MEDICAL PROGRESS

DIETARY FATS, CARBOHYDRATES AND ATHEROSCLEROTIC VASCULAR DISEASE*

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THERE is considerable evidence relating nutrition, presumably through its influence on the levels of circulating lipids, to the relentless progression of atherosclerotic vascular disease and to the well known clinical sequelae that plague contemporary, highly developed societies. Unfortunately, it is difficult to unravel the precise and unique role of diet or of blood lipids in a disease in which a great many other factors are known to be involved – a severe limitation to descriptive clinical and epidemiologic studies. On the other hand, since dietary alterations can significantly influence blood lipids, nutrition may be of some importance in the treatment and presumably in retarding or preventing atherosclerotic vascular disease. It may seem perfectly reasonable that "normalization" of one of the factors known to be associated with coronary heart disease and thrombotic cerebrovascular accidents would be beneficial. Until there is more than the currently available meager, direct evidence on the value of nutritional management, however, there will inevitably be doubt and controversy. In this respect, dietary recommendations designed to reduce the level of blood lipids have much in common with other investigative but unproved medical practices – specifically, the use of various drugs to lower blood lipids. Undoubtedly, such drugs will be of increasing importance as part of the treatment of coronary heart disease. It is highly unlikely that any type of drug therapy can ever take the place of dietary changes for essentially the total population, particularly the adolescent and young adult males, whose rising levels of blood lipids lead to marked coronary atherosclerosis even in the third or fourth decade of life.

Dietary fats and carbohydrates, which together contribute about 85 per cent of a person's total caloric intake, have attracted the greatest attention as major factors influencing blood lipids. The wide variety of their sources makes possible a considerable diversity in the chemical makeup of each. The degree of saturation and the cholesterol content of dietary fats, the content of simple (monosaccharides and disaccharides) and so-called complex carbohydrates are the qualities of great current interest. The ratio of fat to carbohydrate calories can be varied widely. Although it is clearly important that specific dietary alterations be as effective as possible, a consideration of the long-term practicability of a dietary program must not be neglected; such a consideration most often limits the results achieved with dietary management.

One objective of this review is to consider some of the pertinent literature in this area and to interpret apparent dietary influences in a practical perspective.

Undoubtedly, the least controversial concept of atherosclerotic vascular disease is that a number of environmental factors act and interact with host factors in determining its inception, its progression and the ultimate clinical manifestations. Any reasonable weighing of the evidence from clinical, pathological, epidemiologic and animal studies leads to this concept of multifactorial causation. Equally clear is the certainty that the disease is not an inevitable consequence of aging though its presence and severity differ widely from one population to another and between individuals within populations. A successful resolution and understanding of the independent contribution of each of the factors associated with the frequency of atherosclerotic vascular disease has been retarded and confounded by many problems, including the following: the apparent complexity of the tissue and hemodynamical factors influencing the location and the evolution of the pathological lesion; the still imperfectly understood relation between the underlying atherosclerosis and the subsequent clinical manifestations; the inability to assess conveniently the presence and extent of atherosclerosis in vivo, especially in the coronary and cerebral circulation (thus, in population studies it is difficult to know whether one is investigating the epidemiology of atherosclerosis or of thrombotic events); and the lack of an adequate experimental animal model either for atherosclerosis or for its clinical sequelae in man.

That diet, at least so far as it may influence the levels of blood lipids, is involved in the pathogenesis of atherosclerotic vascular disease is related to the following knowledge:

The elevation of blood lipids – in particular, the

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induction of a hyperbeta-lipoproteinemia — is a *sine qua non* for the production of atherosclerosis in the laboratory animal; dietary manipulation is by far the most convenient way to achieve this.

The extraordinary differences (Fig. 1 and Table 1) in the distributions of the several blood lipids among areas of the world are in general related to cardiovascular-disease mortality. Differences in dietary practices may be related.

The association of an accelerated development of both atherosclerosis and coronary heart disease to disorders in which the levels of blood lipids are grossly elevated has long been recognized. However, it has only been in the past decade that several prospective epidemiologic studies have demonstrated the clear and quantitative association between the level of certain blood lipids and the subsequent incidence of coronary and thrombotic cerebrovascular disease.[1-4]

It is certainly true that serum cholesterol has received by far the most attention in the pathogenesis of atherosclerotic vascular disease. The main reasons for the relative deficit in the knowledge of the distributions of the levels of serum triglycerides or of the several lipoprotein classes in various population groups can be considered as much the difficulty of obtaining fasting bloods in many kinds of studies as the more cumbersome analytical technics required. On the other hand, two prospective studies have failed to demonstrate convincingly that foreknowledge either of lipoprotein levels[5] or of triglycerides[6] provides better predictors of clinical disease than the serum total cholesterol itself.

Population Studies

Dietary practices, and especially those influencing the kind and the amount of dietary fats and carbohydrates, vary enormously among different areas of the world. Over the past several decades efforts have been made to relate these dietary patterns to concurrent differences in the levels of various blood lipids, to observations on post-mortem atherosclerosis and to available data on mortality from coronary heart disease. Unfortunately, there are few reports

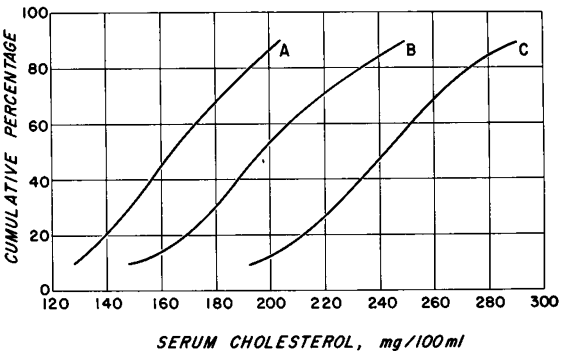

FIGURE 1. *Typical Frequency Distribution Curves for Serum Cholesterol in Various Populations.*

Curve A pertains to boys fifteen years of age in Boston, and men in their forties and fifties in areas of the world where coronary heart disease is rare. Curve B concerns American men in their twenties and men in their forties and fifties in areas of the world where coronary heart disease is uncommon. Curve C shows American men in their forties and fifties.

in which these kinds of data are simultaneously available on well defined groups. Estimates of these variables, especially diet and mortality, are fraught with lack of precision. The report of Jolliffe and Archer,[7] an analysis of the association between several aspects of the diet and death rates from coronary heart disease in many countries of the world, clearly describes some of the limitations to the data available. They regard the intake of saturated fats as the best dietary correlate of mortality. On the other hand, Yudkin[8,9] believes that practically the same data support a closer association between the intake of sugar and mortality. Suffice it to say that the correlation between the consumption of sugar and saturated fat (Fig. 2) ($r=+0.92$) is higher than that between heart-disease mortality and sugar ($r=+0.80$) or saturated fat ($r=+0.82$).

What is indicated by inspection of these reports of international dietary intakes is that economic development is associated with more animal protein and saturated fat, more total fat, an increase in simple sugars and a marked decline in the consumption

TABLE 1. *Serum Triglycerides in 3 Populations.*

Population	No. of Subjects	Age	Serum Triglyceride Level*	Comment
		yr.	*mg./100 ml.*	
Young men in Albany, N.Y.†	36	23-29	96.1 ± 28.3	95% under 146.9 mg./100 ml.
Men in Albany, N.Y.‡	1711	45-59	163.9 ± 110.2	No evidence of coronary heart disease
Bantu in South Africa§	57	20-60	75.0 ± 20.0	No age-related increase 95% < 114 mg./100 ml.
European men in South Africa§	16	<30	86.0 ± 26.0	No evidence of coronary heart disease
European men in South Africa§	15	41-60	174.0 ± 68.0	No evidence of coronary heart disease

*Mean ± S.D.

†Data of Brown et al.[20a]

‡Data of Brown et al.[6]

§Data of Antonis & Bersohn.[20b]

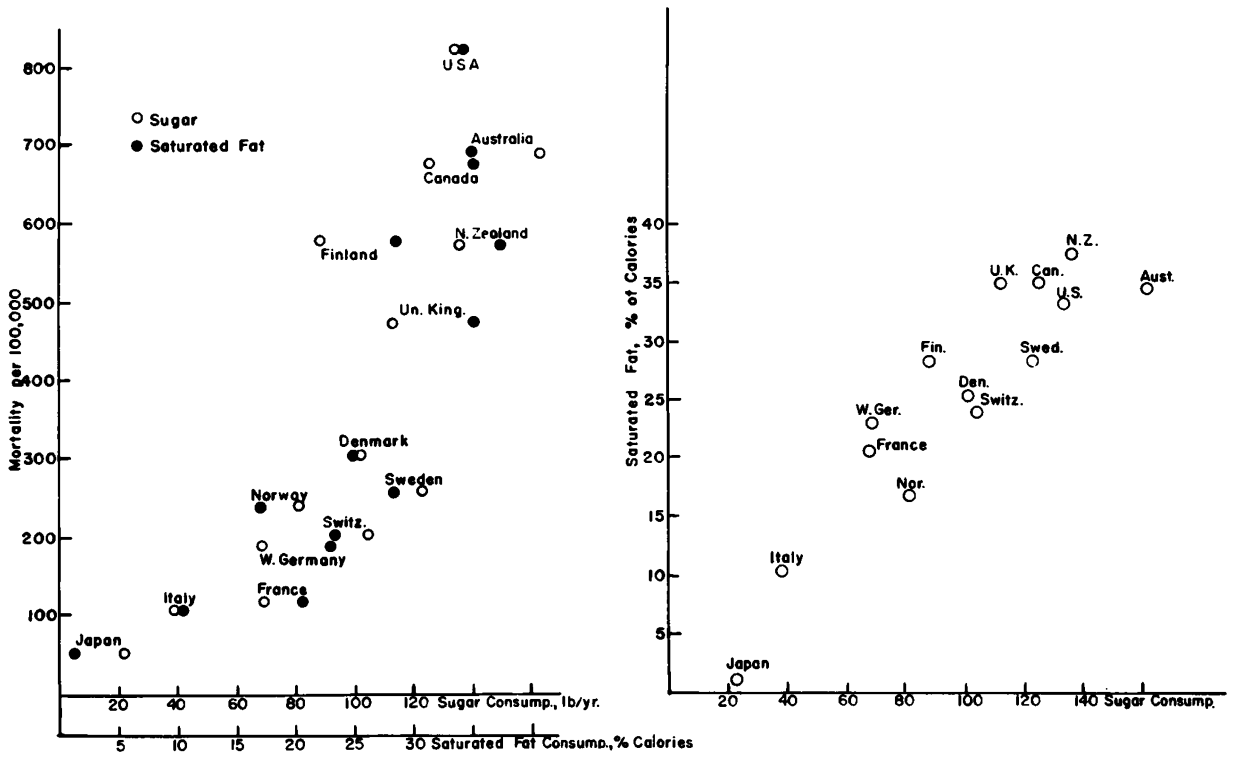

FIGURE 2. *Some Interrelation among Sugar Consumption, Percentage of Daily Calories from Saturated Fat and Mortality from Coronary Heart Disease (Taken from Jolliffe and Archer[7] and Yudkin[8]).*

of complex carbohydrates from cereals, grains and vegetables. Just which of these dietary differences may account for the varying frequency of coronary heart disease cannot be determined by armchair epidemiology. And when one considers the host of other differences associated with socioeconomic development (decreased physical activity, obesity, addiction to cigarettes, elevated blood pressure and perhaps "stress and strain"), as well as those in the prevalence of coronary heart disease *within* a country, one may see how difficult it is to relate specific dietary factors to atherosclerotic vascular disease.

Lopez et al.[10] have utilized ICNND* Survey data, collected in various developing countries over the past twenty years, in an attempt to relate the intake of dietary fat and carbohydrate to the level of serum cholesterol in various population groups. Although they interpret these data as showing that serum cholesterol was more closely related to carbohydrates than to fats, inspection of the ICNND reports simply does not support the validity of this conclusion. Within countries most of the data on food intakes were not calculated for the same population samples in which serum cholesterol was determined; there is a mixture of data from both military personnel and civilians.

Progressive changes in the types and amounts of dietary fats and carbohydrates consumed have been noted in the United States[11] and in Great Britain.[12] A trend toward an increase in the percentage of calories from total and saturated fats, a decline in overall calories from carbohydrate and a replacement of some complex carbohydrates by simple sugars has taken place over the past fifty years. The magnitude of these dietary changes over time is small in comparison to the differences existing between dissimilar countries in the contemporary world. And, again, whether these trends – also accompanied by many other changes in one's way of life – can be uniquely related to the apparently increasing frequency of atherosclerotic vascular disease is a moot point.

The same problems underlie meaningful interpretation of data on migrating populations. For example, several authors[13-16] have reported on the factors associated with the increasing risk of coronary heart disease in Yemenite settlers in Israel. Among these factors, much emphasis has been given to the increased use of refined carbohydrates – a surmise neither adequately documented nor reasonably interpreted in the light of other dietary and environmental changes.

These are the obvious limitations of international epidemiologic studies. Even with data from the very carefully carried out studies by Keys et al.,[17] it may be impossible to ascribe population differences in blood lipids and morbidity or mortality from coronary heart disease to dietary practices alone.

Although many epidemiologic studies carried out

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in the United States have confirmed the relation between the development of coronary heart disease and the antecedent level of serum cholesterol, there has been a singular lack of success in relating an individual's level of serum cholesterol to estimates of that individual's dietary practices.[18-20] That is, individuals whose serum cholesterol levels are in the highest percentile groups cannot be shown to eat differently from those in the lowest percentile groups. Although the technics of assessing food intake may not be sensitive enough to identify real differences between individuals, estimates show that within a homogeneous population these differences are quite small in comparison to the very large dietary differences between population groups in various areas of the world. Furthermore, closely controlled dietary studies carried out both on man and on laboratory animals are also accompanied by considerable variability between individual subjects consuming a constant diet. When the diet is changed, the average level of serum cholesterol can be markedly altered, though interindividual variability persists in such a way as approximately to preserve the rank order of individuals. An example of this is presented in Table 2. Presumably, this explains why cholesterol variability between individuals in a homogeneous population cannot be accounted for by diet.

In 1964 Yudkin and Roddy[21] reported on a dietary survey of 3 groups of age-matched men: survivors of a recent myocardial infarction; persons with peripheral vascular disease; and control subjects. Assessment of daily sugar consumption in each of these groups showed the first 2 (average of 132 and 141 gm. per day respectively) to be significantly higher than the control group (average of 77 gm. per day). It is interesting that the average sugar intake of the 2 ill groups was about the same as the average per capita consumption in the United Kingdom, which was reported earlier by Yudkin[9] — 139 gm. per day.

TABLE 2. *Observations on the Levels of Serum Cholesterol in Men on a Diet Relatively High in Saturated Fats ("Typical American") and on a Diet in Which 85 Per Cent of the Fat Has Been Replaced by Safflower Oil (Fat Provided 38 Per Cent of the Total Calories on Both Diets).**

PATIENT	SERUM CHOLESTEROL ON "TYPICAL-AMERICAN" DIET	SERUM CHOLESTEROL ON SAFFLOWER-OIL DIET
	mg./100 ml.	*mg./100 ml.*
Du.	287	221
Dl.	282	212
De.	257	217
He.	256	209
Ba.	241	191
Ma.	233	183
Wi.	233	165
St.	228	194
Man.	229	177
Ke.	225	188
Co.	206	169
Ly.	200	155
Bu.	190	133
Averages	235.9	185.7

*Taken from Hegsted et al.[30]

Thus, any differences here seem to have been in the curiously low sugar consumption of the control group. On the other hand, Little et al.[22] reported no significant differences between patients with ischemic heart disease and their control group in consumption of any nutrients assessed — including simple sugars. Papp and his associates[23] reached similar conclusions. Recently, Yudkin[24] attempted to resolve these discrepancies.

CONTROLLED STUDIES ON MAN

Epidemiologic inferences on the nature of the apparent association of diet and blood lipids with atherosclerotic vascular disease have been greatly extended by controlled dietary studies on man. These studies have done much to explain the influence of specific dietary factors that regulate the levels of blood lipids, and evidence is accumulating that an overall reduction in the levels of circulating lipids will, in fact, be accompanied by a reduction in the risk of atherosclerotic vascular disease.

The reports of Antonis and Bersohn,[25,26] long-term trials involving extreme dietary manipulations without resort to formula-diet feedings, have done much to clarify the interrelations between dietary fats and carbohydrates. Two groups of apparently healthy middle-aged prisoners, European and Bantu, were fed a "Bantu-type" diet for thirty-nine weeks (protein, 15 per cent, fat, 15 per cent, and carbohydrate, 70 per cent of total calories). At this point, the whole array of blood lipids, including serum total cholesterol and triglycerides, was very low in both groups — at levels found in free-living Bantu natives. For the following fifty-one weeks, 3 subgroups of 5 Europeans and 5 Bantu each were fed diets providing 15 per cent of calories from protein, 45 per cent from carbohydrate and 40 per cent from either sunflower-seed oil, hydrogenated sunflower-seed oil or butter. With the high fat diet containing the least saturated fat (sunflower-seed oil), all blood lipids remained at the levels previously noted on the Bantu diet. With hydrogenated oil, and more markedly with butter, all values rose — in both Bantu and European — to the usual, high levels found in developed societies the world over (societies consuming 40 per cent or so of total calories from relatively saturated fats). One of the most interesting observations reported derived from a final observation of thirty-two weeks during which all subjects were returned to the original "Bantu-type" diet low in fat and high in carbohydrate. Although serum cholesterol rapidly returned to very low levels, all men showed a dramatic and rapid increase in triglycerides. These levels only gradually fell to the low range associated with this kind of diet. In many subjects this adaptation took five or six months. This explains the apparent paradox in the often reported hypertriglyceridemic response of man to diets high in carbohydrate (and thus low in fat); a long period of adaptation may be required. One might have surmised this from knowledge that pop-

ulations habitually consuming diets low in fat and high in carbohydrate have low levels of all blood lipids, including triglycerides.

That the magnitude of the responses in blood lipids to the kinds of dietary manipulations described above are due almost entirely to the effects of dietary fats has been amply confirmed by Keys,[27] Ahrens,[28] Kinsell,[29] and Hegsted and their co-workers.[30] The chain length and the degree of saturation of the fatty acids in the dietary fat and the quantity of dietary cholesterol can account for essentially all the observed changes in serum cholesterol in closely controlled studies involving manipulations in the type and the amount of dietary fat. The studies of Keys et al.[27] and Hegsted and his associates[30] both dealt with practical, palatable dietary patterns comprising ordinarily available foodstuffs and have about covered the kinds of differences in diet type observed among various populations of the world.

One of a series of articles paying particular attention to the type and level of dietary carbohydrate was the report by Keys et al.[31] Using institutionalized subjects and dietary periods of six weeks' duration, they compared the response of blood lipids to the type of dietary carbohydrate at 2 levels of fat (protein calories constant), specifically with fat providing 16 and 30 per cent of the calories. At both levels of fat, 2 types of high carbohydrate diets were fed, one high in starches (complex carbohydrates) and the other high in sugar (simple carbohydrates). In both cases, the average level of serum cholesterol was 18 mg. per 100 ml. lower on the diets high in complex carbohydrates. There were no differences in serum triglycerides related to carbohydrate pattern. Because the intakes of dietary "fiber" were about 12 gm. per day higher on the diets high in complex carbohydrate, and since other reports[32,33] speculated that fiber might be an important factor in the response of blood lipids, Keys, Grande and Anderson[34] carried out further studies. In these, the relative proportion of simple to total carbohydrates was varied even further, in a diet in which 40 per cent of the calories were provided by fat, and the diet was given for a three-week test period. The differences in blood cholesterol related to carbohydrate pattern were of about the same magnitude as in their previous study. They subsequently added 15 gm. per day of cellulose to these diets and still found no further effect on cholesterol of diets containing either the simple or the complex carbohydrates. However, the addition of 15 gm. per day of pectin in a series of counterpart studies did produce a fall of 10 mg. per 100 ml. in serum cholesterol in both types of diet.

The authors concluded that the addition of these substances (cellulose or pectin) was at the upper limit of intake of either anywhere in the world, and that they were of little practical significance in the regulation of blood lipids. Nor, they further concluded, were the differences in blood lipids related to carbohydrates in this or the preceding study due to the content of fiber in the diets.

Anderson et al.[35] carried out a further series of three-week studies involving the substitution isocalorically of 233 gm. per day of glucose, sucrose and mixed lactose-glucose in diets very low in fat calories (13 per cent). They observed no significant differences in the blood levels of cholesterol or triglycerides related to substitution of these simple sugars; however, the level of serum triglycerides was elevated by about 50 mg. per 100 ml. on all these diets in comparison with the level in the same men on a control diet in which fat provided 35 per cent of the total calories. This demonstrates again the short-term effect of diets low in fat calories reported by Antonis and Bersohn.[25]

Grande et al.[36] have brought these studies up-to-date, in a series of experiments of three weeks' duration, in which fat provided 40 per cent of the total calories. They reported no significant change in serum cholesterol when bread and potatoes were substituted for 128 gm. of dietary sucrose, but they found an 18 per cent decrease in cholesterol after substituting carbohydrates from legumes for 123 gm. of sucrose. Dietary protein was kept constant in these studies. They concluded that either the carbohydrate or some other substance in leguminous vegetables led to the modest cholesterol reduction observed.

In 1964 Irwin et al.[37] reported a slight, nonsignificant, lowering of the level of serum cholesterol upon substitution of 164 gm. of rice for dietary sucrose. The subjects consisted of a group of 6 young male students and twenty-five-day feeding periods with a crossover in the source of carbohydrate. Antar and Ohlson[38] described the responses of blood lipids (total lipids, neutral lipids and phospholipids) in 8 persons consuming diets providing 40 per cent of the calories from fat and 44 per cent from carbohydrate. A crossover design was used in which either 20 or 80 per cent of the total carbohydrates was derived from simple sugars; the remainder was provided by starch from cereals and potatoes (the amount of lactose, fruits and vegetables was constant). All the lipid moieties tended to be higher (significance not shown) during the periods when the intake of simple sugar was high. These studies were done on outpatient subjects who took their meals for each of the four-week periods on the metabolic wards; the numbers involved were too small to evaluate the significance of the changes in blood lipids.

McGandy and his associates[39] reported on the response of the blood cholesterol of 18 institutionalized males who were given a series of diets simultaneously varied in both the type of fat (safflower, olive and coconut oil) and source of dietary carbohydrate (high sugar, high sugar and lactose and low sugar). Fat provided 38 per cent, and carbohydrate 45 per cent of the total daily calories. Simple sugars comprised

either 75 per cent or 25 per cent of the carbohydrates, lactose being constant except in the periods of high sugar and lactose feedings, when it constituted half the simple sugar intake. The increased starch in the periods of low sugar was provided by potatoes, cereals and flours. At the end of the experimental periods of four weeks, levels of cholesterol were slightly but significantly lower, about 10 mg. per 100 ml., on the periods with low sugar. The effects induced by changes in the dietary fat were much larger and apparently independent of the kind of carbohydrate. The periods of high intake of sugar and lactose were comparable to those of the high sugar, except on coconut oil, with which a substantial elevation of cholesterol was found.

In summary, these controlled studies, which have all used carbohydrate variations within practical and palatable ranges of intake, and have included ordinarily available foodstuffs, have demonstrated slight reductions in blood lipids when dietary simple sugars are replaced by complex carbohydrates. However, these changes are of such a small order as compared with those obtained by changes in fats that in our opinion they have no practical importance.

That the carbohydrates in leguminous vegetables may be more efficient than those in potatoes and cereals in this regard suggests that undefined factors may be involved. No differences related to the type of simple sugars (glucose, sucrose or lactose) have been observed in these studies except for the single observation of McGandy and his co-workers[39] that a high level of dietary lactose enhanced the hypercholesterolemia on a diet of highly saturated fat (coconut oil).

A number of studies using semipurified-formula diets, in which variations in type and level of carbohydrates can be more extreme, have been reported. It should be clear that such studies even though they demonstrate dietary effects, do not implicitly reveal knowledge of practical applicability or usefulness for the general population. Winitz et al.[40] fed 18 subjects a completely chemically defined diet made up of amino acids, necessary vitamins and salts, glucose and 2 gm. per day of ethyl linoleate as the sole source of dietary fat. After four weeks of formula feeding, the mean level of total cholesterol in the serum had declined from 227 to 160 mg. per 100 ml. When sucrose was substituted for 25 per cent of the glucose in these diets, a rapid increase in mean serum cholesterol to 208 mg. per 100 ml. was noted after three weeks on this diet. A return to the all-glucose diet for twelve more weeks resulted in a drop of the level to 151 mg. per 100 ml.

Macdonald and Braithwaite[41] reported on the changes in blood lipids in 7 young men fed sequentially 500 gm. of sucrose or a like amount of raw maize starch for periods of twenty-five days. The remainder of the diet consisted of lean meats, vegetables and skim-milk powder — fat provided 10 to 13 per cent of total daily calories. The two experimental periods were interrupted by twenty-five days on ordinary self-selected diets. Total lipids, phospholipids and cholesterol decreased on the starch diet in comparison with the self-selected diet, whereas only serum glycerides were increased on the sucrose diet. This fraction was not changed on starch. An average decrease of 1.1 kg. in body weight on the starch diet occurred. Changes in fatty acids in total serum lipids and adipose tissue were also described.

In 1965 Macdonald[42] reported further studies using semipurified formula diets essentially free of exogenous fat. Seven men consumed these diets for experimental periods of five days on alternate weeks. Maize starch, sucrose, liquid glucose, maltose and glucose, eaten at a level of 7.5 gm. per kilogram of body weight per day, were the test carbohydrates. A significant weight loss (highest on starch — 1.2 kg. in five days) was observed during each experimental period. Serum cholesterol was significantly decreased, in relation to the control level, on all except the sucrose diet. Glycerides were increased by sucrose, lowered by glucose and unchanged by starch. But, in contrast to previous papers, neither phospholipids nor total lipids were changed during the periods of feeding sucrose or starch.

Macdonald[43] also administered diets to 5 young women, duplicating his report[42] on men. The mean weight loss of 0.6 kg. on both the sucrose diet and the starch diet was stated to be insignificant. A decrease in total lipid, phospholipid and cholesterol was reported for *all* experimental periods, whether starch or sucrose. Serum glycerides were reduced on the sucrose diet but not on the starch diet. Macdonald concluded that in men on diets high in sucrose lipid patterns become similar to those of men with coronary heart disease, quite in contrast to young women.

That Macdonald's findings may, in part at least, be due to his having used raw maize starch is suggested by Lees.[44] Seven young men and a woman were fed purified diets for four to fourteen days. These diets contained 10 per cent of the calories from protein and 90 per cent of the calories from either cooked wheat and rice starch or sucrose. Test periods were separated by three to seven days of a self-selected diet. The expected increase in serum triglycerides was not different on the sucrose (an increase of 88 mg. per 100 ml.) as compared with the starch (an increase of 109 mg.) diet. Cholesterol response was also identical. Lees suggested that raw starch might be poorly absorbed.

Thus, it appears that alterations in the level, type or source of carbohydrate in the diet influence certain blood lipid components, but there is less consistency in the effect of specific carbohydrates or the magnitude of response obtained. Since Antonis and Bersohn[25] have shown that the serum triglyceride

response to the feeding of a diet low in carbohydrate is a transient rise, with a gradual diminution over time, the results of short-term feeding trials must be interpreted with caution.

(To be concluded)

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