Effect of Vegetable Fat on Hypercholesterolemia and Hyperphospholipidemia

Observations on Diabetic and Nondiabetic Subjects Given Diets High in Vegetable Fat and Protein

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As previously reported, the administration of formula diets containing large amounts of vegetable fat to nondiabetic patients, with or without elevation in serum lipids, results in a major decrease in the level of cholesterol and phospholipids in the plasma[1]. This statement applies to patients with such diverse conditions as simple obesity, nephrosis, myxedema, hyperthyroidism, rheumatoid arthritis, retinitis pigmentosa, etc. In the present paper will be described the findings in diabetic patients, and in one patient with familial hypercholesterolemia, maintained on formula and non-formula diets containing large amounts of fat which, as indicated in specific instances, is of vegetable, of animal, or of mixed origin.

METHODS

The chemical methods have been described previously[1, 2] as have also the preparation of the formula diets used[3]. The mixed diets containing large amounts of vegetable fat have included considerable quantities of nuts† as a source of such fat, and also as a source of a significant portion of the dietary protein. The initial "vegetable lipid diet" consisted of the addition of nuts in an amount equivalent to 800 calories, to an 800 calorie, high protein, reducing diet. More recently, a variety of nut dishes have been devised which permit of the preparation of a variety of palatable "vegetable lipid diets," in a calorie range from 1500 to 2700, as shown in Table 1.

TABLE 1
Standard diabetic diets

Diet Number	Approximate Calories	Carbohydrate Gm.	Protein Gm.	Fat Gm.	Daily Calories
1	1500	135	98	66	1526
2	1800	118	108	101	1813
3	2100	135	119	123	2123
4	2400	143	132	143	2387
5	2700	160	150	163	2707

OBSERVATIONS

Formula, High Fat Diets in Diabetic Patients

Fourteen diabetic patients have been maintained on such diets in the course of extended metabolic studies. Two of these patients (DID and GAR), on a routine

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†A portion of the nuts used in this study has been supplied through the kindness of Mr. Jenanyan of Circus Foods, Incorporated.

diabetic maintenance program (see Table 1), had hypercholesterolemia and hyperphospholipidemia. In both patients, the administration of formula diets, containing large amounts of vegetable fat together with relatively large amounts of protein, resulted in a rapid and maintained fall in the levels of serum cholesterol and phospholipids. In patient GAR, the resumption of an average diabetic diet resulted in a prompt return of the serum lipids toward their previous levels (Figures 1 and 2). This increase in serum lipids was associated with a marked worsening of vision, which up to that time had been steadily improving. This may or may not have been coincidental.

Patient EDM, a boy of eighteen with diabetes of considerable severity (insulin requirement on an average diet in excess of 70 units daily), but with no clinical evidence of vascular disease, during a period of twenty days on a formula diet containing 176 gm. of vegetable fat had a progressive fall in serum total cholesterol from 220 mg. per 100 cc. to 107 mg. per 100 cc., and

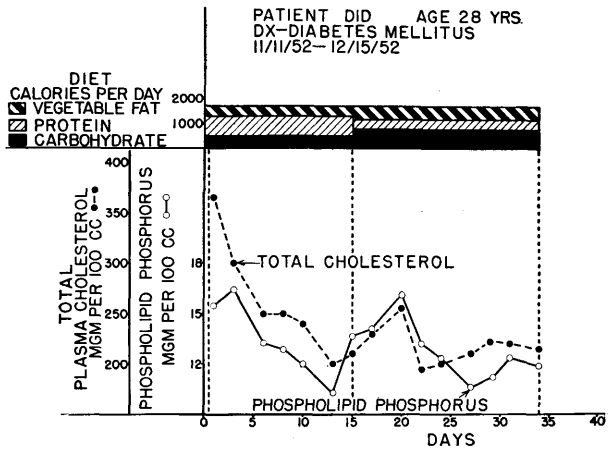

FIGURE 2. Changes in plasma cholesterol and phospholipids in a severe juvenile diabetic during the intake of a diet relatively high in vegetable fat. Previously he had been maintained on a "diabetic No. 2" diet, containing 101 gm. of animal fat. On this "animal fat diet," his cholesterol varied between 350 and 450 mg. per 100 cc. Despite chemically constant hourly feeding throughout the 24 hours and constant insulin, his diabetes was never under optimal control. Courtesy "J. Clin. Nutrition."

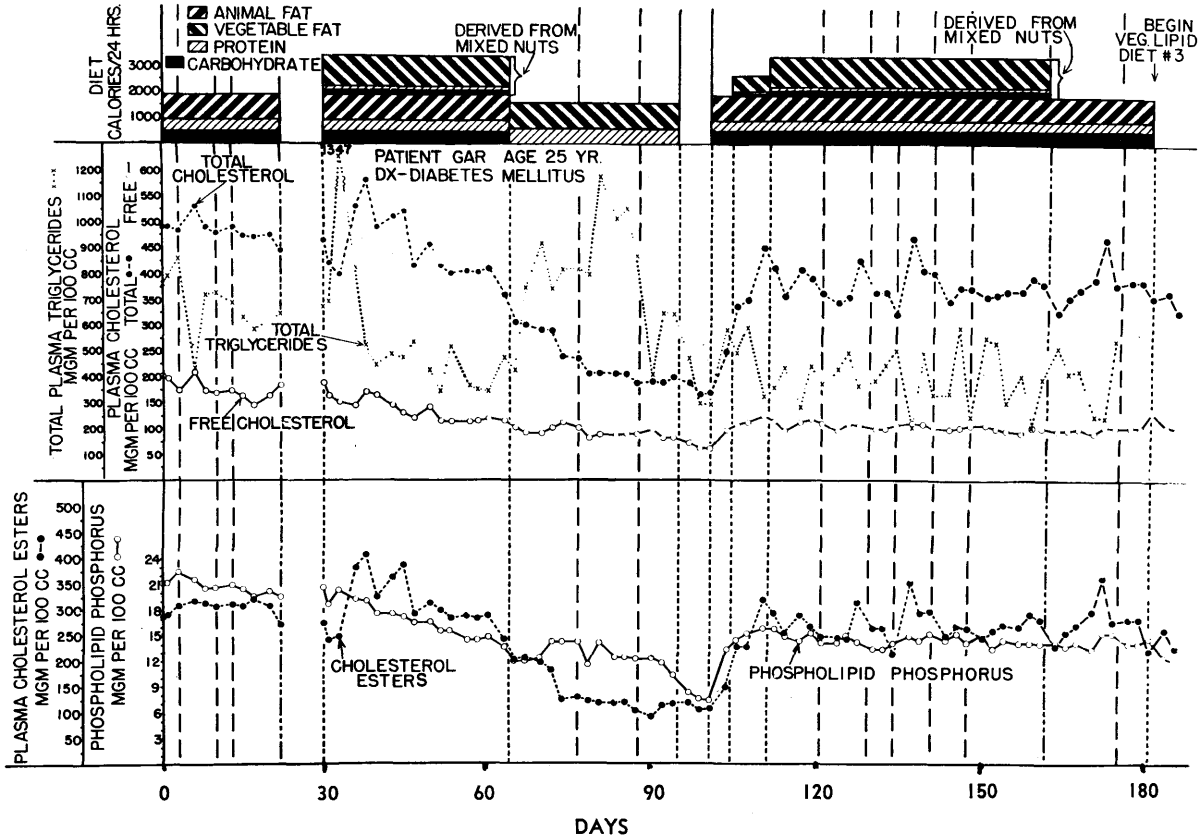

FIGURE 1. The addition of 134 gm. of vegetable fat, derived from nuts, to a high animal fat diet, was associated with a significant fall in serum lipids. The administration of a high vegetable fat formula resulted in a fall to completely normal levels. Despite hourly chemically constant feeding during this period of study, the diabetes was never under optimal control. Courtesy "J. Clin. Nutrition."

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of phospholipid phosphorus from 14.75 to 7.25 mg. per 100 cc. (Figure 3).

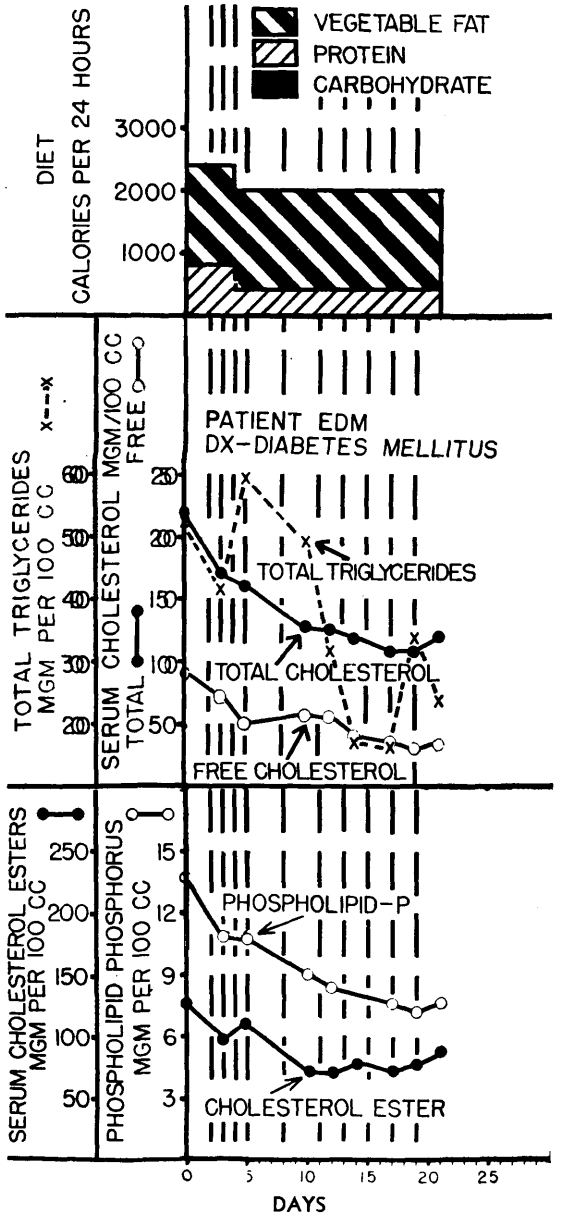

FIGURE 3. Fall in plasma cholesterol and phospholipid during the intake of a high vegetable fat formula in a severe juvenile diabetic.

Effect of Mixed Diets, High in Vegetable Fat, and Containing Little or No Animal Fat, in Diabetics and in a Patient with Familial Hypercholesterolemia

As reported in part elsewhere[4], five patients with diabetes of moderate or marked severity, all of whom had previously been maintained on diets containing relatively large amounts of animal fat and protein, after suitable "base-line observations" of plasma lipids had been obtained, were placed on diets containing amounts of protein, fat and carbohydrate, identical with their previous diets, the fat and a portion of the protein being entirely or almost entirely of vegetable origin. The findings in these patients, all of whom had been selected because they had significantly elevated or high normal cholesterol and phospholipid values, are shown in Figure 4. All of these patients experienced a significant fall in the plasma lipids, in some instances of major magnitude, during the intake of the high vegetable lipid diet. Resumption of the original diet by some of these patients resulted in a prompt return to elevated plasma lipid levels.

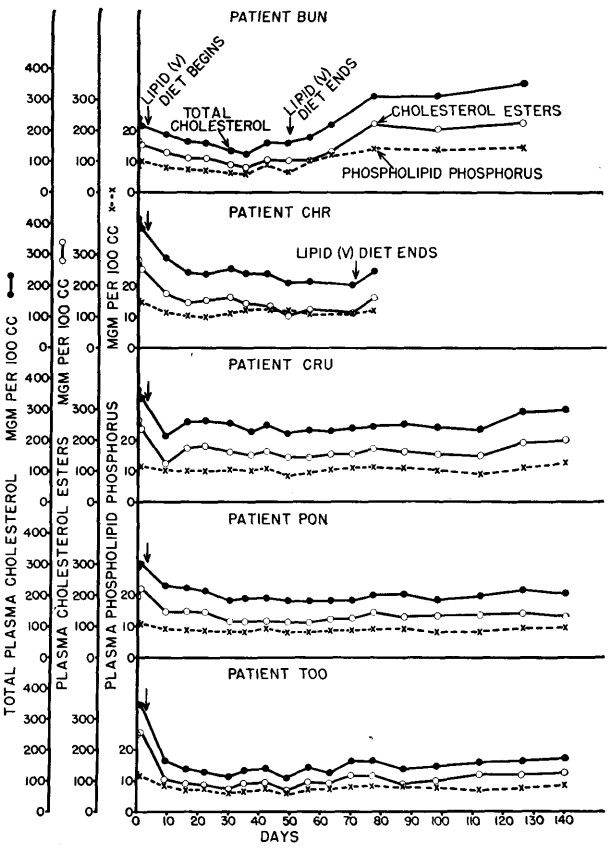

FIGURE 4. Changes in plasma lipids in five diabetics. Patient CRU did not adhere strictly to the vegetable lipid diet after the second or third week.

A patient with "idiopathic hypercholesterolemia" whose plasma lipids had been followed during the intake of an average diet, was placed on the high vegetable lipid, mixed diet, and later returned to an average

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diet. The findings are shown in Figure 5. In this patient, and in all of the above patients, the diets administered were fully adequate in a nutritional sense, i.e., they were not associated with weight loss and were associated with at least an equal degree of well being as compared to that experienced on an average diet.

It appeared then that in diabetics, as in nondiabetics, the ingestion of diets containing large amounts of vegetable fat resulted in a predictable fall in the level of serum cholesterol and phospholipids. The question arose as to the reasons for this effect. One might postulate that the change was related primarily to the *absence* of cholesterol in the vegetable fat. (This would not appear to apply in the case of phospholipids, inasmuch as the phospholipid content of the nuts used in the mixed vegetable lipid diets averaged more than 750 mg. per 100 gm. of nuts.) Another explanation would be that vegetable lipids contain sterols or other elements which exert some significant effect upon cholesterol and phospholipid metabolism. It is also thoroughly possible that some other dietary entity or combination of dietary entities in the formula or mixed vegetable lipid diet is in a measure responsible for the effect upon plasma cholesterol and phospholipids.

In an effort to explore further the possibilities, a variety of derivatives of vegetable lipids have been administered to patients in conjunction with high cholesterol diets. Among these agents have been crude "soy-bean sterols"; a mixture of soy-bean lecithin and cephalins; more highly purified soy-bean sterols; and most recently, dihydrocholesterol.

Such a study, under controlled metabolic ward conditions, is shown in Figure 6. The patient, GLI, 52-year-old male with mild diabetes and advanced vascular disease, received in sequence: crude "soy sterols," lot No. 1, emulsified with "Tween 80"*; "Tween 80" alone; crude "soy sterols," lot No. 1, without "Tween 80"; more highly purified soy sterols, lot No. 2, without "Tween 80." Each of the above was administered in conjunction with a "standard diabetic No. 2 diet" (see Table 1).

He was then placed on a chemically constant formula diet containing 120 gm. of vegetable or animal fat respectively (as indicated in Figure 6). During the course of the animal fat formula, he received in se-

*Polyoxyethylene (20) sorbitan monooleate, manufactured and sold by Atlas Powder Company under the trade mark of "Tween 80."

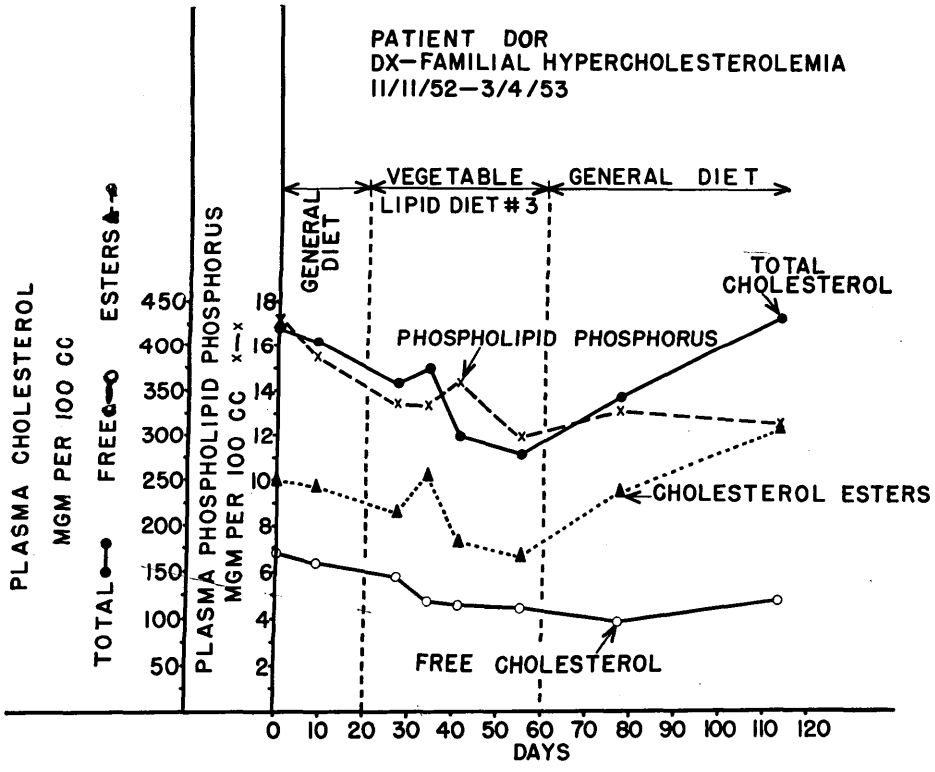

FIGURE 5. Changes in plasma cholesterol and phospholipid in a patient with "idiopathic familial hypercholesterolemia" in association with a high vegetable lipid mixed diet.

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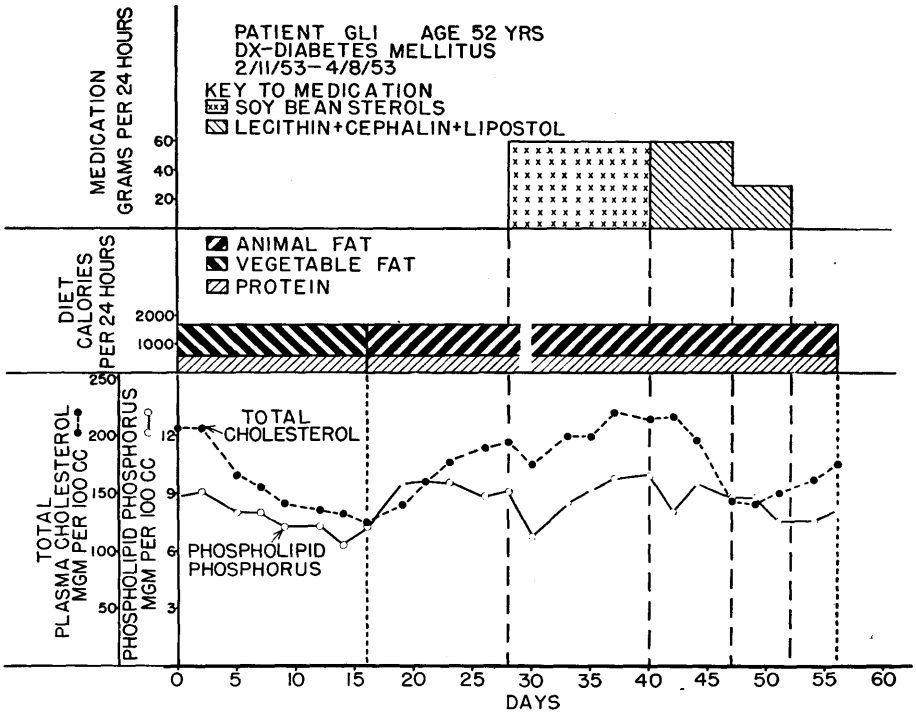

FIGURE 6. Changes in plasma lipids during the administration of soy-bean sterols and soy phosphatides in a middle-aged diabetic with extensive vascular involvement.

quence: soy sterols, lot No. 2; and a lecithin-cephalin mixture derived from soy. The findings are compatible with the interpretation that:

1. The crude soy sterols produced a significant fall in plasma cholesterol which was not dependent upon the presence of "Tween 80." The more highly purified soy sterols produced little or no effect.

2. Intake of a soy lecithin-cephalin mixture was associated with a fall in cholesterol of a magnitude comparable with that occurring during the intake of the crude "soy sterols."

The usual fall in plasma lipids occurred during the intake of the vegetable fat formula.

The foregoing findings suggest that under these conditions some component of a crude soy lecithin-cephalin mixture results in a fall in plasma cholesterol and phospholipids.

If one refers to Figure 1, however, it will be noted that no depression in plasma lipids occurred in juvenile diabetic patient GAR under the conditions of use.

Further studies with lecithin-cephalin mixtures are under way. Also being investigated are compounds which allegedly inhibit intestinal absorption of cholesterol. The administration of 20 gm. of dihydrocholesterol daily to a young severe diabetic, DID, was associated with a fall in plasma cholesterol from 251 to 211 mg. per 100 cc.

COMMENTS

The foregoing studies, and others currently under way, have a two-fold objective—first, to evaluate some of the hormonal and other metabolic abnormalities in diabetic patients; second, to evaluate the effects of diet and of other agents upon the serum lipids in diabetic patients, and if possible to determine whether any correlation exists between serum lipid changes and the progress of existing vascular disease. Only the second problem is considered in this paper.

There is abundant evidence that vascular disease manifests itself at an earlier age period and progresses more rapidly in the diabetic population than in the general population. The reasons for this are by no means clear. Among the possibilities are the following:

1. Recurrent hyperglycemia per se aids and abets in the production of damage to the intima.

2. Abnormal metabolism of lipids results from abnormal energy metabolism, with resultant increase in circulating lipids and increased deposition of lipids in the intima.

If either or both of items one and two are correct,

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optimal dietary-insulin control would be of obvious importance from the standpoint of prophylaxis of vascular damage.

3. Abnormal protein metabolism resulting from abnormal energy metabolism and/or from abnormal "hormonal balance" (see below) results in intimal damage with secondary deposition of lipid materials.

4. The production of excessive amounts of adrenal cortical and/or pituitary diabetogenic factors causes abnormalities of protein and/or lipid metabolism with resultant vascular damage.

Whatever the pathogenic factors may be, it has seemed to us that evaluation of as many aspects of lipid and protein metabolism as possible, in the diabetic, should aid in clarifying this very confused field.

As previously described[1], the original observation that in the nondiabetic, diets high in vegetable fat were associated with a fall in serum lipids, was incidental to other studies. The further evaluation of this relationship in the diabetic has been purposeful. In our experience to date, all diabetics maintained on the formula diets, and all but one on the mixed "vegetable lipid" diet, have had profound diminution in the level of their plasma lipids. Young diabetics with extensive vascular disease and hypercholesterolemia appear to be more resistant, that is, a greater period of time may elapse from institution of the diet until the lipids have fallen to normal than in middle-aged diabetics, or than in juvenile diabetics without extensive vascular disease. This observation might suggest the mobilization of depots of endogenous lipids during the early part of the dietary program. (We are aware that this may be a somewhat naïve explanation.)

The reason for the decrease in plasma lipids is as yet not fully apparent. Since the same change occurs in nondiabetics, modification of the diabetic state per se would not appear to provide a suitable explanation. Further, there is little obvious change in the diabetic state in terms of insulin requirement in most patients thus far studied; and the relative stability of the diabetic state per se seems to bear no relationship to the diet-induced changes in serum lipids.

The observation that some lipid material, apparently present in the "crude phosphatide fraction" derived from soy-bean, may cause a fall in serum lipids, at least in some patients, suggests that the effect is an active rather than a passive one. This concept is further supported by the fall in plasma lipids which may occur when large amounts of nuts are added to a high animal fat (high cholesterol) diet.

Peterson's observation with "crude soy-bean sterols"[5] suggested to Siperstein, Nichols, and Chaikoff[6] that dihydrocholesterol might inhibit the absorption of cholesterol. This apparently occurred in their experimental animals. Whether this can be duplicated consistently in humans is still to be determined.

Our own observation in one patient at least calls for further studies of the same kind.

No sweeping clinical implications should be drawn from our findings thus far. Despite a voluminous literature, it is yet to be proven that the level of any serum lipid constituent per se is either of necessity correlated with or responsible for any form of vascular disease in the diabetic or nondiabetic. This statement is documented nicely in a recent paper by Wilkinson et al[7]. Our findings do, however, demonstrate beyond any reasonable question that fat per se does *not* result in increased serum cholesterol levels[1c]; that quite the contrary is the case when diets containing large amounts of vegetable fat are ingested. Further, the observation of significant improvement in vision in two severe diabetics, with advanced retinal pathology during the period of diet-induced fall in serum lipids, would suggest that at least no deleterious effect upon this form of vascular disease results from such a dietary program.

SUMMARY

Administration of diets containing large amounts of vegetable fat to diabetic patients, with or without hypercholesterolemia and hyperphospholipidemia, consistently results in a fall in these lipids. A prompt rise occurs when isocaloric amounts of animal fat are substituted. The evidence available to date suggests that this, at least in part, may represent a positive effect of some lipid material, possibly phosphatide in nature, present in vegetable fat.

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DISCUSSION

HOWARD A. EDER, M.D., (*New York*): These data suggest the presence of some factor or factors in vegetable fats which can cause reduction of plasma cholesterol.

At the onset it should be noted that these results are at variance with the experiences of Hildreth et al and of Keys et al. These workers demonstrated that severe restriction of dietary fat caused reduction in plasma cholesterol. When vegetable fats were added to the diets of patients on those diets there was a prompt elevation of plasma cholesterol to control levels. The quantity of vegetable fat used was of the same order of magnitude in all these studies. It is possible that the quality differed.

Since the high vegetable fat diet is effective in the presence of animal fats which contain cholesterol it seems likely that explanation of decreased cholesterol intake will not suffice. Plasma cholesterol is probably in equilibrium with cholesterol in the gastro-intestinal tract and with cholesterol in the tissues. The gut equilibrium is of considerable importance since large amounts of free cholesterol are normally secreted into the bile and then reabsorbed by the small intestine. It now is known that fatty acids and bile acids participate in this reabsorption. When either of these groups of substances is absent from the gut, absorption of cholesterol is impaired. It has been suggested that the plant sterols which are not absorbed by the gut combine with fatty acids and remove them from participation in cholesterol absorption. In these diets so high in fat, it would seem that fatty acids would be present in large excess so that the removal of some would be of little overall importance. Certainly one possibility is that these vegetable fats do contain substances which decrease intestinal cholesterol absorption.

Little is known about the mechanisms concerned in the equilibrium between plasma cholesterol and tissue cholesterol. We have recently observed that administration of estrogens causes a decrease in plasma cholesterol while androgen administration will often cause the opposite effect. It seems likely that these hormones affect the tissue equilibrium. Large and rapid shifts in plasma lipid concentration can occur and these must be the result of changes in the plasma-tissue equilibrium. An example of such changes is seen in the data we recently obtained in a mild diabetic with gross hyperlipemia. Twenty-four hours after 20 units of insulin, the plasma neutral fat had fallen from 4,240 mg. per 100 ml. to 318, the plasma cholesterol from 605 to 164, and the plasma phospholipid from 712 to 224. It is a possibility that this vegetable fat mixture contains unknown substances which can act on the plasma-tissue equilibrium.

Since all of the plasma cholesterol is present as a constituent of lipoprotein molecules of relatively constant composition, it is not sufficient to consider plasma cholesterol solely. Changes in plasma cholesterol are in reality reflections of change in lipoprotein concentrations. Since phospholipids are also constituents of these lipoproteins it could be expected that plasma phospholipid concentrations would parallel the cholesterol concentration, as Dr. Kinsell has demonstrated. The changes in the ratio of cholesterol to phospholipid may be a reflection of an altered distribution of lipoproteins.

We should not neglect to emphasize that although a variety of means are now at hand for reducing plasma cholesterol concentration, there is little direct clinical evidence to suggest that doing this has any effect on atherosclerotic disease. Certainly widespread clinical application of these procedures should await more definite proof of their usefulness in human disease.

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