Precursor Therapy With Orthomolecular Nutrition

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Abstract

The importance of Orthomolecular nutrition is recognized to provide the optimum concentration of nutrients in the diet with supplementation as required. Precursors, or building blocks of essential biochemicals are not utilized at times because of a deficiency in enzymes. At other times, there are not sufficient precursors in our bodies to provide adequate levels of their corresponding biochemicals. Phosphatidylcholine is the natural precursor to acetylcholine, the biochemical fuel needed for a proper functioning brain and nervous system. Acetylcholine is needed for proper memory and has been demonstrated to be deficient in disorders relating to aging and senility, tardive dyskinesia and Alzheimer's disease. Phosphatidyl choline is also needed to maintain cholesterol levels in the body. The omega-3 unsaturated fatty acids derived from fish body oils, namely eicosapen-taenoic acid and docosahexaenoic acid, are precursors to certain biochemicals called prostaglandins. These particular prostaglandins have been shown to be useful in helping to prevent and treat cardiovascular disease by inhibiting the formation of blood clots, inhibiting platelet stickiness which extends bleeding time and reducing the viscosity of blood. The prostaglandins are involved also in the regulation of cholesterol and triglycerides and have been shown to be useful in treatment and prevention of atherosclerosis. Beta-carotene is converted into vitamin A in our bodies. Studies have been performed to document that ingestion of beta-carotene, such as in the food we eat, has reduced the incidence of lung cancer — even in smokers. I.

INTRODUCTION

A review of the published medical literature describing neurological and psychiatric disorders indicates a large number of patients receiving drugs, electric shock therapy and psychoanalysis. Many of these patients were considered hopeless — having symptoms that were seemingly incapable of being alleviated.

In 1968, a novel method was published by Dr. Linus Pauling — the theory of "Orthomolecular psychiatric therapy" (59). The theory described treatment as follows:

"Orthomolecular psychiatric therapy is the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally

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present in the body.

...Several arguments may be advanced in support of the thesis that the optimum molecular concentrations of substances normally present in the body may be different from the concentrations provided by the diet and the gene-controlled synthetic mechanisms, and, for essential nutrilities (vitamins, essential amino acids, essential fatty acids), different from the minimum daily amounts required for life or the "recommended" (average) daily amounts suggested for good health."

This theory, and the method of treatment that is described, are based on consumption of a proper diet that is sufficiently nutritious. An equilibrium of all organ systems in the body is maintained by the foods we eat, with supplementation as needed. It is important to recognize that sometimes an individual's diet will not provide the optimum concentration of a particular nutrient. Furthermore, a precursor or substrate may not be utilized because of deficiencies in enzymes or coenzymes. In these cases, supplementation is required. This determination must be made on a case basis as every individual is different.

With this basic foundation, we can proceed to discuss the subject of this paper — precursors in Orthomolecular nutrition. We will review phosphatidyl choline and the omega-3 unsaturated fatty acids and their clinical applications, and briefly highlight beta-carotene.

II. PHOSPHATIDYL CHOLINE A. Biochemistry

1. Sources

In order to describe phosphatidyl choline (PC), it is important first to discuss the relationship with lecithin and choline (2,11, 76, 77). Lecithin is a mixture of phospholipids that are found commonly in plants and animals. These phospholipids occur as phosphatides which are associated with fats and oils. In the case of phosphatidyl choline, the phosphatide is glycerol esterified with fatty acids and phosphoric acid. The phosphoric acid moiety is also esterified with a nitrogenous base, choline.

The three phosphatides found in lecithin most predominantly are phosphatidyl choline, phosphatidyl ethanolamine and phosphatidyl inositol. Phosphatidyl choline is a triglyceride containing two fatty acid groups and one phosphoric acid group with an organic nitrogenous base, choline. Generally speaking, the fatty acid groups are saturated in phosphatidyl choline contained in animal tissue and unsaturated if contained in vegetable tissue. Saponification of lecithin such as with hydrochloric acid results in choline, glycerophosphoric acid and fatty acids.

Phosphatidyl choline, the phosphatide of most interest today, is the important part of lecithin — which is the body's major source of choline. It is the biochemical choline, precursor to the neurotransmitter acetylcholine that is so important in the prevention and treatment of neurological and psychiatric disorders. Choline, and phosphatidyl choline, are being utilized also in the prevention and treatment of hyperlipidemia and atherosclerotic plaque. Choline is transported and stored in the body as phosphatidyl choline.

The medical studies that have been conducted utilize phosphatidyl choline (or lecithin) as a dietary supplement. We ingest lecithin in our diets from the foods that we eat and also from the addition of lecithin to certain processed foods. Therefore, supplementation of a diet with phosphatidyl choline (or lecithin) is natural. Sources of lecithin in our diets include soybeans, eggs and liver. Processed foods that contain lecithin as an emulsifer include chocolate, confectionery products and baking dough. Lecithin is derived commercially from soybeans.

B. Cholinergic Activities

I. *Synthesis of Acetylcholine*

The level of acetylcholine in the brain varies in direct proportion to the brain and plasma choline levels (11). Choline is the precursor to acetylcholine, the biochemical required for proper cholinergic function. Choline cannot be synthesized in the brain and is obtained from the blood plasma. Acetyl coenzyme A combines with choline, catalyzed by choline acetyltransferase, to synthesize acetylcholine (36,37,74,76). The reaction is reversible, and acetylcholine can be converted back to choline by the enzyme acetylcholinesterase. The first enzyme mentioned, choline acetyltransferase, is usually present in excess so that as the level of

choline increases the acetylcholine level will increase accordingly.

Materials pass between the brain and blood in bidirectional transport which is discriminatory (76). This discrimination is called the blood-brain barrier and allows choline to pass freely. The major source of choline in the brain is not free choline in the blood but rather the hydrolysis product of phosphatidyl choline and acetylcholine.

2. ***Choline Transport***

The system by which choline is transported into or out of the brain is usually highly unsaturated. Therefore, a significant change in the plasma choline level will stimulate a concomitant change in the brain choline level. This change will then directly affect the level of brain acetylcholine.

The sequence of events begins with ingestion of lecithin (phosphatidyl choline) which increases the level of choline in the brain fluid (11). The rate of uptake of choline by cholinergic neurons is then increased. Choline is converted to acetylcholine in presynaptic neurons and nerve terminals release the neurotransmitter acetylcholine into synapses. Neuronal receptors are activated by acetylcholine. The acetylcholine released is hydrolyzed which generates choline that is transported back into presynaptic neurons, available again for synthesis of acetylcholine (74).

C. Lipid Alteration Activities

In addition to their role as precursors to the neurotransmitter acetylcholine, phosphatidyl choline and choline have been shown to be intimately involved with fat absorption (58,77). The site of this activity is the transport of triglycerides out of the intestinal mucosa.

The formation of chylomicrons, or lipid particles, requires a small amount of phosphatidyl choline which covers the spherical surface of those particles (52). The intestinal mucosa needs phosphatidyl choline for synthesis and secretion of chylomicrons. The absorption of small amounts of triacylgly-cerols may be accomplished with endogenous sources of phosphatidyl choline. However, an additional source of phosphatidyl choline may be necessary in the event that high levels of dietary fat are ingested or if endogenous synthesis is simply inadequate.

Lecithin (phosphatidyl choline) is also involved in alteration of the body's fat deposits. There are certain lipids that are contained in plasma and which are directly related to atherosclerosis and heart disease (14). These lipids are total cholesterol, low density lipoproteins, very low density lipoproteins and triglycerides. The higher the content of these compounds in plasma, the greater the risk of heart disease. In opposition are the high density lipoproteins which are indirectly related — a high level is desirable.

At this point we have discussed four basic types of lipoproteins which transport cholesterol in the plasma — namely chylomicrons, VLDL, LDL and HDL (78). Each is comprised of proteins, triglycerides, free cholesterol, cholesterol esters and phospholipids. Chylomicrons facilitate the absorption of triglycerides and cholesterol in the intestine. VLDL transport triglycerides from the liver. LDL transport cholesterol from the liver to tissues. HDL are unsaturated and able to remove cholesterol from tissues and arterial walls and transport it to the liver.

Phosphatidyl choline is needed in the esterification of cholesterol, catalyzed by lecithin-cholesterol acyltransferase (LCAT), to mobilize or emulsify cholesterol from arterial lesions and to prevent arterial plaque from constricting an artery.

D. Dietary Effects and Control

The intake of choline, or compounds containing choline, in the diet can provide significant increases in plasma choline levels (15, 16, 34, 40, 44, 71, 74, 76). One of these compounds, lecithin (phosphatidyl choline), is derived from natural sources (soybeans) and is commonly found in the food that we eat.

Several studies have been conducted to demonstrate that administration of choline produces a concomitant increase of choline in the blood and brain (11).

In 1975, Drs. Cohen and Wurtman at MIT studied the effect of choline chloride on rats (15). They administered 60 mg/kg intraperitoneally which produced a 123 percent increase in brain choline and a 22 percent

increase in brain acetylcholine in 40 minutes. Animals injected with saline at 1 mg/kg were used as controls.

In 1977 and 1978, Drs. Hirsch, Growdon and Wurtman at MIT reported that ingestion of choline by humans produced an increased choline blood level and that this effect may provide an effective treatment of patients with tardive dyskinesia (43, 72). Initially, 10 healthy people ingested either choline chloride 3 grams or lecithin (10 to 20 percent PC) 100 grans, both equivalent to 2.3 grams of choline, in a meal and then fasted for 12 hours. Blood choline levels were measured and results showed that lecithin (PC) was more effective than choline chloride.

The choline level in subjects taking lecithin rose higher and persisted for a longer period of time. Its peak level was 265 percent above the baseline level after 8 hours and it remained at that level for at least 12 hours. The choline chloride subject level reached its peak, 86 percent above baseline, after 30 minutes and then dropped.

In 1980, Dr. Zeisel and co-workers at MIT and Tuffs-New England Medical Center published that a lecithin-supplemented low-choline diet significantly increased blood choline levels (73). It was demonstrated that when 6 healthy individuals ingested a meal that included 25 grams of lecithin (80 percent PC, equivalent to 2.3 grams of choline), their choline plasma levels rose within 2 hours, reached their peak after about 6 hours (at a level about four times higher than normal) and remained elevated for 12-13 hours.

E. Clinical Uses of Choline and PC in Orthomolecular Nutrition

1. Megavitamin Therapy

There is a huge number of case studies reported in the published medical literature that describes the use of megavitamin therapy and Orthomolecular nutrition for treatment of various types of medical disorders. We have discussed this subject in depth recently in relation to neurological and psychiatric disorders (11). In that paper, we referred to studies published by physicians on treatment of more than 3,500 patients with B vitamins (16,17,19). Those patients, who suffered from B vitamin deficiency, were diagnosed as having neurological or psychiatric disorders such as depression, schizophrenia, mental retardation (in children), hallucinations, confusional states in the elderly and hyperactivity and brain damage (in children). Some patients were treated with tranquilizers and other drugs, electric shock therapy and psychoanalysis — and some were referred to as being hopeless and their useful lives ended. However, and fortunately, they were found to be suffering from a vitamin deficiency that was corrected relatively easily and within a reasonably short period of time.

Following are highlights of the clinical uses of choline and phosphatidyl choline in neurological and psychiatric disorders (11): *2. Aging and Memory*

In 1974, V.C. Hachinski (from Canada), N.A. Fassen (from Denmark) and J. Marshall (from London) identified two types of dementia in aged people (38). Senile dementia, the typical slowly deteriorating dementia associated with old age is the first type. Multiple cerebral infarcts, caused by vascular disease or atherosclerosis, is the second type. Both conditions, mental deterioration and cerebral atherosclerosis, increase in frequency with age. The investigators reported also that the same changes identified in senile dementia were found to occur in Alzheimer's Disease, pre-senile dementia. In both of these cases, a decrease in choline acetyltransferase activity was demonstrated (9).

In 1977, W.D. Boyd and associates in Edinburg studied the use of choline in 7 patients with severe Alzheimer-type senile dementia (13). The patients were given choline chloride 5 grams per day orally for two weeks, then 10 grams per day for two weeks. The results indicated a significant improvement in cognition. The investigators concluded that choline or other precursors should be tried in patients less severely demented.

A conference was held at the National Institutes of Health in 1977 to discuss "Alzheimer's Disease, Senile Dementia and Related Disorders", with a report presented by Saul Kent subsequently (49). The relationship of the cholinergic system in normal aging and dementia and its role in memory and cognition were reviewed. Dr. David A. Drachman reported that administration of

scopolamine, an anticholinergic and receptor-blocker, to young people caused a decreased ability to remember new information. This poor cognitive performance was similar to that observed in normal aged people. Thus, the dementia normally associated with aging was related to an impairment of the cholinergic system. Dr. Drachman also discussed physostigmine, an antagonist of scopolamine and a cholinergic drug, which was shown to improve memory and IQ in people with scopolamine dementia.

N. Sitaram and co-workers at the National Institute of Mental Health reported in 1978 on the effect of choline on memory (65). Ten normal subjects were given either 10 grams of choline orally, or placebo, on two days. The subjects were then tested for serial learning, remembering ten unrelated words in sequence and also selective reminding, recalling 12 different words in any order. The results showed that choline improved serial learning, recall and memory. Also, this improvement was more significant in slower subjects.

In 1980, Dr. Raymond T. Bartus at Lederle Laboratories reported on studies conducted on rats, monkeys and humans (9). He published that a common symptom of aging in humans and monkeys was a gradual memory loss. Cholinergic neurotransmitter mechanisms were shown to become impaired with increasing age and were related to loss of memory. Medical research was stimulated and clinical trials became very active in the search for an acceptable treatment for memory impairment and age-related cognition loss through manipulation of the cholinergic system. *3. Tardive Dyskenesia*

The most conclusive clinical studies of any neurological or psychiatric disorder have been published on the usefulness of choline and lecithin in treating tardive dyskinesia.

In 1968, George E. Crane, M.D. at the National Institute of Mental Health published a brief history of tardive dyskinesia (19). He referred to 21 papers by 18 authors on approximately 500 patients, from 1959 to 1968. Dr. Crane described tardive dyskinesia as a neurological disorder that appeared in patients treated with phenothiazines and other neuroleptic drugs.

Drs. Kenneth L. Davis, Philip A. Berger and Leo E. Hollister at the Stanford University School of Medicine published in 1975 on the use of choline for tardive dyskinesia (20). A 39-year-old man received a passing dramatic reduction in abnormal movements with 3 mg physostigmine intravenously. Valium 10 mg intravenously produced no change. Deanol, up to 2 grams per day orally, produced no improvement either. Choline chloride 16 grams daily was then administered which resulted in significant decreases in abnormal movements.

Medical researchers at the Stanford University School of Medicine in 1976 studied 4 patients with tardive dyskinesia (21). The patients were first administered physostigmine 3 mg intravenously as a test. Then, choline chloride was administered up to 20 grams daily for each patient for 3 to 8 weeks. Placebo was administered at the end of the time period. The results indicated that physostigmine decreased abnormal movements in all 4 patients. Choline chloride reduced involuntary movements significantly in 3 of 4 patients. After placebo administration, the relapse was delayed, possibly because of the long-lasting effect of choline.

In 1977, Drs. John H. Growdon, Richard J. Wurtman and William Wiener and Ms. Madelyn J. Hirsch at MIT and Medfield State Hospital reported on 20 tardive dyskinesia patients who ingested choline following a double-blind crossover program (31). The study included administration of choline chloride 150 mg per kg body weight daily for one week and 200 mg for the second week, in three divided doses. Ten patients received choline and the other 20 placebo for 2 weeks. Then, a 10 day washout period was allowed and the schedules reversed. Choreic movements were reduced in 9 of the 20 patients, one got worse and the other 10 . remained unchanged.

In 1978, Drs. John H. Growdon, Alan J. Gelenberg and Richard J. Wurtman and Ms. Joanne Doller and Madelyn J. Hirsch at Tufts - New England Medical Center and MIT reported on the use of lecithin," ... the naturally occurring source of dietary choline" (35). Lecithin was administered to three patients, two of whom had previously responded favorably to choline chloride. The number of abnormal movements

decreased in all patients.

Drs. Alan J. Gelenberg and John H. Growdon and Ms. Joanne C. Doller-Wojcik published in 1979 on choline and lecithin (29). Five patients were given choline chloride 150 mg per kg per day in three divided doses, increased to 200 mg and maintained for 6 to 8 weeks. Then, there was a washout period of approximately 2 weeks followed by lecithin (20 percent PC) administration. Initially, the dose was 21 grams daily in three divided doses, increased to 105 grams. The results indicated that both choline and lecithin provided improvement, with better results obtained from lecithin. *4. Alzheimer's Disease*

In 1978, P. Etienne and colleagues in Montreal reported on the use of lecithin in treatment of Alzheimer's Disease (27). This disease has been associated with large decreases in activity of choline acetyltrans-ferase, more so than in normal aging (9). Seven patients in an early stage were given lecithin 25 grams daily, and increased by 25 grams weekly until side effects were evident. The lecithin used contained 7.3 grams of choline per 100 grams of lecithin. Lecithin was used instead of choline because the effect of lecithin had been shown to persist longer with fewer side effects (35, 72). The effects of lecithin treatment on cognition were measured by memory, facial recognition, visual retention and construction ability. The patients were observed for 2 weeks to establish a baseline, 4 weeks on lecithin and 2 weeks washout. Three of the 7 patients improved in new learning ability, understanding instructions faster, verbal rambling was reduced and they were more cooperative. The other patients did not exhibit any outstanding improvement; however, as a group, scores achieved during peak plasma choline levels were higher than baseline.

M. Mesulam, M.D. and Sandra Wein-traub, Ph.D. of Boston reported in 1979 on patients treated with choline and lecithin (54). Choline chloride was administered 20 grams daily over four doses, lecithin 100 grams over four doses. Six patients participated in the study of choline for 8 weeks, washout of 4 to 8 weeks and lecithin for 8 weeks. Two patients improved after choline treatment. After lecithin, they improved in memory, language functions and daily living. One patient was not able to act independently before treatment and became able to go on errands and stay at home alone safely. Another who was slow in thought, speech and movement became more alert and able to interact socially.

Studies to this date are continuing with phosphatidyl choline used in combination with drugs for enhanced efficacy.

5. *Other Neurological and Psychiatric Disorders*

Choline and lecithin (PC) have been and continue to be used in the treatment of other disorders, i.e. Huntington's Disease, mania and depression, schizophrenia, Gilles de la Tourette's Disease, Friedreich's Ataxia, spinocerebbar degeneration, learning disabilities and mental retardation in children, Parkinson's Disease, levodopa-induced dyskinesia and myasthenia gravis (2,3, 7,8,12, 17, 32, 33, 47, 51, 53, 76).

6. *Cardiovascular Disorders*

There are many studies in the published medical literature that describe the use of lecithin (PC) in the treatment and prevention of cardiovascular disorders. Following are some highlights.

In 1943, Drs. David Adlersberg and Harry Sobotka reported on 5 patients with hypercholesterolemia (1). By adding lecithin as a supplement to the diet, significant decreases in the cholesterol level were obtained. The patients ingested 12 to 15 grams of soybean lecithin daily that resulted in cholesterol drops from 360mg to 235mg in six weeks, 620mg to 300mg in three months, 440mg to 260mg in two months and 1370mg to 445mg in three months.

In 1958, Dr. Lester Morrison reported that serum cholesterol could be reduced with the aid of lecithin dietary supplements (55). He published that 12 of 15 hypercholesterolemic patients exhibited an average reduction of serum cholesterol by 41 percent (or 156mg) after ingesting 36 grams of lecithin daily for three months. Dr. Morrison added that 6 to 12 grams would be adequate to maintain a normal cholesterol level.

In 1965,0. Davis and co-workers administered 25 grams of lecithin (750mg choline) daily to 362 hypercholesterolemia patients (22). Serum cholesterol was measured initially and after 6, 12 and 18 weeks of

treatment. The initial average level was 291.7mg, which was reduced to 243.8mg after 18 weeks. Administration of lecithin was stopped and 6 weeks later the average level was 277.8mg. Then, administration was resumed and the average cholesterol level was 260.2mg, 6 weeks later.

In 1974, Svanberg and colleagues in Sweden reported a study on 5 patients with hypertriglyceridemia (7). The patients ingested orally 1144mg of "essential phospholipids" every day for 9 weeks. Results indicated a 17 percent reduction in triglycerides but no change in total cholesterol. However, there was a decrease in VLDL and an increase in HDL.

In 1977, Dr. L.A. Simons and colleagues in Australia reported that nutritional supplementation with lecithin 20 to 30 grams daily to 3 healthy subjects and 7 hypercholester-olemics reduced cholesterol levels by as much as 18 percent (64). Even more important was the fact that the reduction was in the LDL level for the most part.

In 1981, Childs and colleagues at the University of Washington reported on the effects of dietary supplementation with lecithin as compared to corn oil in 6 hypercholesterolemia patients and 12 subjects with normal lipid levels (14). Lecithin was administered 36 grams per day and corn oil at 30.5 grams daily, equivalent to lecithin in polyunsaturated fatty acid content. The results indicated that HDL cholesterol was increased with lecithin but unaltered by corn oil, +4.4 percent for normal lipid levels and +8.7 percent for hypercholesterolemics. LDL cholesterol was reduced by corn oil -12.3 percent and -9.8 percent respectively, and by lecithin -6.2 percent and -4.4 percent respectively. Total cholesterol was not changed by lecithin but was reduced by corn oil. Triglycerides were reduced in those subjects with normal lipid levels on either supplement but increased in hypercholesterolemics taking lecithin and were unaltered by corn oil.

F. Side Effects

1. Choline

The effects of large doses of choline (more than 16 to 20 grams per day), of salts such as choline chloride or bitartrate, include nausea, salivation, sweating and anorexia (13, 20, 21,29,31, 54,65, 76). The same effects, more pronounced, are observed with cholinomimetrics such as physostigmine and arecholine. Subsequent to the ingestion of choline salts, bacterial action in the intestine produces trimethylamine which causes a foul "dead fish" body odor in the sweat and urine. 2. *Phosphatidyl Choline*

Commercially available lecithin (10 to 20 percent PC) has been administered to patients in quantities as high as 100 grams per day (13, 27, 29, 35, 54, 72, 76). The major objections reported have been the gritty nature of granules or the large number of soft gelatin capsules required of the liquid form. The effects of more than 25 grams per day have been reported on an individual basis and include anorexia, nausea, abdominal bloating, belching, gastrointestinal pain, and diarrhea. However, soft gelatin capsules containing 35 percent (420 mg) PC are available commercially. Investigations are being conducted to provide a capsule with a higher level of PC. Also, research is being conducted on preparations of 80 to 90 percent PC, at a daily dosage of 20 to 40 grams, without difficulty.

III. OMEGAS UNSATURATED FATTY ACIDS A. Biochemistry

1. Source

The omega-3 unsaturated fatty acids originated in phytoplankton, organisms that float in the sea and which are a primary food source for sea animals. These fatty acids are concentrated in the body oils of certain marine fish. They are the precursors to prostaglandins and aid in the transport of cholesterol (30, 66, 77, 78, 79).

Fatty acids are generally classified as saturated or unsaturated. The former are fully hydrogenated and have no double bonds; the latter have at least one double bond. Unsaturated fatty acids are classified further by the number of double bonds they contain. The location of the first double bond in the molecule of an unsaturated fatty acid is indicated by the "omega number". Thus, an omega-3 fatty acid is characterized by the first double bond being located at the third carbon atom.

Those fatty acids that we must ingest in

the food we eat are referred to as "essential fatty acids". The group includes linoleic, linolenic and arachidonic acids. They must be included in our food because our bodies cannot synthesize them. Medical studies have been conducted utilizing the omega-3 fatty acids as a nutritional supplement. We ingest these fatty acids in the food that we eat. Therefore, supplementation of a diet with fish body oil that is rich in these fatty acids is natural. Sources in our diets include salmon, mackerel, sardines and anchovies. The omega-3 fatty acids that are most predominant in these fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (30, 60, 66, 79).
formation, a frequent cause of heart and blood circulatory problems and extend bleeding time by inhibiting platelet aggregation. Also, they have been shown to reduce the viscosity of blood. They are precursors to prostaglandins.

The aggregation ability of platelets is regulated in the body by prostaglandins and biochemically related compounds (30, 56, 58, 63). Two pathways are involved in the production of these compounds and are illustrated in figure 1. The first pathway begins with linoleic acid, commonly found in vegetable oils. It is converted to gamma linolenic acid — to dihomo gamma linolenic acid — and then to arachidonic acid. We obtain arachidonic acid also directly from our diets. Oxidation of arachidonic acid, produces what is referred to as the "arachidonic cascade". This is a group of compounds including prostaglandins, thromboxanes and prostacyclins — collectively referred to as eicosanoids. Some of these biochemicals promote platelet aggregation and others prevent aggregation.

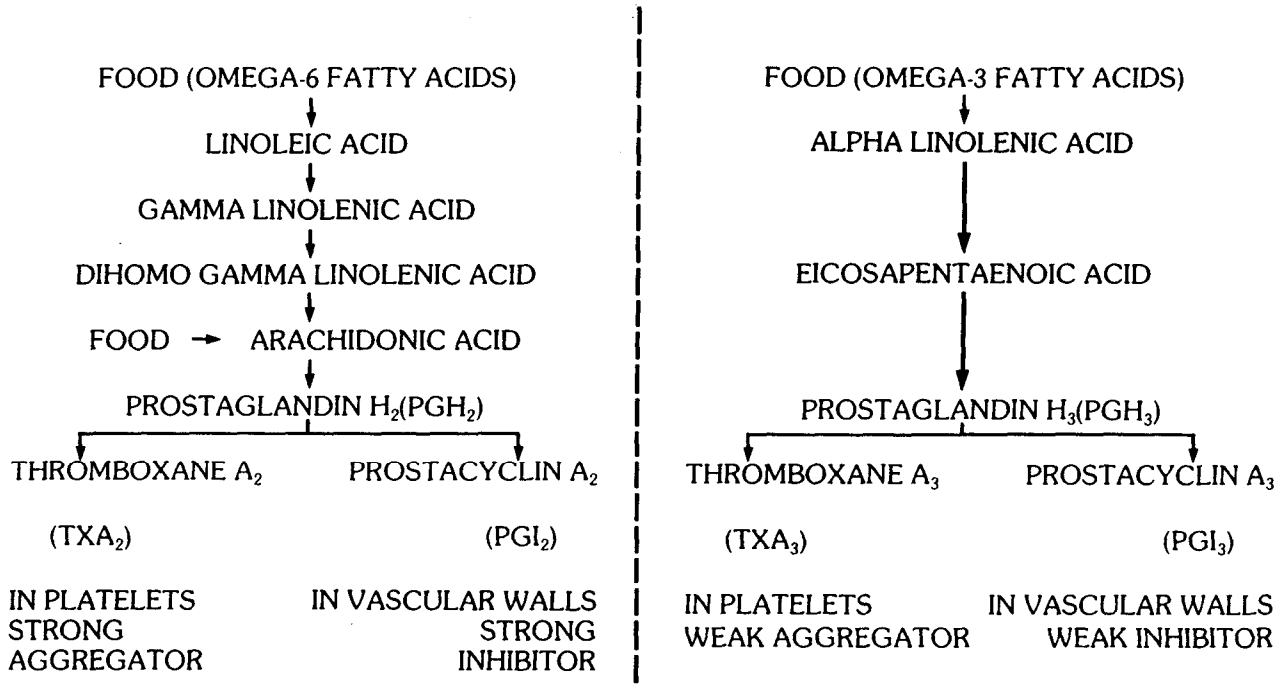

Figure 1. Synthesis of platelet aggregatory and anti-aggregatory biochemicals. 186

As indicated in the first pathway, arachidonic acid is converted to prostaglandin $H_2(PGH_2)$ and then to thromboxane A_2 (TXA_2) or prostacyclin $A_2(PGI_2)$. TXA_2 is a strong platelet aggregator and prostacyclin is a strong inhibitor of platelet aggregation Production of TXA_2 occurs mostly in the platelets and prostacyclin in the vascular walls. Even though the two biochemicals have opposite effects, they are derived from the same precursor. An equilibrium must be maintained in the body, through a mechanism that controls the balance at the proper level.

As indicated in the second pathway, linolenic acid is converted stepwise to eicosa-pentaenoic acid (EPA), prostaglandin $H_3(PGH_3)$ and then to thromboxane A_3 (TXA_3) or prostacylin $A_3(PGI_3)$. This thromboxane and prostacyclin function similarly to those derived from arachidonic acid. That is to say, TXA_3 promotes platelet aggregaton and prostacyclin functions as an inhibitor. However, TXA_3 and PGI_3 are much weaker in their actions. Nevertheless, the four biochemicals are needed for a proper functioning cardiovascular system. A deficiency of EPA, for example, may result in a tendency for platelets to aggregate and form thrombi more easily and also more viscous blood. 2. *Lipid Control*

Another activity in which the omega-3 fatty acids are involved is the regulation of lipid levels. These fatty acids can reduce the levels of cholesterol and triglycerides and increase the level of HDL — and are useful in treatment and prevention of atherosclerosis (6,66). Also, a strong correlation has been demonstrated between elevated plasma cholesterol level and coronary heart disease (68). Saturated fatty acids have been shown to raise the cholesterol level and unsaturated fatty acids to reduce cholesterol. Changes in LDL, VLDL and HDL will not be apparent when only total cholesterol is measured, so that the individual lipoprotein types should be measured as well. The important point is that LDL be kept at a low level and HDL at a high level to help prevent heart and vascular disease.

We touched on this subject partially earlier in discussing phosphatidyl choline. Atherosclerosis, the deposition and accumulation of cholesterol in arterial walls, is a process that develops gradually with no symptoms over as many as 20 to 40 years (57,77). The blood vessels become constricted until serious clinical conditions appear suddenly, such as angina, myocardial infarction or stroke. In order to prevent and treat atherosclerosis it is important to remember that the ratio of saturated to unsaturated fatty acids is high in the atherosclerotic patient.

C. Dietary Effects and Control

The intake of omega-3 unsaturated fatty acids in the diet can provide significant changes in the body's lipid levels and distribution. Eicosapentaenoic acid (and docosa-hexaenoic acid) is derived from natural sources (fish body oils) and is commonly found in the food that we eat.

Many studies have been performed to demonstrate that administration of essential fatty acids, and specifically oils rich in EPA and DHA, reduce cholesterol and triglycerides.

In 1978, von Lossonczy and co-workers in the Netherlands studied the effect of a fatty fish (mackerel) diet on the serum lipid composition (70). A cross-over study was conducted with 19 healthy males and 23 females. The normal diet was used as a control, the test diet being fish including daily ingestion of 8 grams of omega-3 fatty acids. Results indicated that on the fish diet, serum cholesterol was 7.5 percent lower and triglycerides 35 percent lower, with a slight increase in HDL cholesterol. Also VLDL decreased and, in the men, LDL and HDL increased. EPA and DHA levels increased at the expense of omega-6 fatty acids.

In 1979, von Gent and colleagues in the Netherlands studied the effect of ingestion of an omega-3 marine oil concentrate on serum lipid levels (69). Five groups of 10 healthy subjects ingested either 0,1,2,4 or 8 grams of a marine oil concentrate every day for 4 weeks. The oil contained 81 percent DHA. Results indicated that total cholesterol and HDL were not altered significantly. However, triglyceride and VLDL levels decreased by as much as 30 percent in the group ingesting 8 grams.

In 1980, Dr. Meng Tan and colleagues in Nova Scotia and at the University of Washington and University of California studied

the effect of a high cholesterol, high saturated fat diet on HDL cholesterol in 6 normolipidemic subjects (68). As compared to a low cholesterol, high polyunsaturated fat diet, the high cholesterol, high saturated fat diet increased VLDL by 59 percent, LDL by 15 percent and HDL by 30 percent.

Drs. William Harris and William Connor, at the University of Oregon Health Sciences Center, reported in 1980 on the effects of ingestion of salmon oil on fat clearance (39). The investigators compared a typical American diet to a diet fortified with omega-3 fatty acids from salmon oil for 10 days. Ten healthy subjects and 3 patients with type IIb hyperlipoproteinemia were studied. Results snowed that LDL and VLDL levels decreased but HDL remained the same. Plasma triglyceride levels in the normal subjects were reduced by 40 percent and 67 percent in the hyperlipidemic patients. Cholesterol levels were lowered by 17 percent in the normal subjects, and 20 percent in the hyperlipidemic patients.

D. Clinical Uses of Omega-3 Fatty Acids in Orthomolecular Nutrition

Medical studies have been conducted in Europe, Asia, North America and Australia — on Greenland Eskimos and populations living near the sea such as the Japanese. These studies have shown that omega-3 fatty acids in the diet reduce the incidence of heart disease, reduce the stickiness and aggregation of platelets, reduce blood viscosity, reduce blood clotting and lower blood cholesterol and triglyceride levels. Following are some of these studies. *1. Cardiovascular Applications*

In 1978, Jakubowski and Ardlie in Australia reported on the effects of saturated and unsaturated fats in the diet on platelet function (46). They studied 12 healthy male subjects who were on a saturated fat diet followed by a polyunsaturated fat diet. The latter diet produced a reduction in cholesterol and triglycerides, increased blood clotting time, reduction in the number of circulating platelet aggregates and in platelet counts also.

Dyerberg and Bang of Denmark in 1979 reported on the effect of polyunsaturated fatty acids on platelets (25). Because death from cardiovascular disorders has been rare amongst Eskimos, the researchers studied 21 Greenland Eskimos, and 21 Danes for comparison. Their laboratory analysis of platelet lipids correlated a higher level of omega-3 fatty acids in the Eskimos' platelets to a higher intake of those fatty acids in the normal diet. Also, a significantly longer bleeding time in the Eskimos because of reduced platelet aggregation was reported. In 1980, Siess and co-workers in West Germany reported on platelet and plasma fatty acids, platelet aggregation and thromboxane formation (63). Seven healthy men were placed on a mackerel diet for one week. The daily intake was 500 to 800 grams of mackerel, or 7 to 11 grams of EPA. The results showed that EPA in platelets increased from 1.8 to 6.2 *u*g/mg platelet protein and DHA increased from 1.9 to 5.6 *u*g/mg. Also, platelet aggregation and thromboxane A_2 synthesis were reduced.

Hirai and colleagues in Japan reported in 1980 on the effect of EPA on platelet function (42). They based their work on the fact that a diet rich in EPA can alter the distribution of fatty acids in plasma and platelet membrane phospholipids and thereby affect platelet function. The investigators theorized that because fish is the main source of dietary protein in Japan, the low incidence of thrombosis in the Japanese may be explained by the fish diet rich in EPA.

The researchers compared the dietary fatty acid composition, plasma fatty acid distribution and platelet function of 42 people living in a fishing village to 43 people in a farming village, in Japan. The average daily intake of EPA of the fishermen was 2.5 grams, and the farmers 0.9 gram. Plasma levels of EPA averaged 3.8 percent in the fishermen and 2.3 percent in the farmers. DHA averaged 7.1 percent in the fishermen and 4.5 percent in the farmers. Platelet aggregation was reduced significantly in the fishermen.

In 1981, Kobayashi and co-workers in Japan reported on the reduction in blood viscosity produced by EPA (50). They studied 44 people in a fishing village and 46 people in a farming village. The mean blood viscosity in the fishermen was 3.60 cP, significantly lower than 4.00 cP for the farmers.

As a second experiment, EPA was concentrated from sardine oil and prepared in a soft gelatin capsule containing 21.4 percent EPA and 7.4 percent DHA. Subjects ingested 1.4 grams of EPA (18 capsules) daily, the difference in EPA between the fishermen and farmer diets. Blood viscosity and platelet aggregation were reduced significantly after 4 weeks. *2. Atherosclerosis and Lipid Alteration*

In 1969, Insull and researchers in Japan and Case Western Reserve University in Cleveland reported on their comparative studies of Japanese and American men (45). They studied the levels of fatty acids in lipids from adipose tissue of 50 Americans and 56 Japanese who died suddenly and unexpectedly. The Japanese had higher levels of longer chain polyunsaturated fatty acids.

In 1972, Bang and Dyerberg in Denmark published on a comparison of the plasma lipid and lipoprotein concentrations in 130 Greenland Eskimos compared to316 Danes, including 25 Greenland Eskimos living in Denmark (5). Significantly lower values were reported in Eskimos for total lipids, cholesterol, triglycerides and LDL. This trend was found also in the female Greenland Eskimos living in Denmark, whose biochemistry matched the Danes'.

In 1973, Hiroo Kato and colleagues at the National Institute of Health in Japan, National Heart and Lung Institute in Bethesda, Center for Disease Control in Atlanta and also in Hawaii, reported on an investigation of the relationship between serum lipids and diet (48). They studied the diets and associated lipid levels of Japanese men living in Japan, Hawaii and California. Almost 10,000 subjects participated in the study. Results showed that cholesterol and triglyceride levels were much lower in Japan than the other two populations. There was positive correlation between the cholesterol level and dietary ingestion of saturated fat and animal protein.

In 1980, Saynor and Verel in Great Britain reported on the effects of EPA on blood lipids and coagulation (61). Five normal subjects ingested, as a nutritional supplement, a marine oil containing a high content of EPA — 10 ml twice daily. The supplement probably contained approximately 1.8 gram of EPA and 1.2 gram of DHA per 10 ml. The diet and supplement were consumed for 5 weeks. Results indicated an increase in total cholesterol of 3.8 percent, from 4.73 to 4.91 mmol/1; decrease in triglyceride of 35 percent, from 1.16 to 0.75 mmol/1; increase in HDL cholesterol of 22 percent from 1.31 to 1.52 mmol/1.

In 1982, Hay et al. in Sheffield, U.K. published on the effects of EPA in patients with ischemic heart disease (41). They studied 13 patients who took 3.5 grams of EPA daily. After 5 weeks, platelet survival time increased by 10 percent, platelet count was reduced by 16 percent and HDL was increased by 18 percent.

E. Side Effects

Populations such as the Greenland Eskimos and Japanese have been studied and the effects of diet on their well-being correlated. The normal diet of these populations has been reported to include approximately 2.5 grams of EPA daily (42). Diets have been supplemented with omega-3 fatty acids by simply increasing the daily consumption of oily fish (63) containing 7 to 11 grams of EPA or by the addition of natural fish oils (41,42,50,62,69, 70) containing up to 8 grams of omega-3 fatty acids daily. There have been no major objections reported other than a slight increase in weight in a few cases. In this regard, soft gelatin capsules are available commercially which contain 300 mg or 500 mg of EPA and DHA in 1000 mg of a marine oil.

IV. BETA-CAROTENE

A good deal of attention, in recent years, has been focused on prophylactic measures for cancer — and beta-carotene is in the forefront.

Vitamin A is required for normal differentiation of epithelial cells (81). In a malignant tissue, the ability for normal differentiation is absent and a keratinizing form of epithelium develops. However, vitamin A consumed in large quantities can be toxic. Medical studies have indicated that beta-carotene, or pro-vitamin A, which is converted into vitamin A in the body, may be the source of choice for cancer prevention.

In 1975, Bjelke at the Cancer Registry of Norway reported on the relationship between vitamin A and lung cancer in humans

(12). The five year study of 8, 278 men showed that a higher consumption of vitamin A in the diet correlated negatively with the incidence of lung cancer.

Shekelle and colleagues reported in 1981 that the incidence of lung cancer was inversely related to the dietary consumption of beta-carotene (62). The researchers had studied 1,954 men over a period of 19 years and indicated that their results were in agreement with studies conducted in Norway, Japan and the U.K.

Several articles have been published in J.A.M.A., culminating in two events in 1982 (82,83). First, some 200,000 male physicians have been contacted to participate in a cardiovascular and cancer research project (84). Four groups will be established, to be placed on the following program:

Group 1 — alternating 325 mg aspirin and 30 mg beta-carotene capsule every other day.

Group 2 — alternating aspirin and placebo.

Group 3 — alternating placebo and beta-carotene.

Group 4 — two placebos.

The project is expected to continue over a 5 year period.

The second event was the establishment of a "chemoprevention" program of the National Cancer Institute (85). The program is aimed at support of research and clinical trials with vitamins. Almost simultaneously with the initiation of that program was a meeting called the First International Conference on the Modulation and Mediation of Cancer by Vitamins, held at the University of Arizona and attended by researchers from 14 countries.

Also, the National Research Council began publication of general dietary guidelines to reduce the risk of cancer in 1982 (28,81, 86). The precept is that common cancers may be potentially preventable.

V. OUTLOOK FOR THE FUTURE

There have been many studies published on phosphatidyl choline, omega-3 fatty acids and beta-carotene. We are only at the beginning of the medical benefits to be derived from proper nutrition and dietary supplementation. Not all studies have provided the expected results but the evidence is strong in a positive direction and we must continue our work — and try to control the variables, such as the food our subjects consume.

It is important to utilize Orthomolecular therapy, proper diet and nutritional supplements first in treating a patient. The use of drugs, as necessary, should then follow, to minimize the risk to the patient.

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