The Effect of a Fish-oil Fraction on Plasma Lipids

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Since the original report from this laboratory in 1952[1] many investigators have confirmed that the substitution in the diet of vegetable fats containing large amounts of linoleic acid (e.g., corn, cottonseed, safflower, soy oil) for fats containing predominantly saturated fatty acids (e.g., fat from meat, eggs, and dairy products) will result in a marked fall in plasma lipids in most human subjects. It has further been demonstrated that the addition of sufficient amounts of polyunsaturated fats to (a) fat-free diets or (b) diets containing significant amounts of saturated fats will result in a significant fall in the level of plasma lipids.[2] The amount of vegetable fat required under the latter set of conditions is of considerable magnitude and from a clinical standpoint is unfeasible because of the increase in dietary calories.

Recently, Ahrens and his associates[3] reported that menhaden oil, a fish oil with an iodine value in excess of 150, had at least as great an effect upon plasma lipids as an equal amount of vegetable oil containing more than 50 per cent of linoleic acid.

On the basis of existing information there is some reason to believe that the efficacy of a fat in lowering plasma lipids may be in a measure proportional to the total number of double bonds present in its fatty acids. Conceivably, a highly unsaturated fat containing fatty acids of proper molecular configuration would be capable of lowering plasma lipids when added in relatively small quantities to a diet containing considerable quantities of saturated fat. Accordingly, the ethyl esters of menhaden oil were fractionated by appropriate methods with the yield of the fish oil fraction shown in figure 1. The gas-liquid chromatographic pattern of menhaden oil fatty acids is shown at the top of this figure, the menhaden ethyl ester fraction in the center, and a standard fatty acid mixture is shown at the bottom for orientation purposes. It is apparent that the fractionated material contains very much larger amounts of long-chain highly unsaturated material than the original menhaden oil. The iodine value of this material was slightly over 300. It contained 24 per cent of a five double bond C_{20} acid and 35 per cent of a six double bond C_{22} acid. This material was given to patients maintained under quantitatively constant dietary conditions in the metabolic ward.

The three women whose studies are illustrated in figures 2, 3, and 4 were mild diabetics, with adult onset of their disease and no evidence of ketosis at any time. They were forty-five, seventy, and fifty-five years of age respectively. SDEB (figure 2) had no hypoglycemic therapy prior to her metabolic ward admission, except for a diet to which she adhered rather poorly. She had 0—2+ glycosuria and an average fasting blood sugar of 200 mg. per 100 ml. LSOU (figure 3) was known to have had diabetes for one year, and had received a 1,200 calorie "diabetic" diet, to which she adhered rather poorly, and reserpine for mild hypertension, prior to this admission. She also had a fasting blood glucose which averaged approximately 200 mg. per 100 ml. before admission. Her urine sugar tests were usually negative. MMAR (figure 4) had diabetes of eleven years' known duration and had been maintained on 20 to 30 units NPH insulin with no glycosuria and a fasting blood glucose of 120-170 mg. per 100 ml. before her metabolic ward admission. She was maintained on 25 units NPH insulin daily while on the metabolic ward. The other two patients received no hypoglycemic medication. Diabetic control of all three patients was excellent during their stay on the metabolic ward.

In figure 2 a study is shown in which the fish oil fraction, designated as "Escambia Oil," was substituted in calorically equal amounts for 80 gm. of butter fat. There was a prompt decrease in the level of total lipids and of total cholesterol.

The inclusion of this amount of the Escambia Oil resulted in a formula which was quite objectionable in taste. Accordingly, the material was prepared in soft gelatin capsules, each containing one gram of the ethyl esters, and the material was administered in this form to a mildly diabetic patient who was maintained on a quantitatively constant formula in which all of the fat initially was derived from butter (figure 3). Then 12 gm. of

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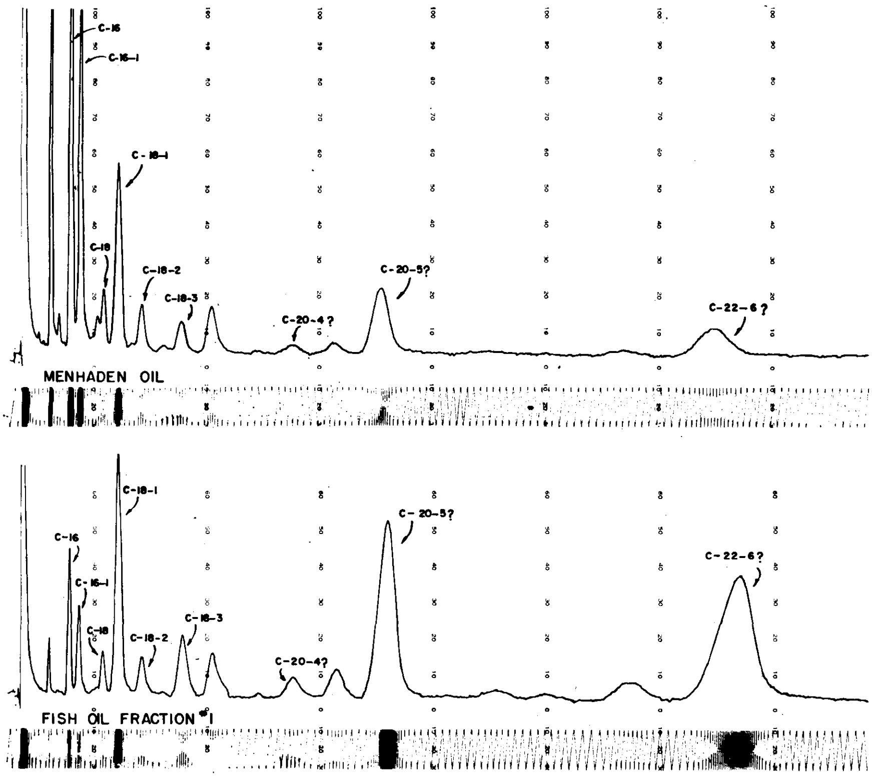

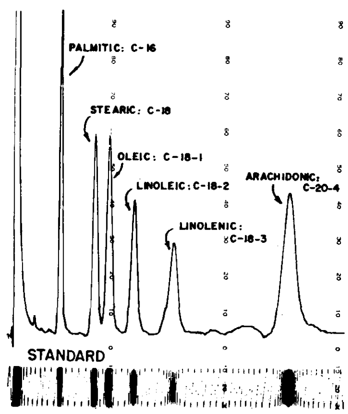

FIG. 1. Escambia Oil contains large amounts of a C_{20}-penta-enoic and a C_{22}-hexa-enoic acid as well as appreciable amounts of other highly unsaturated fatty acids. The actual composition follows. The number of carbons in acid is followed by the number of double bonds and per cent: C_{22}, 6, 40; C_{22}, 5, 4; C_{22}, 3, 6; C_{20}, 5, 30; C_{20}, 4, 2.6; C_{20}, 3, 4; C_{18}, 4, 1.5; C_{18}, 2, 0.5; C_{18}, 1, 5; C_{18}, 0, 1.3; C_{16}, 3, —; C_{16}, 2, —; C_{16}, 1, —; C_{16}, 0, 0.2; C_{14}, 2, —; C_{14}, 0, —.

Escambia was added to the butter fat. Subsequently, 20 gm. of Escambia Oil replaced 20 gm. of butter fat. A significant decrease in the level of plasma lipids resulted.

In figure 4 another study is shown, in which initially 8 gm. of Escambia Oil were added to 80 gm. of butter fat with a prompt fall in plasma lipids. The oil was subsequently increased to 16 gm. with no additional effect.

At the time of submission of this report the material has been administered to four "essential" familial hypercholesterolemic persons and one "essential" hyperglyceridemic individual, all on an ambulatory basis. In none of these patients has there been a response in terms of significant and maintained fall in plasma lipids. In the immediate future the material will be administered to a variety of ambulatory patients with elevated lipids, including diabetic patients with retinal and renal involvement. With the exception of mild diarrhea in one patient, who had previously shown such intolerance to other fats, and abdominal distress in one of the patients who also had biliary calculi, no untoward effects have been noted.

SUMMARY

The present study indicates that a fish oil fraction con-

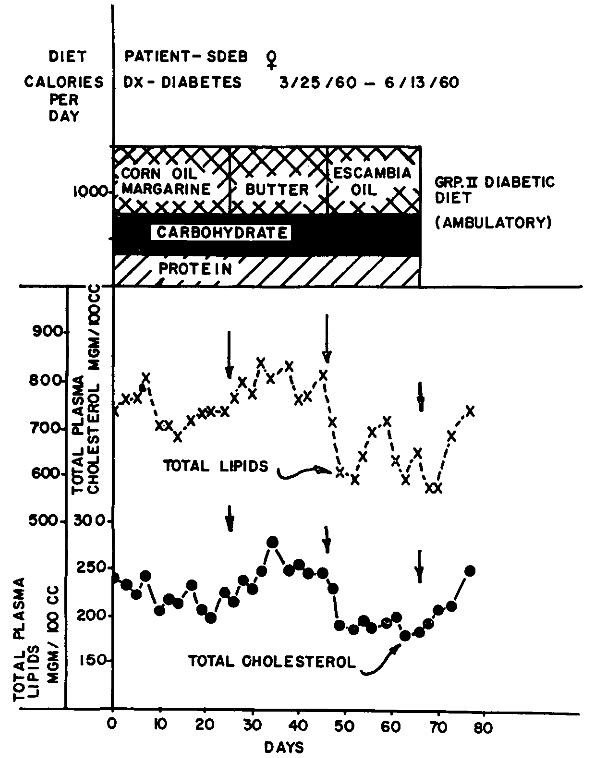

FIG. 2. Replacement of 80 gm. of butter fat by 80 gm. of Escambia Oil was associated with a significant fall in plasma lipids.

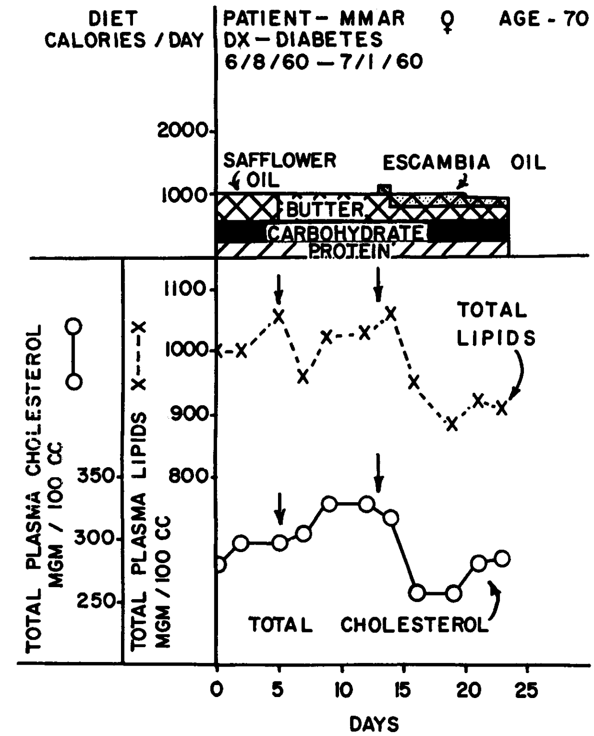

FIG. 3. Replacement of a portion of butter fat by Escambia Oil resulted in a decrease in plasma lipids.

taining large amounts of long-chain, polyunsaturated fatty acids which are not "essential" in the usual sense of the word[3] will produce a significant decrease in the level of plasma lipids in some individuals in the presence of a relatively large amount of dietary saturated fat. The amounts required per day to produce this effect vary from 8 to 30 gm. Effects of this magnitude have not been observed in this laboratory when equal amounts of ethyl linoleate or vegetable fats have been added to diets containing an abundance of saturated fat. It seems probable that the efficacy of this material is in a measure proportional to its unsaturation.

Work designed to produce fractions containing much larger proportions of the penta- and hexa-enoic acids is under way. Such fractions may conceivably produce hypolipidemic effects in much smaller dosage. It seems unlikely that such a preparation will take the place of a dietary modification, but it may possibly be useful as a dietary supplement.

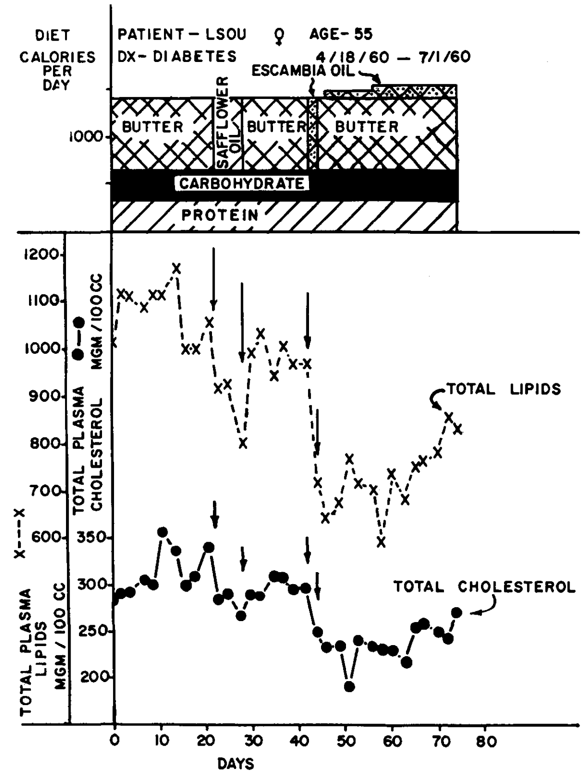

FIG. 4. Addition of 8 to 16 gm. of Escambia Oil to a formula containing 90 gm. of butter fat produced a major fall in plasma lipids.

SUMMARIO IN INTERLINGUA

Le Effecto de un Fraction de Oleo de Pisce Super le Lipidos del Plasma

Le presente studio indica que un fraction de oleo de pisce que contine grande quantitates de poly-nonsaturate acidos grasse a catena longe, non "essential" in le senso ordinari del parola, produce un declino significative del nivello de lipidos de plasma in certe subjectos in le presentia de relativemente grande quantitates de grassia saturate in le dieta. Le quantitates requirite pro producer iste effecto varia ab 8 ad 30 g per die. Effectos de iste magnitude non esseva observate a iste laboratorio quando simile quantitates de linoleato ethylic o de grassias vegetal esseva addite a dietas continente un abundantia de grassia saturate. Il pare probabile que le efficacia de iste material es, in un certe mesura, proportional a su non-saturation.

Es in progresso travalios visante a producer fractiones continente multo plus grande proportiones del acidos penta- e hexa-enoic. Il pare plausibile supponer que tal fractiones es possibilemente capace a producer effectos hypolipidemic post lor administration in quantitates multo minus considerabile. Il non es probabile que un tal preparato pote prender le placia de un modification dietari, sed illo va possibilemente provar se utile como supplemento dietari.

ACKNOWLEDGMENT

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The Escambia Oil was supplied by Dr. Robert Hodgkinson of Parke, Davis and Company.

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Hypoglycemia Induced by Galactose

(Continued from page 315.)

Similar trends were noted in the second premature infant who was jaundiced, and in this case, while the fasting blood glucose was 32 mg. per 100 ml. on the third day of life, it fell to a minimum value of 13 mg. per 100 ml. thirty minutes after feeding and attained a fasting value about thirty minutes later. During this time, the total blood sugar (representing mainly galactose) steadily increased, reaching a maximum value at thirty minutes (90 mg. per 100 ml.). On the fourth day of life, similar levels of blood glucose were noted, but by the ninth day there was an increase in the blood glucose level after ingesting food and the galactose was at its maximum, only 20 mg. per 100 ml.

While none of these individuals showed definite clinical signs of hypoglycemia, the possibility could not be excluded that hypoglycemia produced by galactose could be a clinical as well as a biochemical feature in the neonatal period. The chemical detection of such a hypoglycemia would require the use of the glucose oxidase method.

The means by which the increased blood galactose influences the blood glucose is not known. The possibility exists that the blood galactose stimulates the pancreas directly to produce increased amounts of insulin. Also, the release of glucose by the liver may be influenced by the elevated blood galactose. These investigators suggest that the metabolic regulatory system responsible for maintenance of the blood glucose within its normal narrow limits apparently cannot readily differentiate between glucose and galactose. Thus a sharp rise in the blood galactose will cause a decrease in the blood glucose level.

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