Introduction: Low-Saturated Fat, High-Carbohydrate Diets: Effects on Triglyceride and LDL Synthesis, the LDL Receptor, and Cardiovascular Disease Risk (44564A)

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This symposium was borne out of the observation that low-fat, high-carbohydrate feeding is associated with an acute increase in plasma triglyceride concentrations. The observation was first made by Ahrens *et al.* (1) at the Rockefeller Institute in the late 1950s. Based primarily on long-term observational studies, it was believed that the effects of high-carbohydrate feeding diminish with long duration of exposure (2, 3). Current reviews indicate that this issue is unsettled (4).

However, recent studies from the Northwest Lipid Research Clinic (5) and data presented at this symposium indicate that the hypertriglyceridemic effect of a low-fat, high-carbohydrate diet is sustained for at least a year and in subanalyses, for 2 years (6). That is, as long as the increased carbohydrate intake of the diet is sustained, the hypertriglyceridemic effect persists.

It is not known if the carbohydrate induction effect and all that it may entail may diminish the otherwise beneficial effect of a low-fat diet on cardiovascular disease (CVD) risk; however, it has become apparent that individuals with combined or familial combined hyperlipidemia, that is, elevations in triglyceride as well as LDL cholesterol, have a greater risk for cardiovascular disease than those individuals without the hypertriglyceridemic phenotype (7–9). In addition to being the hyperlipidemic disorder most commonly associated with coronary artery disease (10), the combined hyperlipidemia (CHL) phenotype is a leading feature of the insulin resistance syndrome, or so-called Syndrome X (11, 12). In each of these instances, the association of high triglyceride, low HDL, and small-dense LDL appear to add to the risk associated with an elevation of LDL cholesterol (7–9). In fact in some studies, the CVD risk associated with plasma triglyceride increases above a plasma concentration of ≈ 110mg/dl (the junction of the first and second quartiles) (13). Because the plasma triglyceride and HDL perturbations of low-fat, high-carbohydrate feeding so resemble the abnormalities associated with Syndrome X or the familial CHL phenotype, we asked in this symposium whether the lipid abnormalities of low-fat, high-carbohydrate feeding might have a similarly negative effect on cardiovascular health.

This symposium also posed the more fundamental question, What is the mechanism of the induction of hypertriglyceridemia and might it affect the regulation of the LDL receptor and the LDL cholesterol response to diet? Palmitic acid is the primary saturated fatty acid that is synthesized endogenously by the body (4). Should the synthesis of palmitic acid be enhanced during carbohydrate induction, this compensatory effect would have the unwanted effect of cancelling out or subverting the dietary reduction in intake of saturated fat, which is the central goal of the low-fat diet teaching approach. The investigations of Hudgins *et al.* (14) provide evidence of enhanced palmitate synthesis with a high-carbohydrate, low-fat diet.

The paper of Deckelbaum (15) addresses the importance of LDL receptor upregulation in reducing LDL cholesterol concentrations. Deckelbaum's observations show that not only cholesterol intake but also fatty acid chain length and unsaturation favorably regulate sterol regulatory element binding protein (SREBP) activity in model systems. Of equal interest is the effect of fatty acids on SREBP regulation of enzymatic pathways of carbohydrate metabolism. These molecular studies point to the possibility that long-chain polyunsaturates (i.e., the essential fatty acids) may have unexpected beneficial effects on glucoregulation, insulin sensitivity, and possibly obesity, as well as LDL lowering.

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0037-9727/00/2253-0175$15.00/0

The Willet paper (16) finally brings the metabolic observations to a level of association with cardiovascular disease employing observational epidemiology. His research indicates that fat restriction *per se* is not associated with a reduction in coronary artery disease (17). More specifically, the substitution of saturated fat with carbohydrate is associated with no reduction in coronary artery disease whereas substitution of saturated fat with mono- or polyunsaturated acids is associated with a reduction in coronary artery disease in prospective cohort studies (18). As if saturated fat were not bad enough, Dr. Willet's studies point to the fact that *trans* fatty acids cause even greater increases in LDL cholesterol concentrations than saturated fat and reduce HDL cholesterol and increase Lp(a) concentrations.

Our own studies are directed at the question of whether incrementally greater fat restriction as advocated by some authors (19–22) has a proportionally greater benefit in lipoprotein levels, weight reduction, and indices of carbohydrate metabolism. In a prospective, randomized, long-term, out-patient study in free-living subjects lasting up to 2 years, the data show that fat restriction below a fat intake of 25% and carbohydrate intake exceeding 60% in subjects with simple hypercholesterolemia are associated with no further reductions in LDL cholesterol but increases in plasma triglyceride levels and reductions in HDL cholesterol levels. In addition, progressive fat restriction was not associated with additional weight loss but was associated with an attenuation of the reductions in plasma glucose, insulin, and apoprotein B levels (5). These studies were not maintained long enough to ascertain cardiovascular disease outcome and were not nearly large enough to do so. Nonetheless, the congruity of these observations with the physiological studies of Dr. Hudgins, the observational epidemiology of Dr. Willet, and the similarity to Syndrome X suggest that extreme fat restriction *per se*, may be deleterious to cardiovascular health.

Lack of time in this symposium precluded discussing dietary alternatives to the extreme fat restriction advocated by some (19–21). Nor was there any sentiment expressed in favor of very high-fat diets associated with short-term weight loss and improved lipid levels in some subjects (22). Consensus was reached that restriction of saturated fat is an important long-term focus of the heart disease prevention diet; however, emphasis was also placed on the importance of other dietary constituents including fruits, vegetables, micronutrients, and type of carbohydrate as important issues in overall cardiovascular health benefit.

This symposium exemplifies the broad interests of the Society for Experimental Biology and Medicine. The Society is a multidisciplinary body of basic and clinical investigators open to all who wish to apply and open to all scientific techniques to solve important biological questions. This symposium is a perfect example of the synergy that can be attained among physician and PhD investigators working at the virtual extremes of molecular biology and observational epidemiology and in between to answer great medical questions of the day. I am grateful to the participants for their enthusiastic participation and contributions to these pages of *Proceedings for the Society of Experimental Biology and Medicine.*

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