It is somewhat refreshing to transfer some attention to the subject of carbohydrates and away from the more controversial nutrient constituents, e.g., saturated and polyunsaturated fats, trans fatty acids, oxidized and polymerized products of heat-abused fatty acids, and cholesterol and its esters. So much has been written about the role of these lipids in health and, especially, in disease, so many experiments have been performed on a gamut of experimental insects, birds, and mammals, and so many theories and hypotheses have been proposed on the bases of results from these and from epidemiological studies, that, by comparison, reports on effects of carbohydrates in normal and pathological situations, with the exception of diabetes, have been practically neglected. Although the Food and Agriculture Handbook for 1959 (9) contains the statement "there is no definite nutritional requirement for carbohydrates," it is a well known fact that carbohydrate is the preferred source of energy for the body. In addition, carbohydrate is necessary for certain other phases of metabolic behavior. For example, the ketosis which arises in starvation and in diabetes can be mimicked by feeding normal individuals a diet containing only protein and fats. The carbohydrate, glucose, provides the substrate for the Krebs Cycle, and the metabolism of carbohydrates acts as a regulator for lipid metabolism.

It has been recognized for a long time that carbohydrate metabolism and lipid metabolism are very closely related. For example,

1. In uncontrolled diabetes, the derangement in carbohydrate metabolism is accompanied by elevated serum triglyceride and, often, also elevated serum cholesterol levels (2). When the disease is controlled, serum lipids may return to normal (27).

2. It is an established fact that carbohydrate is readily converted to fat in the body. Also, relationships between the rate of glucose breakdown in the cell and fatty acid synthesis and oxidation, cholesterol synthesis, and the accumulation of ketone bodies have been reported by many investigators (25).

3. It has been reported by Ahrens at the Rockefeller Institute (1) that serum triglyceride levels increase when carbohydrate is substituted for dietary fat in formula feeding studies.

For many years we have been concerned with the possible involvement of diet in the disease process, atherosclerosis. The fact that there is a higher incidence of atherosclerosis in the United States as compared with some European and Asian societies has prompted numerous comparisons of diet, cultural habits and other potentially contributing factors. There have been many correlations drawn relating the level of consumption of saturated fatty acids, the ratio of saturated to unsaturated fats in the diet, and the amount and type of cholesterol-containing foods ingested to serum cholesterol levels and to the incidence of heart disease among population groups. There has been a decided
increase in heart disease in the United States in the last fifty years, and although the amount of saturated fats in foods has increased as well, there is also a much greater availability of polyunsaturated fatty acids (4).

The amount of carbohydrate in the diet is greater than the amount of fat. In 1962, 47% of the calories consumed in the United States were carbohydrate calories (26). Surveys have shown, moreover, that there has been a tremendous increase in the consumption of sugar in the last fifty years at the expense of the decreasing utilization of more complex carbohydrates such as cereal products, potatoes, and other starchy vegetables.

Sucrose and Heart Disease

As early as 1957, Yudkin (29) reported that sucrose showed the highest correlation of any item in the diet with the incidence of ischemic heart disease. Then, about 5 years ago, he further reported that the British were eating over two pounds of sugar each per week and that the amount was still increasing (30). He estimated that sugar was providing approximately 1/5th of the calories of the diet and suggested that the high consumption of sugar, like that of protein and fat, was a measure of affluence. In 1963, Cohen (7) reported on his study of Yemenite Jews who had emigrated to Israel. These people, who had formerly subsisted on a diet containing mutton, beef, and milk, with starch coming from grains and vegetables as their carbohydrate source, gradually converted to a more Western type diet, which included the addition of vegetable oils to the animal fat in their diets and also the substitution of 25% sucrose for the more complex carbohydrate content of the diet. With this change in dietary habits, there was a marked increase in the prevalence of both diabetes mellitus and atherosclerosis. More recently, Yudkin (31) reported that surveys of the dietary history of patients with a history of myocardial infarction or peripheral artery disease revealed that these patients averaged a sugar intake twice as high as a control group of patients. It seems possible then that dietary changes other than those involving dietary fat may be responsible for the increasing incidence of cardiovascular disease.

Sucrose and Abnormal Lipid Deposits

Different types of carbohydrates seem to affect lipid metabolism in different ways and to varying degrees. For example, it has been found that cholesterol-containing gallstones form more easily when guinea pigs are fed sucrose than when given starch (18). It has also been observed (18) that more fat tends to accumulate in the liver of rats fed sucrose as compared to animals fed starch at a comparable caloric intake.

Carbohydrate Source and Serum Lipid Levels

Within the last few years, there have been several studies on the influence of the type of dietary carbohydrate on serum lipid levels. (Serum lipids are composed primarily of cholesterol, cholesterol esters, triglycerides, and phospholipids.) Although there is considerable evidence that in both humans and experimental animals there is an increase in serum cholesterol, total lipids, and triglycerides when a simple sugar is substituted for a complex carbohydrate in the diet, some reports indicate no correlation at all between carbohydrate source and serum lipid levels.

For example, studies were reported by Keys (15) in which the serum lipid responses of young men to typical American and Italian diets were compared. After 3 weeks on the experimental diets, the subjects eating either the high- or low-fat Italian diets with most of the carbohydrate as bread, macaroni, and beans, showed lower serum cholesterol levels than did the men on the American diets who were ingesting diets with similar fat and protein content but a larger proportion of the carbohydrates as sucrose. The serum phospholipids were also higher on the American diet, but the triglycerides did not follow as obvious a pattern. On the other hand, Grande et al. (10) found identical serum cholesterol levels in men fed either a sucrose or a bread and potatoes diet, but a diet containing leguminous seeds caused a lower serum cholesterol level than did the sucrose diet. In another study, these investigators found no significant differences between the effects of three simple carbohydrates, glucose, sucrose, and lactose, on serum cholesterol and phospholipids in male subjects (3). To add to the controversy, Hodges et al. (12, 13) observed that substitution of cereal starches and potatoes for sugar in the diet of healthy young men and women causes a significant reduction in serum cholesterol and triglyceride levels, whereas Irwin et al. (14) found no difference in serum cholesterol levels after exchanging rice for sucrose in the diets of healthy young men.

Responses in female subjects have shown similar variations. Antar and Ohlson (5) have reported that serum total lipids decrease to a similar extent in men and women after four weeks on a diet in which 80% of the sucrose had been replaced by starch. In a study similar to this, MacDonald (19) reported that when
sucrose was substituted back for starch, total serum lipids in women not only did not increase but decreased still further. In the male subjects, total lipids did increase as did also the total cholesterol levels when sucrose was substituted back for starch.

Other reports indicate that although the effects of dietary carbohydrate are real, they are much less extensive than those attributable to dietary fat.

Interpretation of data and comparison of results of various investigators are made more difficult because of other variables which differ in the various reports. Not only does the experimental animal differ—experiments have now been done on man, rat, rabbit, hamster, guinea pig, and dog—but the dietary protein may be low or high and different, the dietary fat may be saturated, polyunsaturated, high or low in medium chain-length fatty acids; the experimental period varies; the experimental design varies; some investigators feed sucrose first and change to starch; some feed starch first and change to sucrose; some feed natural foods high in a particular carbohydrate rather than a purified substance and compare these with a pure sugar, e.g., bread and potatoes versus sugar. Obviously many more controlled studies must be done before answers are forthcoming.

Proposed Mechanisms by Which Carbohydrates Affect Lipid Metabolism

In spite of the active interest in these gross effects of the type of dietary carbohydrate on lipid metabolism, few investigations have been designed to elucidate the mechanism of the apparent hypercholesterolemic response when starch is substituted for simple sugars in the diet. One possible explanation results from an observation of MacDonald (18) who found that when sucrose is fed to animals, the proportion of the polyunsaturated fatty acid, linoleic acid, in their lipids decreases more rapidly than when starch is fed. This might have the effect of decreasing cholesterol transport and other lipid transport from liver to blood.

Another possibility involves the role of intestinal flora in regulating the turnover rate of bile acids, the major degradation products of cholesterol in the enterohepatic circulation. Portman et al. (24) measured the rate at which cholic acid (a bile acid) is metabolized and excreted in rats fed either sucrose or starch diets for one month and found that it was decreased in rats on the sucrose diet. In other experiments to test the involvement of intestinal flora, Kritchevsky (17) measured the serum and liver cholesterol levels of chicks reared under normal and germ-free conditions, and fed for one month either glucose, sucrose, or starch as the sole carbohydrate source, plus 3% cholesterol. The sucrose-fed animals showed considerably higher serum and liver cholesterol values than did the starch group. And, although the germ-free condition did increase the cholesterol levels in the glucose-fed and starch-fed groups, no increase was observed in the sucrose-fed chicks. This indicates a similarity in the mechanism of the hypercholesterolemic effects of sucrose and the germ-free environment. Further evidence supporting this theory of the association of the sucrose-hypercholesterolemic response with intestinal bacteria was presented by Portman (23) working with rats given sulfasuxidine, and by Kritchevsky (16) working with aureomycin administered to chicks. However, Guggenheim (11) working with rats given aureomycin, did not confirm these studies. These investigators found no significant difference among serum cholesterol levels of glucose, sucrose, or starch-fed animals, with or without cholesterol in the diet. The addition of cholic acid or cholesterol to the diets did not increase serum cholesterol levels except when both were included, but the greatest increase in serum cholesterol content still occurred in the sucrose-fed rats. Serum cholesterol levels in rats fed any of the carbohydrates did not respond to the drug.

Another interesting report has been presented by Wells et al. (28) working with the effects of succinyl sulfathiazole in rabbits fed either lactose or sucrose with and without cholesterol supplements. They found that serum and liver cholesterol values were consistently higher in the lactose group and the effect of the drug in the lactose diet was similar to the drug-sucrose combination previously discussed, that is, the drug did not cause an increase in liver and serum cholesterol levels on the lactose diet but significant increases in both levels (liver and serum cholesterol) did occur with sucrose. But here, the mode of feeding was important. Interval feeding of the sucrose and cholesterol diets resulted in higher values than did ad libitum feeding; the mode of feeding had no effect on values of the lactose-fed group.

Although these data are not entirely definitive, there is evidence supporting the hypothesis that the type of dietary carbohydrate exerts its influence on cholesterol metabolism, at least partially, by influencing the activity of the intestinal bacteria which degrade cholesterol to its excretion products. If there is depressed reabsorption of cholesterol metabolites, which may occur when starch replaces sucrose as the
dietary carbohydrate, then the synthesis of bile acids from cholesterol would be stimulated. This should result in lower cholesterol levels. This theory has been supported by Portman et al. (22) who found that biliary bile acid excretion is increased by starch and inhibited by sucrose and dextrose.

**Carbohydrate Effects on Cholesterol Metabolism**

If the type of dietary carbohydrate influences bile acid production, it is probable that there is also an effect on cholesterol biosynthesis. We could find no information in the literature on the effects of various carbohydrates on cholesterol biosynthesis. Since, also, the reports on the effects of carbohydrate on serum and tissue lipid levels were often contradictory, we decided to investigate the rates of hepatic cholesterol and fatty acid biosynthesis in rats which had been fed diets containing the carbohydrates sucrose, glucose, and corn starch and either a saturated fat, butter, or the unsaturated corn oil, with and without cholesterol added. We selected weanling male rats and decided on a 12-week experimental feeding period which is considerably longer than the usual experimental period of 30 days or less which had been reported. Although our analyses are not complete, I should like to show the results of one of our experiments. The diet we used contained approximately 53% carbohydrate and 15% fat. Cholesterol and bile salts, when used, were added at the expense of the carbohydrate.

At the end of the experimental period the sucrose-fed animals were heavier than either the groups fed glucose or corn starch on both fat diets, even though the amount of food consumed in each group was essentially the same which indicates a difference in absorption and/or food efficiency. Plasma cholesterol levels on the cholesterol-free diets are shown in Figure 1. Although the plasma cholesterol is higher in the sucrose-fed group than in the animals fed either glucose or corn starch when the fat fed is butter, the values obtained with corn oil are similar with the sugars and corn starch. Cholesterol feeding (Figure 2) causes much more marked elevations in the butter-fed group than in the corn oil-fed animals, where only the elevation in serum cholesterol of the animals fed the glucose diet is significantly higher than values obtained on similar diets without cholesterol. Liver cholesterol levels are also reported (Figure 3). Here, the values in the butter group are lower than the corn oil group in the glucose-fed animals; the values for the sucrose-fed animals are the lowest in each category. Levels of liver cholesterol are not significantly different in the animals fed either sucrose or corn starch regardless of the type of fat in the diet. When cholesterol is added
to the diet (Figure 4) all the values are increased from approximately 2 to 4 mg/g to 30 mg/g—no significant differences are apparent in any group with any carbohydrate.

Investigations on cholesterol biosynthesis from acetate (Figure 5) reveal that cholesterol biosynthesis is lower in the animals fed butter than in those fed corn oil. This is in agreement with our previous work on the depressing effect of linoleate deficiency on cholesterol biosynthesis (21) and also that of Merrill (20) and Carroll (6). In the butter group biosynthesis is higher in the animals fed sucrose and glucose than in the starch-fed animals. In the animals fed corn oil, biosynthesis, in general, is much higher. The sucrose-fed animals have the greatest hepatic biosynthesis followed by the starch-fed group and finally the glucose-fed animals. This also agrees with our previous work where we found that the lower cholesterol concentration in the liver was associated with the higher rate of biosynthesis. Cholesterol feeding and subsequent elevations in liver cholesterol levels resulted in marked depressions in cholesterol biosynthesis (Figure 6) as has been reported many times in studies on experimental animals. It seems unlikely that the stimulation in rate of hepatic cholesterol biosynthesis caused by either dietary sucrose or linoleate in the corn oil-fed groups involves the same mechanism. If the starch and sucrose groups are compared, there is a suggestion that these factors operate independently. Dietary linoleate causes a four-fold increase in both the sucrose-fed and starch-fed rats (from 2900 cpm/g liver on the butter diet to 11200 cpm/g liver on the corn oil diet in the sucrose diet and from 1800 to 7200 on the starch diet). In the change from starch to sucrose in the butter group and in the corn oil group, biosynthesis increases by 1.6 times.

Fig. 4. Liver cholesterol levels for butter-cholesterol and corn oil-cholesterol diets.

Fig. 5. Cholesterol biosynthesis from acetate on butter and corn oil diets.

Fig. 6. Cholesterol biosynthesis on carbohydrate diets containing butter-cholesterol and corn oil-cholesterol.

Our results do not entirely agree with those reporting generally higher lipid values in sucrose-fed animals as compared with starch-fed animals. Perhaps one of the reasons is our longer experimental feeding period. If intestinal flora play a role in the carbohydrate-lipid relationship, adaptations to another environment could be achieved in twelve weeks. The marked differences in results with the different fats used indicate that the effect of dietary lipids on serum and tissue cholesterol and cholesterol biosynthesis in liver is much greater than the carbohydrate effect. One of the conclusions to result from our study is that it is impossible to define the effects of a particular nutrient from one set of experimental conditions and without due consideration of the other constituents of the diet. Nutrient-nutrient interrelationships are becoming more and more important in nutrition and disease conditions.

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References


