A reduction in serum cholesterol with niacin therapy in humans was first described in 1955, when Altschul and colleagues reported, in a letter to the editor, the findings in 11 healthy medical students and 57 patients. Subsequent clinical studies showed multiple favorable effects of niacin therapy on lipid particles, including decreases in levels of low-density lipoprotein (LDL) cholesterol, triglycerides, small dense LDL cholesterol, very-low-density lipoprotein, lipoprotein(a), and apolipoprotein B and increases in levels of high-density lipoprotein (HDL) cholesterol and selective lipoprotein A-1 particles. The mechanism of action of niacin is complex, involves several biochemical pathways, and is still not well defined.

The current indications for niacin — reducing the risk of reinfarction, favorably altering lipid levels, and slowing the progression of atherosclerosis — are derived from three lines of evidence: the Coronary Drug Project (CDP), studies of combination therapy consisting of niacin and a second lipid-lowering agent, and evaluation of surrogate markers.

From 1966 through 1969, the CDP enrolled 8341 men, 40 to 64 years of age, with a prior myocardial infarction to one of five lipid-modifying therapies. There was no significant difference between the men who were treated with niacin (1119 subjects) and those who received placebo (2789 subjects) in the primary end point of the rate of death from any cause (24.4% and 25.4%, respectively) over a minimum follow-up period of 5 years. However, the rates of myocardial infarction and of cerebrovascular events were significantly reduced with niacin — by 26% and 24%, respectively. It is worth noting, however, that 40 or more years ago, many therapies that have since been proved to reduce mortality or morbidity after myocardial infarction either were not routinely administered (e.g., aspirin and beta-blockers) or were not yet available (e.g., statins, inhibitors of the renin–angiotensin–aldosterone system, P2Y12 inhibitors, and implantable defibrillators). The second line of evidence, derived from studies of combined therapy consisting of niacin and a second lipid-lowering drug, do not inform us about the benefit of adding niacin alone to background therapy; for example, in the HDL-Atherosclerosis Treatment Study (ClinicalTrials.gov number, NCT00000553), was it simvastatin, simvastatin plus niacin, or niacin alone that was responsible for the observed clinical benefit? Finally, studies using surrogate markers (e.g., carotid intima–media thickness) remain controversial, since they have shown inconsistent results, even when proven lipid-modifying therapies that clearly reduce clinical end points have been evaluated by these means.

Thus, a critical appraisal of the prior studies of niacin reveals three shaky pillars supporting its clinical efficacy and identifies a need for large, modern trials of clinical end points. The first of these is reported in this issue of the Journal. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial (AIM-HIGH, NCT00120289) was designed with 85% power to show a 25% reduction in the primary end point (a composite of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization), with the
addition of 1500 to 2000 mg of niacin per day in patients 45 years of age or older with established cardiovascular disease and an atherogenic dyslipidemia. The trial was cast as a test of the HDL-raising effects of niacin, but as shown in the causal diagram in Figure 1, any clinical benefit observed with niacin would be difficult to attribute solely to the effect on HDL. The strengths of the trial design include the efforts made to maintain the double-blinding (blinding of lipid values other than LDL and administration of very low doses of niacin in the placebo group), the well-controlled LDL cholesterol level achieved (a median of <70 mg per deciliter [1.81 mmol per liter]), the event-driven design, and the low rates of loss to follow-up (0.7%) and withdrawal of consent (0.8%). Despite achievement of the expected favorable changes in the levels of HDL cholesterol (an increase of 25%), LDL cholesterol (a decrease of 12%), and triglycerides (a decrease of 29%) with niacin, the clinical results were chillingly null; niacin did not reduce the incidence of the primary composite end point, nor did it show any clinical benefit overall or in a major subgroup. The trial was stopped early by the independent data and safety monitoring board because the boundary for futility had been crossed, and an unexpected higher number of ischemic strokes was observed in patients assigned to niacin.

What are the potential explanations for these findings? It is important to understand that although the event rate was lower than initially projected, it would be incorrect to conclude that the study was designed with insufficient power, since by definition, an event-driven trial is adequately powered for the number of events and the treatment effect specified. Rather, the assumption of a 25% treatment effect appears to have been too generous given the modest absolute difference between the treatment groups in the HDL cholesterol levels achieved (a difference of 4 to 5 mg per deciliter [0.10 to 0.13 mmol per liter]), the low LDL cholesterol levels achieved owing to potent background lipid therapy (with approximately 75% of the patients in the placebo group receiving simvastatin at doses ≥40 mg, and approximately 20% receiving combination therapy consisting of ezetimibe plus simvastatin), and a 25% rate of premature discontinuation in the niacin group. Although the numeric excess in ischemic strokes (which, after inclu-

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**Figure 1. Causal Diagram of the Relationships among Niacin, Major Lipid Levels, and Clinical Outcomes.**

In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial (AIM-HIGH), niacin was compared with placebo, with a primary outcome of a composite of cardiovascular events. Niacin also has many favorable effects on the lipid profile, including a reduction in low-density lipoprotein (LDL) cholesterol and triglyceride levels and an increase in high-density lipoprotein (HDL) cholesterol levels. It has been clearly established that lowering LDL cholesterol levels reduces cardiovascular outcomes, whereas the clinical benefits of lowering triglyceride levels and raising HDL cholesterol levels with pharmacologic therapy are less well established. Given the design of the AIM-HIGH trial, any benefit (or harm) observed with niacin could not be attributed solely to its effect on HDL cholesterol levels.
sion of three upgraded events identified during a post hoc re-review of investigator-reported transient ischemic attacks, yielded a borderline significant result) is of concern, there are several reasons, internal and external to the study, that raise doubts regarding a causal relationship. No prior study or meta-analysis with niacin had observed a similar imbalance in ischemic stroke (in fact, the rate of total stroke was reduced by approximately 20% in the CDP), and no plausible biologic mechanism has been advanced. Furthermore, eight patients (all in the niacin group) had a stroke 2 months or more after discontinuation of the drug. Finally, the specter of a spurious association between a therapy and a low-frequency unexpected event in a moderate-sized trial, when multiple end points are evaluated without statistical adjustment for multiplicity of testing, is not new to the lipid field.11

Nonetheless, the disappointing results of AIM-HIGH do not provide support for the use of niacin as an add-on therapy to statins in patients with preexisting stable cardiovascular disease who have well-controlled LDL cholesterol levels. Given the lack of efficacy shown in this trial, the frequent occurrence of flushing with niacin therapy that some patients find intolerable, and the unresolved question of an increased risk of ischemic stroke, one can hardly justify the continued expenditure of nearly $800 million per year in the United States for branded extended-release niacin.12 However, before holding a final retirement party for niacin, it would appear to be more prudent to assign it to occasional part-time work, such as in statin-intolerant patients (see the Perspective article by Maningt and Breslow13), while we await the results from the much larger Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events trial (HPS2-THRIVE; NCT00461630), which is targeted to be completed in 2013. Regardless of whether niacin is ultimately retired or not, one should not abandon the HDL-raising hypothesis altogether. Several ongoing studies15,16 with other promising drugs that raise HDL cholesterol levels substantially (by as much as 150%) by means of different mechanisms, and that in some cases can lower LDL cholesterol levels by as much as 40%, are well under way.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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