demonstrate that the degree of glycemic control in these two populations remains insufficient throughout the age span, even for those patients routinely followed in university centers. Optimizing treatment modalities, deliveries, and education to achieve levels of glycemic control comparable to those obtained during the DCCT or in similar, intervention-modified, environments, requires more medical and paramedical resources, thus producing a significant long-term demand for human and financial support.

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# Response to Paris et al.

## Pediatricians and diabetologists

Should it be methodologically correct to compare French and Belgian patients and doctors? We thank Dr. Paris and colleagues (1) for reassuring us collectively, as pediatricians taking care of young patients with diabetes. As a young resident in endocrinology 20 years ago, I was trained in the intangible idea that the results of adult diabetologists' efforts were indisputably more efficacious in terms of glycemic control than those of pediatricians. Was it true in those times? Remember that in many countries, including France, pediatricians were advocating free diet (freedom meaning a lot of sugar) and one insulin shot daily and discouraging the use of capillary blood in favor of the good old urinary measurements.

Those times are gone, fortunately for our patients, and we can now enjoy shameless comparisons of results with our colleagues. As an echo to Dr. Paris's letter, let us regret that besides well-known intervention studies of intensive therapy in highly selected centers and patients, there are too few reports of actual glycemic results in large cohorts (mostly adult) of patients with type 1 diabetes.

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# LDL Cholesterol and Troglitazone Therapy

The recent study by Tack et al. (1) reported larger average LDL size in individuals on troglitazone therapy and appears to suggest that the increases in LDL cholesterol concentration typically observed with this agent (2,3) are not ultimately harmful to patients with type 2 diabetes because they are offset by potentially beneficial changes in lipoprotein composition and susceptibility to oxidation. This conclusion must be interpreted with caution for several reasons.

First, although several observational studies have shown an association between small, dense LDL and coronary heart disease (CHD) in patients with diabetes (4,5), the effects of changing LDL size have never been directly evaluated in any patient population. In contrast, increases in LDL cholesterol concentrations have been shown to be a strong and consistent risk factor for coronary artery disease in both cross-sectional and longitudinal analyses of individuals with or without diabetes. Furthermore, lowering LDL cholesterol concentration has been proven to decrease the incidence of cardiovascular events in several interventional studies (6,7).

Neither the American Diabetes Association nor the National Cholesterol Education Program has treatment recommendations suggesting that increases in LDL concentration are ameliorated by changes in LDL size. Thus, increases in LDL size should not be construed to negate the known risk of increases in total LDL cholesterol concentrations.

Second, the data from Tack et al. (1) showed decreased susceptibility to oxidation in the LDL after troglitazone therapy. This is consistent with the change in size because small, dense LDL are known to be more susceptible to oxidation in vitro (8). Although there are a large number of in vitro studies pointing to the importance of LDL oxidation in the atherosclerotic process, there are no clinical trials showing that changes in LDL oxidation can alter CHD risk. Manipulations that decrease oxidization ability might be of potential benefit; until clinical trial data are available, however, such manipulations associated with increasing LDL cholesterol concentrations cannot be assumed to be beneficial.

Finally, the study reported by Tack et al. (1) was not conducted in patients with diabetes. Individuals with diabetes are known to have increases in several CHD risk factors and to be at significantly increased risk for cardiovascular disease (CVD). Thus, any therapeutic regimen that results in increased LDL cholesterol concentrations in patients with diabetes must be viewed as increasing the risk of atherosclerosis in affected indi-

viduals, even if LDL size is larger or in vitro susceptibility to oxidation is diminished. Statements to the contrary should be established by clinical trials before their acceptance for the care of patients with diabetes.

Improvement in insulin sensitivity in type 2 diabetes would be expected to improve the dyslipidemia associated with this syndrome. The relative role of this dyslipidemia versus LDL cholesterol concentrations in the etiology of CVD in diabetic individuals remains an unanswered question. Interventions aimed at investigating this issue are needed.

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## Response to Howard and Howard

Drs. Howard and Howard (1) express caution about the suggestion that the risk of an increase in LDL cholesterol, as observed during troglitazone treatment, may be offset by beneficial changes in LDL composition and LDL susceptibility to oxidation. Although we largely agree with the points they raise, we would like to add the following comments.

There is indeed firm evidence that the absolute plasma concentration of LDL cholesterol is the major determinant of cardiovascular morbidity and mortality in nondiabetic, as well as diabetic, populations and that lowering LDL cholesterol concentration is of clinical benefit. Regarding the susceptibility of LDL for in vitro oxidation, this evidence is less strong. A number of observations suggest that lipid peroxidation does occur in humans (2). Epitopes of oxidized LDL and autoantibodies against these epitopes can be detected in human plasma. Patients with coronary heart disease show an increased susceptibility of LDL to oxidation (3). Cross-sectional studies have reported an association between higher dietary antioxidant levels and reduced risk of CVD (4). However, only a few studies have reported on the relation between oxidation parameters and coronary heart disease, and there is only one randomized intervention trial suggesting a beneficial effect of vitamin E treatment on nonfatal myocardial infarction but not on total mortality (5). We found, in an animal model for familial hypercholesterolemia (Watanabe rabbit), that improving LDL susceptibility to oxidation by administration of vitamin E, without changing the absolute level of LDL cholesterol, had no effect on the progression of the atherosclerotic process (6). Thus, whether enhancing susceptibility of LDL to oxidation is of any clinical benefit is not (yet) supported by clinical evidence.

Regarding particle size and cardiovascular disease, the situation is complex. Small, dense LDL is part of the atherogenic lipoprotein phenotype, which is characterized by raised plasma triglycerides and low HDL cholesterol in addition to the presence of small, dense LDL particles. This so-called "pattern B" confers increased risk for coronary heart disease (7). Prospective studies have shown that the small, dense LDL particle predicts the risk of ischemic heart disease, an effect that may be partly independent of plasma lipoprotein concentrations (8). Studies showing a beneficial clinical effect of changes in particle size are currently lacking. Treatment with fibrates may shift the LDL particles to a subpopulation of intermediate density and larger size (9); treatment with gemfibrozil has a proven beneficial effect on cardiovascular mortality (10). Changes in LDL composition are difficult to dissect from changes in HDL and triglyceride metabolism. Therefore, it cannot be determined whether changing LDL composition alone (if at all possible) would change cardiovascular risk. The effects of troglitazone on lipids in larger trials show a small increase in HDL cholesterol and/or a decrease in triglyceride concentration (11,12). In our sample of 15 subjects, HDL cholesterol did not change during troglitazone; triglycerides tended to decrease, albeit not significantly.

The fact that our studies were performed in obese subjects is of methodological advantage; a short-term study like this, however, is not able to answer study questions regarding atherosclerosis-related cardiovascular events, no matter whether it is performed in obese or in diabetic subjects.

In summary, we agree that with currently available scientific evidence, the risk of the troglitazone-induced increase in LDL concentration is not necessarily offset by a more favorable LDL composition profile or an enhanced susceptibility of LDL to in vitro oxidation. However, evidence that LDL composition may be clinically relevant is emerging. Awaiting the results of formal clinical trials studying the effect of troglitazone on cardiovascular disease, clinical decisions will have to be based on available indirect evidence.

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