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Medical Effects of Fish or Fish Oil in the Diet

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MEDICAL EFFECTS OF FISH OR FISH OIL IN THE DIET

by

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Preface

In 1969 I published a paper, Nutritional Properties of Fish Oils in World Review of Nutrition and Dietetics, Volume 11, pages 16-105. This long review paper contained considerable background information on the fish oil industry. Much of the nutritional properties in that review dealt with nutrition for animals. In the 16 years since the detailed review was prepared, a great deal of research has been carried out upon nutritional effects on medical conditons, especially heart disease.

This paper discusses these more recent findings but does not repeat the more general topics included in the earlier report. The information on these newer research areas is not a complete review, but rather discusses highlights of such findings.

Maurice E. Stansby

I Introduction

Various beneficial effects have been claimed or are indicated for fish oil in the diet upon a number of diseases. These diseases include heart disease, strokes, various inflammation diseases such as arthritis, multiple sclerosis, cancer, healing of wounds and burns, and several other medical condition. Only in the case of one of these, heart disease, has there been sufficient detailed study to make it quite certain that such an effect exists. The evidence for such beneficial effects of fish oil in the diet upon heart disease will therefore be first discussed here in some detail and then in a briefer form the situation regarding the other diseases will be gone into.

In addition to medical effects of fish oils for humans, fish oils also possess nutritional properties when fed to animals. Both the human medical effects and the nutritional effects were discussed in detail in a long review article published 16 years ago (Stansby 1969). This report updates the medical effects.

II Effects of Dietary Fish Oil on Heart Disease

A Introduction

Two types of effects of fish oil which may benefit incidence of heart attacks are known. First, fish oils which contain highly polyunsaturated fatty acids can, as do the polyunsaturates of other oils such as vegetable oils, lower serum cholesterol levels. Lowered serum cholesterol level is quite generally associated with decreased risk of heart attacks.

The second effect is based upon the unique omega-3 type of polyunsatuates present only in oils of marine origin. Ingestion of such oils results during metabolism in the formation of a different pattern of prostaglandins from that resulting from other dietary oils on fats. Presence of such altered prostaglandins can reduce the likelihood that blood platelets will coagulate which then could result in a heart attack.

Depending upon what sort of scientific evidence is used by an investigator to determine the effect of fish oil in the diet upon heart disease, the effects may be classified as direct effects (measured by incidence of subsequent fatal heart attacks by patients ingesting the fish oil as compared to those who do not) and as indirect effects (effects upon blood chemistry or other such observations).

B Direct Effects

In order to obtain information on the direct type of effects, both individuals consuming fish oil and those who do not must be followed over a period of many years since the deaths from heart disease will occur to a significantly large extent only after the patients have been under observation for a considerably lengthy period of time. To the best of this writers knowledge only two such investigation have ever been carried out employing fish oils in the diet. The first of these was performed by a Seattle cardiologist, Dr. Averly Nelson, between 1953 and 1972. He specialized in treating patients who had suffered a heart attack by use of a diet which involved partaking of at least 3 main meals in which fish was the entree per week. During this 19-year period he had more than 300 patients under observation. After eliminating such cases as where the patients moved away

and were lost to observation or died of some other causes than heart disease, 80 patients were observed who followed his diet at least 16 years and 123 who did not consume the fish at least three times per week as a part of their diet. During this period, the percentage of patients suffering a fatal heart attack was 4-1/2 times that among those who did not follow the fish diet as for those on the fish diet (Nelson 1972). At that time nothing was known about the effect of the omega-3 fish oil fatty acids toward a diminishment of clotting of the blood cells so the effect was attributed solely to the lowering of serum cholesterol levels which were following rigorously for control and dieted individuals. That the effect of the fish omega-3 fatty acids played a role is indicated, however, by comparison to another different test of 7 years duration conducted by Dr. Semour Dayton at the Los Angeles Veteran's Hospital (Dayton et al. 1969) where fatalities of individuals consuming large amounts of vegetable oil polyunsaturates in their diet was compared to that of those who ate a normal diet. In this case while there was a small improvement in deaths from heart attacks among those consuming the vegetable oil diet over the controls, deaths among the control diet patients were considerable less than twice that of the polyunsaturated vegetable oil group. It now seems apparent that in all probability, the much more favorable results using oily fish in Dr. Nelson's 19-year study was influenced to a large extent by the action of the omega-3 fatty acids and to a lesser extent by the mechanism involving the reduction of serum cholesteral levels.

It must be remembered, that in Dr. Nelson's results, all patients had suffered a heart attack before start of the experiment. It is thus a possibility, at least, that results with patients who had never suffered a heart attack might have had a different effect from inclusion of fish in their diet.

Another aspect of Dr. Nelson's program that should be pointed out is the fact that all of his dieted patients did not for the full period of the experiment consume fish as a main course 3 times per week. In the late 1940's Dr. Nelson while attending classes at UCLA to learn about nutrition and related subject to prepare for his later dieting work, discussed at length results on incidence of heart disease in countries like Norway during and after the German occupation. There were at that time ideas that decreased incidence of heart disease during the occupation by the Nazi forces might be related to the substitution of fish for meat during that period. Dr. Nelson was so impressed by this theory that when he began his 19-year study in 1972, he strongly recommended that his patients consume fish as a main course 3 times per week. However, current thinking in 1972 was that polyunsaturates of vegetable oils were of value in reducing serum cholesterol levels but because of the relatively low $\frac{P}{S}$ ratios in fish oils, fish were of no value in this regard. Up to that time no tests had been conducted on the value of fish oils for this purpose. However, in 1956, the results showing fish oils possessing even greater serum cholesterol levels than vegetable oils were published by Bronte-Stewart et al. From that point on for the remaining 15 years of Nelson's dieting study, the inclusion of fish as a main course 3 times per week became a requirement for his dieted patients. Thus only a portion of Nelson's dieted patient included the fish requirements during the first 1 to 4 years of the 16 - to 19 - year study.

A very recent paper (Kromhout et al. 1985) also gives a definite relationship between fish intake and coronary deaths over a 20 year period. Unlike Nelson's clinical test where all subjects had suffered a previous heart attack, the Kromhout subjects, which totaled 852 middle-aged men, were randomly selected from the village of Zutphen, Holland and were all free of

heart disease at the start of the test. Of these subjects, 20% ate no fish at all; the remainder consumed 1 to 307 grams fish per day. The average fish consumption for all subjects was 20 grams per day. At the end of the 20 year study, of the 852 subjects involved in the test 78 had died of coronary heart disease. For comparing the relative risk as a function of the amount of fish consumed, the 20% of the individuals who ate no fish at all were assigned a risk level of 1.00. The risk ratios were calculated for those who consumed 1-14 grams fish per day, 15-29 grams per day, 30-144 grams per day and 45 or more grams per day. These resulted in risk ratios of 0.64, 0.56, 0.36, and 0.39. Thus increasing the amount of fish up to a level of 44 grams per day gave increasing protection against risk of coronary fatality. Those who consumed 45 or more grams fish per day had no greater protection than those consuming 30-44 grams per day.

It was noted that protection against development of heart disease was no less among those who ate relatively low fat content fish (average 1.5% oil) than among those consuming much fatter varieties of fish. The authors believe that this indicates one of two alternatives. Either (a) the amount of omega-3 long chain fatty acids required for the protection was so small that more than an adaquate amount occurred in the lean (1.5% fat) fish. Or (b) in addition to the effect of the action of the omega-3 long-chain fatty acids some other component in the fish was involved.

The results of the Kromhout test were not so positive as were those in the Nelson experiment. In the latter case more than 4 times as many coronary fatalities occurred for those not consuming fish as those who did. This greater protection probably was due to a greater need for protection by patients who were suffering from heart disease at the very beginning of the

test as compared to those in the Dutch study who were all free of coronary disease at the start of the test.

C Indirect Effects

1. Introduction

Studies of indirect effects of feeding fish oils upon incidence of heart attacks are largely based upon two different factors namely (1) effects on serum cholesterol levels and associative aspects and (2) effect of omega-3 fatty acids upon changes in the characteristics of the blood which may affect the aggregation of the blood platelets. Research along the first of these lines has been going on since the mid-1950's. Research along the second line has been under way only since the early 1970's. It was started as a result of observations on the Greenland Eskimos who live in remote areas of Greenland and whose food is almost entirely flesh of fish or of marine mammals. Such individuals only very rarely have heart attacks.

2. Studies based upon measurements of levels of serum cholesterol

It was observed before 1950 that serum cholesterol levels were usually high in individuals who had heart attacks and later observation showed similar relationships for triglyceride levels and for certain fractions such as low density lipoproteins. In early research, it was found that feeding polyunsaturated fat tended to decrease such levels. For a time the ratio of polyunsaturates to saturates, $\frac{P}{S}$, in the diet was believed to be a measure of

the effectiveness of the diet as a depressant for such levels. Initial work, therefore, was concentrated in the early 1950's upon use of vegetable oil which often had far more polyunsaturates (P) than saturated fatty acids (S) and with $\frac{P}{S}$ ratios therefore quite high. This idea seemed to rule out fish oils as being effective because fish oils while relatively high in content of polyunsaturates often had as much saturates as polyunsaturates thus giving $\frac{P}{S}$ ratio not far from 1. It was not until the mid 1950's when several workers e.g., Bronte-Stewart et al. (1956) showed that fish oils were not only effective cholesterol depressant agents but that they were usually more effective, weight for weight, than vegetable oils. The most comprehensive research along these lines employing animals fed fish oils was carried out by Peifer (1967). In general the same serum cholesterol depressive effect of a stipulated amount of fish oil is achieved as by about three times as much vegetable oil in the diet.

In addition to fish oil research involving test animals with respect to effects on serum cholesterol levels which was carried out by many investigations, a few short term clinical tests were conducted by a few individuals (e.g., Ahrens et al. and Kingsbury et al. 1961) and which gave similar results as for animal tests. At the time that such cholesterol depressant research on effects of fish oils was being carried out in the 1950's and 1960's, the reason why the fish oil was a superior cholesterol depressant over other polyunsaturated oils was never clearly understood. The fact that the $\frac{P}{S}$ was far, far lower in fish oils than in vegetable oil seemed in contradiction to the superior action of fish oils in this regard. Investigators generally assumed that the difference might be laid to the fact that the fish oil polyunsaturates contained largely 5 and 6 double bonds as compared to vegetable oils where most of the polyunsaturates contained 2, 3,

or at the most 4 double bonds. Such differences might be related in some way to the increased cholesterol depressant activity of the marine oils. Or, alternately, the omega-3 configuration of the double bonds in long chain fatty acids of fish oils, unique to them, might somehow be responsible (Stansby 1969, page 85 and 87). Even today it is not uncommon to see statements in current literature attempting to show cholesterol depressant properties as a function of the $\frac{P}{S}$ ratio. Such a ratio, of course, has validity only when applied to vegetable oils and gives entirely meaningless inferences when applied to fish oils.

The oil from several species of fish show cholesterol depressant properties whether it is fed as extracted oil or as the fish flesh which contains the oil (Table 1). A somewhat greater depressant occurred when the extracted oil was fed.

Table 1. Reduction of serum cholesterol levels in rats fed either extracted fish oil or flesh of several species of fish.[1/]

Species of fish	Marine oil in diet (%)	Serum cholesterol level mg per 100 ml	
		When extracted oil fed	When fish flesh fed
Tallow control	-	507	507
Menhaden	4.9	223	250
Silver salmon	5.3	162	193
Mullet 3.8	263	359	
Ocean perch	2.5	190	398

1/ From Peifer (1967).

In the research of Peifer (1967) using rats, it was shown that when the rats were fed a diet high in saturated fat and otherwise altered so as to result in high total serum cholesterol levels, the content of C22:6 in the heart muscle of the rats was raised from almost zero to significant levels. In cases where fish oil was present in the diet such C22:6 values in the heart muscle after one month of feeding reached about 5 mg per gram of heart tissue. What was even more surprising, however, was the fact that even when the rats were fed a diet free of any oil containing any measurable amount of C22:6, the values of this fatty acid rose to around 0.7 mg C22:6 per gram of heart tissue. In research by Kingsbury (1961) on fatty acids in the heart tissue of human patients who died of a heart attack (and who had high serum cholesterol levels) there was a similar high content of C22:6 in the heart tissue--highest when the patients had been consuming cod liver oil but still a small increase in the C22:6 content when no fish oil was in their diet. This might seem to indicate that when serum cholesterol levels are abnormally high, the body mobilizes from whatever source is available C22:6 fatty acids and deposits them in the muscle of the heart.

3. Studies based upon effects of omega-3 fatty acids

As a result of research reported in more than 100 papers published since the early 1970's, it has been established that long chain omega-3 fatty acids[1/] found to any appreciable extent only in oils of marine origin have special properties which can be of benefit in connection with heart attacks.

1/ Fatty acids having the first double at the third cabon atom counting from the methyl end.

Such research stemmed from observations and subsequent preliminary research made by Danish scientists in Aalborg, Denmark, on heart disease among Eskimos living in remote areas of Greenland. This work, which indicated that an extremely small incidence of heart attacks among such Greenland Eskimos (due to their fat intake being almost exclusively of a type containing omega-3 fatty acids), was continued by the Danish investigators (Dyerberg 1982). Subsequently this type of research spread to many laboratories in different parts of the world. In this section of this report the results of such research will be described.

For some years before 1970 it had been known that heart disease was a great deal less common among Eskimos in Greenland than elsewhere (Berthelsen 1940; Ehrstrom 1951). In 1970 a long term investigation on heart disease was initiated at Aalborg Hospital at Aalborg, Denmark, by Drs. H. O. Bang, J. Dyerberg and co-workers. These earlier statistics and some current ones were re-examined (Dyerberg 1982) especially records of deaths from heart disease from 1963-67 in the Umanak district whose population was about 2,600. No deaths from acute myocardial infarction and only 3 cases of atherosclerosis disease were found. Research was therefore begun to see whether the low incidence of heart disease might be related to diet of the Eskimos and if so whether some specific component of the diet might be involved. Dyerberg (1982) has reviewed this work which was begun in the early 1970's and has been continuing since then. It soon became apparent that there was a connection between the content of long chain omega-3 fatty acids derived from the all marine food diet of the Eskimos. Particular attention was paid in this research to effects of the C20:5 omega-3 fatty acid, eicosapentaenoic acid which is analogous to the omega-6, arachadonic acid which is, of course, of more common occurrence when the normal Western diet devoid of long chain

omega-3 fatty acids is concerned. These two fatty acids are identical except for the position of the double bonds and the addition of one more double bond in the C20:5 acid.

In the research in Denmark it was established that during metabolism of the C20:5 fatty acid in the food of the Eskimos, the type of prostaglandins produced was different from that occurring from analogous metabolism of arachadonic acid. The over-all effect of the consumption of the omega-3 fatty acids such as C20:5 was that there was a slower coagulation of the blood. This fact has been known about Greenland Eskimos for many decades since they are what is known as bleeders. When there is a flow of blood such as occurs from a nosebleed or a cut, the blood flows for a longer time before coagulation than is the case of individuals on the ordinary Western type diet where arachadonic acid (20:4 omega-6) is predominately present. The research, therefore suggests that the reason that the incidence of much lower death rate from heart attacks among the Eskimos of Greenland stems from the presence of altered prostaglandin patterns which decreases the likelihood that the blood platelets coagulate within the body which would occur during a heart attack.

During the same period of time when the research was going along to investigate the cause of decreased heart attacks among Greenland Eskimos, certain investigators were establishing an analogous situation with regard to the action of aspirin. It was shown that consumption of aspirin altered the types of prostaglandins forming so as to decrease the tendency toward coagulation of blood platelets. For this research three individuals, received the Nobel Prize in medicine in 1982. One of these three, Dr. John Vane had also participated with some of the Danish investigators on the similar action of omega-3 fatty acids from marine foods. Thus we can be quite certain that

this activity of omega-3 fatty acids from marine oils in the diet is based upon sound principles and does indeed have effects on heart disease.

After publications from the Danish group of investigators began to appear, research laboratories in other parts of the world undertook similar research. In much earlier work, it had been shown that families of Japanese fishermen who consumed large quantities of fish had a lowered incidence of heart disease. This had previously been supposed to have been the case because of the serum cholesterol depressant activity of the oils of fish in the diet. Investigation by Japanese researchers (Hirai et al. 1980) have now showed that the bleeding time of such Japanese who ingested large amounts of fish was significantly longer than that of individuals eating much less fish. This suggests that the action of the omega-3 fatty acids in fish toward lowering blood coagulation must also be involved.

Research is continuing at dozens of laboratories throughout the world. Some aspects of the field of heart disease and effects of omega-3 fatty acids which need much more work are (1) General research to get more information on the mechanism involved; (2) Find out how important omega-3 fatty acids other than C20:5 are, especially the role of C22:6 which has had very little attention; (3) More research is needed on the quantitative aspects to determine how use of relatively small amounts of fish in the diet effect heart disease. Much of the work up to now has involved use of relatively high quantities of fish or fish oil. We do not know for example, whether consumption of medium high oil content fish 2 or 3 times per week would have significant beneficial effect. (4) Information is needed especially in connection with the possibility of development of capsules containing omega-3 fatty acids just what chemical form they should be such as triglycerides, ethyl esters or fatty acids. (5) Long term over a period of years

investigations would be especially helpful where the effects on incidence of fatal heart attacks might occur. Most of the present clinical tests are of relatively short term where the effectiveness of the omega-3 fatty acids is assessed by some chemical on other observation (such as bleeding time) rather than to obtain results involving effects resulting in heart attacks.

III Effects of Dietary Fish Oil on Medical Conditions Other than Heart Disease

A Inflammation Diseases

As was previously indicated, heart conditions are the only medical ones for which there is quite definite, well-established evidence for the beneficial effects of dietary fish oils. Ironically for another medical condition, inflammation diseases, specifically arthritis, the use of fish oil preceded the use of fish oil for heart disease by almost 200 years. In the mid 1770's at a large hospital in Manchester, England, it had been the custom to suggest that arthritic patients "oil" their squeaky joints with cod liver oil. In about 1770 someone in the hospital suggested to such a patient they should try to take the cod liver oil internally. Upon doing so, within a few weeks nearly all of her arthritic symptoms disappeared. The hospital staff did not take this result seriously believing it was more likely that a change in the weather (which often affected the course of arthritis) to be the reason. However about a year later this individual returned to the hospital with an even worse arthritic condition and asked for the internal cod liver oil treatment which quickly was successful. Thereafter the Manchester Hospital routinely used internal dosage of cod liver oil for arthritis

patients at their establishment. This continued for 10 years with uniform success. By that time the hospital was using cod or ling liver oil (most of which was imported from Newfoundland) at a rate of more than 500 lb per year.

The results of these clinical tests with many patients over a ten-year period were read at a meeting of the Royal Society of Physicians in Paris on October 7, 1782. This paper was published (Percival 1783) in the London Medical Journal by Dr. Thomas Percival who was a physician at the Manchester Hospital.

Presumably this use of fish oil continued at Manchester for some time after publication of the paper. Nevertheless such use eventually died out and was completely forgotten. Probably one reason for the failure of this practice to gain wide acceptance was the extremely bad flavor of cod liver oil made at that time. It was manufactured by letting the livers rot until the oil was released and then separating the oil. In the paper by Percival it states that the ordinary sufferer of arthritis not in a hospital could never be induced to take the cod liver oil internally because of its atrociously bad flavor. Only patients in a hospital used it when they were forced to do so by the hospital attendants. Although the Manchester Hospital found a way to remove a portion of the objectionable flavor, it still remained tremendously unpalatable. At any rate this finding based on effectiveness of cod liver oil was eventually relegated to the status of an "old wives" tale and was eventually forgotten.

Today a reason for this effect of such oil on arthritis - presence of omega-3 fatty acids - is stimulating interest in studying anew this possibility. Based upon the same principles as that of the effets of omega-3 fatty acids, it is accepted that aspirin is valuable both in connection with reducing risk of heart attacks but also as a useful substance for treatment of

various inflammation diseases such as arthritis and nephritis. Several fish oil investigations are now under way (e.g. Zurier et al. 1984, Robinson et al. 1984) on value of omega-3 fatty acids for arthritis. Also the glyceryl ethers of fish oils have been reported (Chalmers et al. 1966) to be useful in treatment of arthritis. Likewise beneficial effects of omega-3 fatty acids on nephritis are being investigated (Kelley et al. 1984, Robinson et al. 1984). The broad picture of the situation regarding role of omega-3 fatty acids and inflammation diseases - a field still imperfectly understood is discussed by Lands and Bimbo (1983) pages 43-49.

B. MULTIPLE SCLEROSIS

Multiple sclerosis is a disease for which it has been suspected for some time that something to do with the type of fat in the diet might possibly be important. These ideas did not go back hundreds of years such as was the case with arthritis. However, around the middle of this century some observations made upon incidence of multiple sclerosis suggested that excessive consumption of fat from meat in the diet might have a harmful effect. Much of this work stemmed from effort by Swank and co-workers (e.g. Swank and Backer 1950 and Swank, Lersted, Strom and Backer 1952. It was observed by them that inhabitants of Norway living in the central areas where meat consumption was high had a much greater incidence of multiple sclerosis than those who lived along the coast and who ate considerable quantities of fish and much less meat. These findings received some confirmation by a Norwegian survey made in the early 1960's by Preshus 1962.

In 1967 Bernsohn and Stephanides discussed at some length the epidemiology indication that populations consuming diets high in omega-3 fatty

acids had far lower incidence of multiple sclerosis than those in which such levels were lower. Although there had been many suggestions prior to 1967 that low levels of unsaturated fatty acids might be responsible for increased incidence of multiple sclerosis, Bernsohn and Stephanides were the first to suggest that omega-3 fatty acids might be a critical factor. They further suggested that it might be the longer carbon chain (C-20 or more) which were of greatest importance among the omega-3 fatty acids. They thought that perhaps some of those who ingested C_{18} omega-3 fatty acids like linolenic acid, and who still developed multiple sclerosis, did so because of a metabolic deficiency which retarded ability for chain-lengthening of omega-3 fatty acids to C_{20} or C_{22}.

During the 1960's biochemical studies of the brain, of the serum and of red blood cells of multiple sclerosis patients showed that with such patients the unsaturated fatty acid content was less than with normal individuals Gerstl et al. (1961) and Gul et al. 1970. Thompson (1966) reported that a specific decreased content of linoleic (omega-6) acid existed in analyses of tissues of multiple sclerosis patients.

Beginning in 1981, an investigation was begun in the United Kingdom to look into the effect of omega-3 fatty acids upon the course of development of multiple sclerosis. This latest investigation is described in a preliminary way by French (1983) and she also gives an excellent review of older investigations of multiple sclerosis. As of early 1985, results available on this long term study are limited to the effects on serum fatty acid levels of feeding MaxEPA oil capsules. There has been a definite increase in serum levels of omega-3 fatty acid levels for such patients. The values over an 18 month period were about 3 times as high as in the controls. This long-term work is continuing, and it will be interesting to find out when the experiment

is farther along, how much if any effect the supplementing of the diet with omega-3 fatty acid would have.

C. STROKES

Because the action of *in vivo* platelet aggregation which occurs in heart attacks is also involved in strokes, it might appear that the same reduction in incidence of strokes might result from diets containing considerable amounts of omega-3 fatty acids as is the case with heart attacks. Actually, however, statistics on Greenland Eskimos (Kroman and Green - 1980, also Lands - 1984) would indicate that such Greenland Eskimos are somewhat more prone to develop strokes than are a matched population of Danes living in Denmark. However, based upon animal experiments of Lands (1982) with cats, the tissue damage among cats fed omega-3 fatty acids following a stroke is considerably less than is the case of cats with strokes who did not include omega-3 fatty acids in their diet.

D. CANCER

Although research on the effects of omega-3 fatty acids upon cancer has only recently been undertaken some preliminary information obtained at two laboratories by animal experiments have given some indication that omega-3 fatty acids in the diet might reduce certain types of cancer incidence. At Sloan-Kettering Institute for Cancer Research, research by Karmali (1984) employing mice have indicated reduced breast cancer incidence when omega-3 fatty acids (from MaxEPA) were included in the diet. In mice experiments of a different Investigation (Levine *et al.* 1984) inclusion of omega-3 fatty acids also reduced tumor growth.

E. OTHER MEDICAL CONDITIONS

Several other medical conditions may be improved by omega-3 long chain fatty acids in the diet. Most of these have so far resulted in only preliminary research results. They include effects of long chain omega-3 fatty acids upon eczema (Rhodes 1983), upon lowering of high blood pressure (Schoene, 1984 and Weber 1983) and effects relating to the immune system (Mertin 1983).

IV. EFFECTS OF FISH OIL ALKOXYDIGLYCERIDES UPON MEDICAL CONDITIONS

In a number of species of fish a considerable portion of the lipid which in most fish occurs primarily as triglycerides is present as alkoxydiglycerides. The presence of such compounds in fish was first reported by Tsujimoto and Toyama (1922). These alkoxydiglycerides or diacyl glyceryl ethers as they are more generally referred to (sometimes called just glyceryl ethers) occur to the greatest extent in the liver oil - to a lesser extent in the body oil of sharks. They also occur more rarely in the lipids of other species of fish. A very general, long review of the biochemistry of lipids containing ether bonds has been published by Snyder (1969). A shorter review of marine lipids containing the ether bond has been published by Malins and Varanasi 1972.

Several medical effects have been described for use of glyceryl ethers from fish lipids following publication of a Bodman and Maisin (1958) review article. In this paper the idea is advanced that glyceryl ethers such as batyl alcohol occur in embryos at a very early stage before other lipids have appeared. They suggest that the glyceryl ethers play some role in the subsequent embryo development to produce other lipids. From these hypotheses they came to believe that in certain non-healing wounds, glyceryl ethers might

promote healing. In tests with such wounds mostly connected with surgical operations, they report initiation of healing by use of external application of glyceryl ethers to the wound when previous attempts without use of glyceryl ethers failed to result in healing.

In a very short paragraph (2 sentences) Bodman and Maisin state that "no effect whatever has been observed in the use of glyceryl ethers in the treatment of accidental burns in otherwise fit individuals." This statement is not repeated in the discussion or summary of their paper. As a result of publication of the paper of Bodman and Maisin, pharmeceutical manufacturers (either ignoring or not noticing the very short statement that the results do not apply at all to accidental burns or wounds) began putting out preparations for healing of burns or wounds with glyceryl ethers as a main ingredient. The myth that glyceryl ethers were of great value in ordinary burn or wound healing was thereby established

In 1966, our laboratory having a great doubt about the efficacy of the use of fish oils for use in an ointment (by then commonly recommended as a sure cure for healing wounds or burns) carried out on a contract with Mayo Clinic work which quite definitely disproved any such beneficial activity. Hairless mice were given burns in other cases wounds under standard conditions and treated using a double blind system with external applications of fish oil with (1) high content of glyceryl ethers, (2) no glyceryl ethers, (3) high vitamin A content but no glyceryl ethers, and (4) of mineral oil disguised to seem to be identical to the fish oil Another control used was no treatment with oil of any kind. There was no improvement in healing rate for any of the treatments at all. When no oil of any kind was used there was a barely statistically significant increase in healing time over all the other oil treatments (Stansby, Zollman and Winkelman - 1967). In spite of the

publication of these results, at least one commercial product with glyceryl ether containing fish oil is still sold with fantastic claims for its healing properties for burns.

Glyceryl ethers are also used for a variety of other medical purposes in which, however, tests by different laboratories do not always agree as to whether the glycerol ethers serve a useful purpose. Perhaps the leading such use is for the purported value of glyceryl thers (predominately selachyl alcohol) when taken internally to reduce undesirable side effects during radiation treatment.

Most of the research on the desirability for taking internally of selachyl alcohol from fish liver oils containing it as well as batyl alcohol and other glyceryl ethers stems from work by Astrid Brohult. She and coworkers worked at Radiumhemmet in Stockholm, Sweden. This work began in the 1950's and resulted in publication in 1963 of a 99 page report entitled "Alkoxyglycerols and their use in Radiation Treatment" (Brohult 1963). As a result of this research, it is our understanding that selachyl alcohol or other glyceryl ether preparations are used routinely at the Radiumhemmet for patients receiving radiation treatment. These findings have been confirmed by workers at other laboratories e.g. Sviridov et al. 1954 and Edlund 1954. On the other hand in several other laboratories e.g. Snyder (1969), no such effects could be found. It was Snyder's contention that many of the other reports which seemed to support the view that glyceryl ethers were effective in radioprotection were based upon inadequate numbers of subjects to draw significant statistical conclusions.

Evans et al. (1958) reported that batyl alcohol injections could cure cattle which had developed poisoning from consumption of bracken fern. On the other hand Dalton 1964 was unable to confirm this effect of batyl alcohol.

Abaturova and Shubina (1964) reported a marked depression of carcinoma in rats fed batyl and selachyl alcohol. By contrast, Delmon and Biraben (1966) were unable to obtain any such effect.

In summary it would appear that glyceryl ethers have the best documentation for diminishing harmful radiation treatment effects. At the other end of the scale, beneficial effects of external application of glyceryl ethers to wounds and burns have been generally disproven. The other purported effects for glyceryl ethers require additional research before we can assess their value.

V SUMMARY

At present there is sufficient evidence based upon publication of very many dozens of papers to show that there is a definite relationship between incidence of heart disease and the presence of long chain omega-3 fatty acids in the diet. Much research still needs to be done particularly to allow us to fully understand the mechanism of how this takes place. We also need much more information to establish the quantitative aspects, i.e. how much effect does different amounts of omega-3, long chain fatty acids in the diet have upon frequency of heart attacks.

There is considerable evidence to indicate that long chain omega-3 fatty acids may diminish symptoms of inflammation diseases such as arthritis and nephritis. Such a situation seems logical since there is strong evidence that aspirin is beneficial for both heart and inflammation diseases, and the same general mechanism seems to be involved for both action of long-chain omega-3 fatty acids and aspirin. Nevertheless, the amount of research on action of the fish oil fatty acids and inflammation diseases is relatively meagre and

considerably more research will be required before we can have the same degree of assurance here as is the case with heart disease.

Many other disease conditions are possibly benefitted from inclusion of more omega-3 long-chain fatty acids in the diet and for which only a small amount of research has yet been performed. These include multiple sclerosis, strokes, and certain types of cancer. It is possible that with much more research evidence, these and perhaps many other medical conditions will be definitely shown to be beneficially effected by omega-3 fatty acids. As of now, however, relationships between these disease conditions and dietary omega-3 long-chain fatty acids are only speculative.

VI REFERENCES

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