparation and spectroscopic characterization of molecular species of brain phosphatidylserines. Chem Phys Lipids 1980;27:289.
127. Cenacchi T, Bertoldin T, Faarina C, Fiori MG, Crepaldi G, participating investigators. Cognitive decline in the elderly: a double-blind,

placebo-controlled multicenter study on efficacy of phosphatidylserine administration. Aging Clin Exp Res 1993;5:123–33.
128. Glen AIM, Glen EMT, Horrobin DF, et al. A red cell membrane abnormality in a subgroup of chronic schizophrenic patients: evidence for two diseases. Schizophr Res 1994;12:53–61.
129. Mellor JE, Laugharne J, Peet M, Horrobin DF. Eicosapentaenoic acid and schizophrenia. Neuropsychopharmacology 1994;10:256S.
130. Stockert M, Buscaglia V, De Robertis E. In vivo action of phosphatidylserine, amytryptyline and stress on the binding of [^{3}H] imipramine to membranes of the rat cerebral cortex. Eur J Pharmacol 1989;160: 11–6.
131. Giannelli A, Rabboni M, Zarattini F, Malgeri C, Magnolfi G. A combination of hypothalamic phospholipid liposomes with trazadone for treatment of depression. Acta Psychiatr Scand 1989;79:52–8.
132. Casacchia M, Meco G, Pirro R, et al. Phospholipid liposomes in depression: a double blind study versus placebo. Int Pharmacopsychiatry 1982;17:274–9.
133. Roccatagliata G, Maddini M, Iyaldi M. Treatment of depression with cerebral phospholipids. (Trattamento delle depressioni con fostolipidi cerebrali.) Rass Studi Psichiatr 1978;67:921–34(in Italian).
134. Nizzo MC, Tegos S, Gallamini A, Toffano G, Polleri A, Massarotti M. Brain cortex phospholipids liposomes effects on CSF HVA, 5-HIAA and on prolactin and somatotrophin secretion in man. J Neural Transm 1978;43:93–102.
135. Argentiero V, Tavolato B. Dopamine and serotonin metabolic levels in the cerebrospinal fluid in Alzheimer's presenile dementia under basic conditions and after stimulation with cerebral cortex phospholipids. J Neurol 1980;224:53–8.
136. Drago F, Continella G, Mason G, Hernandez D, Scapagnini U. Phospholipid liposomes potentiate the inhibitory effect of antidepressant drugs on immobility of rats in a despair test (constrained swim). Eur J Pharmacol 1985;115:179–84.
137. Mills DE, Ward R. Effects of n−3 and n−6 fatty acid supplementation on cardiovascular and neuroendocrine responses to stress in the rat. Nutr Res 1989;9:405–14.
138. Mills DE, Prkachin KM, Harvey KA, Ward RP. Dietary fatty acid supplementation alters stress reactivity and performance in man. J Hum Hypertens 1989;3:111–6.
139. Rudin DO. The psychoses and neuroses as omega-3 essential fatty acid deficiency syndrome: substrate pellagra. Biol Psychiatry 1981; 16:837–50.
140. Muldoon MF, Rossouw JE, Manuck SB, Glueck CJ, Kaplan JR, Kaufmann PG. Low or lowered cholesterol and risk of death from suicide and trauma. Metabolism 1993;42:45–56.
141. Sinclair AJ, O'Dea K, Dunstan G, Ireland PD, Niall M. Effects on plasma lipids and fatty acid composition of very low fat diets enriched with fish or kangaroo meat. Lipids 1987;22:53–9.
142. Horrobin DF. Possible role of PGE, and essential fatty acids, in mania, depression and alcoholism. Prog Lipids 1983;20:539–41.
143. Smith RS. The macrophage theory of depression. Med Hypotheses 1991;35:298–306.
144. Jesberger JA, Richardson JS. Neurochemical aspects of depression: the past and the future? Int J Neurosci 1985;1–2:19–47.
145. Hibbeln JR, Palmer JW, Davis JM. Are disturbances in lipid-protein interactions by phospholipase A_2 a predisposing factor in affective disorders? Biol Psychiatry 1989;25:945–61.
146. Horrobin D. The relationship between schizophrenia, essential fatty acids and eicosanoid metabolism. Prostaglandins Leukot Essent Fatty Acids 1992;47:71–7.