# Essential Fatty Acids and the Problem of Atherosclerosis

LAURANCE W. KINSELL, M.D.,* GEORGE D. MICHAELS, PH.D.,† PRISCILLA WHEELER, PH.D.,‡ PAUL F. FLYNN, M.D.,§ AND GEOFFREY WALKER, M.D., M.R.C.P.‖

With the technical assistance of H. P. Chin, Marjorie Coelho, Joyce Conklin, Yvonne Fisher, George Fukayama, Florence Olson, and Sadie Smyrl



IN 1950 we had occasion to carry out studies designed to evaluate the effects of certain hormonal entities upon fatty acid oxidation. As part of this study we placed patients upon diets containing very large amounts of fat. Since vegetable fat is liquid at room temperature, and emulsions made from liquid fat are easier to work with, vegetable fat was selected for this study. In the course of this work we noted a very profound decrease in the level of plasma cholesterol and phospholipids. Initially, it was felt that the decrease was the result of hormonal agents which were co-administered, but subsequent studies in which no hormones were used indicated that the effect could be produced essentially at will by inclusion of adequate amounts of a variety of vegetable fats.[1–4]

These observations, which were first confirmed by Ahrens,[5] and since by many other workers, raised the question as to whether this effect of vegetable fat was referable to the *presence* of something or the *absence* of something. When equal amounts of animal fat were substituted for the vegetable fat, a prompt rise in the cholesterol and other lipids occurred. However, when very large amounts of cholesterol were added to the vegetable fat diet, little or no increase in the level of the plasma lipids was noted. It therefore seemed proper to say that this effect was referable not merely to the absence of cholesterol.

Vegetable fats contain sterols other than cholesterol as well as a variety of phospholipids. Accordingly, for several years in the period after 1950, studies were undertaken in which vegetable sterols and related substances were administered under controlled conditions. In a few instances some decrease in the level of plasma lipids was noted. However, these changes were inconstant and usually of relatively slight degree. Much the same statement applies to the administration of phospholipids of vegetable origin, although in a few instances the administration of vegetable phosphatides did produce a very significant decrease in the level of plasma lipids. Subsequent studies have shown that those phospholipid preparations which produced such an effect were compounds containing relatively large amounts of polyunsaturated fatty acids.

This then left us with essentially one probable explanation—that specific fatty acids present in vegetable fats were responsible for the decrease in plasma lipids.[6]

During the past one and one-half years, studies have been carried out using purified preparations of ethyl oleate, ethyl linoleate, tri-olein, and tri-linolein. These studies have demonstrated beyond any reasonable doubt that the administration of diets con-

From the Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, California.

* Director, Institute for Metabolic Research; † Senior Research Biochemist, Institute for Metabolic Research; ‡ Research Associate, Institute for Metabolic Research; § Research Fellow, Institute for Metabolic Research.

‖ Nutrition Foundation Fellow.

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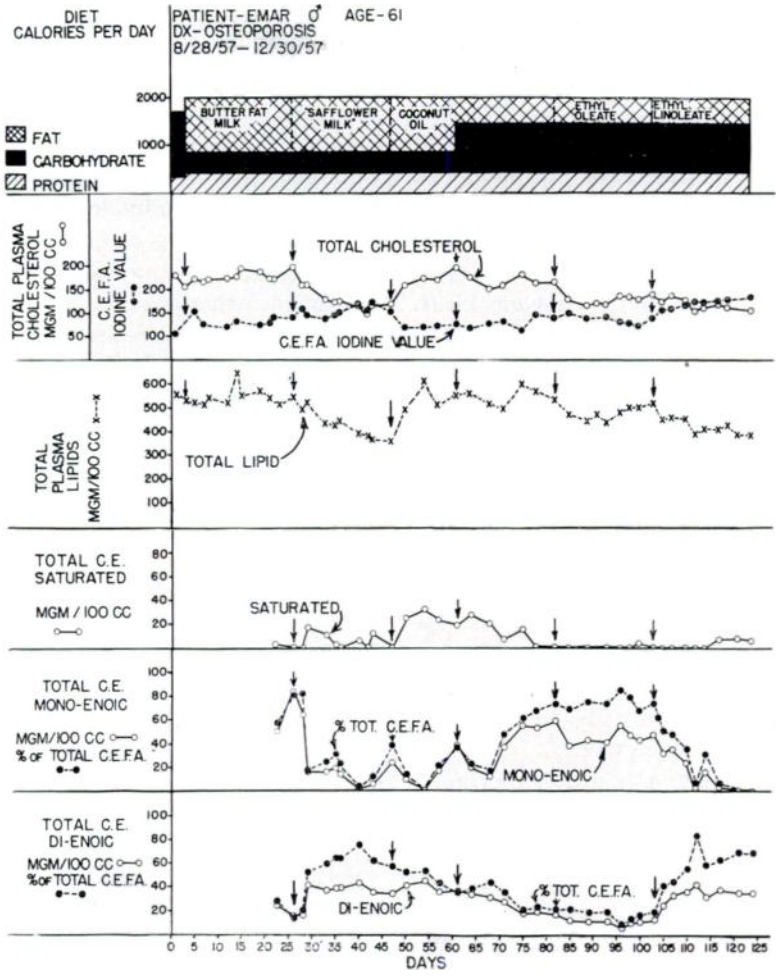


Fig. 1. Effects of different fats upon plasma lipids. The monoenoic and dienoic acid content of the cholesterol esters mirrors the type of fat fed,* particularly in the case of ethyl oleate and ethyl linoleate.

taining purified linoleic acid preparations as compared to diets containing saturated fats, purified oleate or fat-free diets will produce a decrease in plasma lipids of at least as great a magnitude as will vegetable fats containing equal or greater amounts of linoleic acid.[7]

In Figure 1 is shown a portion of a study in patient EMAR in which oleate is compared with linoleate. The plasma lipid levels during linoleate administration are significantly lower than those observed during oleate ingestion. Also, the mono- and dienoic acid content of the plasma cholesterol esters mirrors the type of fatty acid which is being administered.

These observations raise two major questions: First, what is the mechanism of this effect? And second, is the lowering of plasma lipids noted under these conditions associated with a desirable effect on atherogenesis or upon existing atherosclerosis?

The mechanism of the effect is still unclear. As a working hypothesis, we would advance the following proposal: Fatty acid is the prime fuel of the body. It is probable that 70 per cent or possibly more of the total energy expended in a 24 hour period is obtained from the combustion of fatty acids. Consequently,

* Safflower milk—"Saf-Lac" (Carnation Co.).

a large amount of such material must be solubilized and transported daily. Solubilization is essentially a function of the lipoproteins.

Fatty acids are transported in four types of compounds: the glycerides, the phospholipids, the cholesterol esters, and the unesterified fatty acids. The precise sequence of "passage" of fatty acids from one of these compounds to the next is by no means clear. We postulate that common fuel fatty acid is carried in the glycerides; that, in order to be passed on for final utilization in the tissues, perhaps by way of the unesterified fatty acids, the fuel fatty acids are carried by the lecithin-type phospholipids.

Lecithin contains one polyunsaturated fatty acid and one fuel (saturated) acid. The former, together with one molecule each of glycerin, phosphoric acid, and choline, represent the "basic skeleton" of the phosphatide which transports the saturated fatty acid. The saturated acid is turned over rapidly, the "basic skeleton" quite slowly.

Cholesterol esters serve as a donor of polyunsaturated fatty acid for new phospholipid formation. So long as all of these factors are in equilibrium, with particular reference to an adequate supply of polyunsaturated fatty acid, the rate of formation of cholesterol and phospholipid is at a minimum and the blood level is low.

If essential fatty acid is in short supply, there is an increased rate of cholesterol and phospholipid formation, an increased level of both materials in the plasma in an effort to make up in quantity what is lacking in quality, and, consequently, an increased tendency to abnormal deposition of these compounds in tissues such as the intima of arteries. Supply of an adequate amount of linoleic acid reverses this entire trend. We again emphasize: this is a working hypothesis (vintage of 1957–58) which is being subjected to progressive experimental evaluation.

We are aware that some reported data indicate that there is an increased excretion of cholic acid and an increased excretion of sterols in the stool when unsaturated fats are fed.[8] These data are interpreted as indicating increased excretion of cholesterol and its metabolites as a major avenue of unsaturated-fatty acid-induced cholesterol lowering. In our own experience, the sterol excretion is highly inconstant. Increase may occur with fats which do not decrease the level of plasma lipids and may fail to occur when linoleic acid is fed. We have no data regarding cholic acid excretion.

Regarding the question as to the relationship between atherogenesis or the resorption of existing atherosclerosis, on the one hand, and lowering of plasma lipids by essential fatty acids, on the other, two parts of a dilemma exist. The first is that, because of major species differences, no laboratory animal can be used satisfactorily to supply data regarding the human subject. The second part of the dilemma relates to the obvious fact that one cannot examine and re-examine the interior of arteries in the human subject.

During the course of the last three years we have had an opportunity to observe a variety of patients with known atherosclerosis. In individuals with peripheral vascular disease associated with intermittent claudication, we have seen highly significant improvement in a number of such patients during the intake of polyunsaturated fatty acids. Since this group represents a segment of the population that can be objectively evaluated, we feel that if the trend proves to be consistent and predictable, one would have increasing reason to believe that the lowering of plasma lipids induced by linoleic acid is, in fact, associated with favorable effects upon either formation of plaques or resorption of existing plaques. The recent *in vitro* observations of Rutstein seem to be compatible with this concept.[9]

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