For some time, evidence that apoproteins may provide information about the risk of premature coronary disease beyond that evident in the plasma or lipoprotein lipids has been accumulating. However, almost all of this has been derived from cross-sectional studies, and therefore, appropriately, there has been reluctance to endorse the use of these measurements for routine clinical use. We believe the recent results of Brown et al. should result in a reassessment of this view. Brown and his colleagues studied patients with documented coronary disease and elevated apoprotein (apo) B treated with dietary and pharmacologic regimens that were designed to lower the apo B particle number in plasma. The trial was prospective and blinded, and hard end points were used. The “aggressively” treated groups displayed clearcut evidence of angiographic regression, whereas the control group did not. More important still, the treatment groups fared better clinically than did the control group. The differences were all highly statistically significant, and the parameters that best predicted angiographic regression and favorable clinical outcome were the percent decrease in apo B and the percent increase in high density lipoprotein (HDL) cholesterol, the same two parameters, in fact, that earlier had been shown to predict the progression of disease in native coronary vessels and in saphenous vein bypass grafts.

But if the issue is to be joined, on what grounds should we reach judgement? We suggest that such decisions should not be based entirely on the results of multiple regression analyses. This view does not ignore or minimize the major achievements, which have come from the application of this technique. It does, however, maintain that we should not ignore the limitations inherent in this method. The extent of the first of these may be easier for the lipidologist than the epidemiologist to appreciate: namely, that multiple regression treats all examined variables as if they were physiologically independent. And clearly that is often not the case; important metabolic interactions exist between triglycerides, HDL cholesterol, and cholesterol ester transfer protein—interactions that have been studied in some detail by the lipidologist but are not usually taken into account by the epidemiologist.

More relevant in the present instance is the fact that very low density lipoprotein (VLDL) and low density lipoprotein (LDL) levels can be closely linked because the former is the precursor of the latter. Interestingly, hypertriglyceridemia has, under most circumstances, been dismissed by most epidemiologists as a risk factor for premature coronary artery disease. But hypertriglyceridemia has different causes, and measurement of apo B is one tool that has been used to separate them. Thus, hypertriglyceridemic patients who have elevated apo B—

that is, hypertriglyceridemic patients who have an increased number of hepatic apo B-100 particles in plasma—appear to be at substantially greater risk for coronary disease than hypertriglyceridemic patients with normal apo B levels. Since Brown’s study has shown that hypertriglyceridemic patients who have elevated apo B derive angiographic and clinical benefits from pharmacologic therapy that lowers LDL particle number, surely now, the old debate on the old grounds should end.

The use of total apo B does not imply that all hepatic apo B particles are equally atherogenic. Even in hypertriglyceridemic patients, more than 90% of the apo B is in the d>1.006 g/ml fraction. Moreover, in the study of Brown et al., the relation between regression and change in LDL apo B was virtually as strong as that between regression and total apo B (B.G. Brown, personal communication).

Since the available statistical models cannot adequately reflect the complex metabolic processes involved, it seems sensible to examine relative risk by univariate analysis, that is, the frequency with which a risk factor exceeds a particular level in the disease group compared to the frequency with which it does so in the general population. For example, in a recent survey in Seattle, Washington, one-third of the middle-aged men screened for coronary disease had a total apo B above the 95th percentile of the general population, but only half of these were hypercholesterolemic. This experience is similar to our own. For example, Figures 1 and 2 display the frequency distribution curves for LDL cholesterol and LDL apo B in a disease group of 200 consecutive patients with myocardial infarction before age 60; each parameter was compared to the frequency distribution of that variable in a free-living population. The values of LDL cholesterol were shifted only slightly to the right in the disease group, with the result that 14.5% had a value above the 95th percentile. However, it is obvious that the values of LDL apo B were shifted much further to the right, since 35% of the patients had a value of LDL apo B above the 95th percentile. We would argue that for any therapy that involves substantial risk or cost, we should use those parameters which include as many of the disease group as possible, but as few of the general population as possible. To our knowledge, this aspect of decision-making has not yet been analyzed in detail. Were it to be considered, the case for apo B, if these examples are representative, would seem to be strong indeed.

This leads to the final issue: ease of practice in the clinical setting. At the present time, few physicians are well versed in the physiology and pathophysiology of the plasma lipoproteins. Some lipidologists, therefore, have
have been concerned that introduction of new diagnostic parameters such as apo B would engender confusion among practicing clinicians. Fair enough, yet few lipidologists seem to recognize just how confusing and logically inconsistent the present lipid-based system is to the non-afficianado. Consider hypertriglyceridemia again: Which patients should be treated with anti-apo B therapy, as Brown and his colleagues have done, if apo B is not to be measured? The same dilemma applies to normolipidemic individuals if apo B is left out of the diagnostic approach. Moreover, every lipidologist is well aware of just how frequently the lipid pedigree shifts in patients with familial combined hyperlipidemia; the regular clinician can only be bewildered by it. We would argue that elevated apo B provides a reliable clinical tool to recognize the many lipid guises that overproduction of hepatic apo B particles can present. Working without it conveys no advantage, and given the results of Brown et al. there is considerable disadvantage for both patient and physician. High apo B levels in patients with coronary disease should be lowered regardless of the lipid phenotype.

The only important reservation we now have as to the utility of apo B in clinical practice relates to the unresolved issue of the standardization of clinical assays. Certainly this must be settled. At the same time, though, such issues do not apply only to apo B. The measurement of HDL cholesterol in the real clinical world is often far from perfect, and yet it has gone forward.

We do not argue against further gathering of evidence. At the same time, the results of Brown et al. pose a difficult dilemma: if our theory is valid, large numbers of patients will benefit if the measurement of apo B is introduced into clinical practice. If its introduction is delayed, the corollary holds: large numbers will be injured because they did not have the opportunity to benefit. Although time may yet prove us wrong, given all the present evidence, we have concluded that the practicing physician now has the right to this diagnostic test.

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