nary disease risk as well as do high LDL cholesterol levels — and in some cases even better.

Consider, for example, the landmark Coronary Primary Prevention Trial conducted at 12 U.S. medical centers between 1976 and 1983. This double-blind study of drug treatment, involving 3,800 middle-aged men, established the oft-quoted 2 percent drop in heart attack risk for every 1 percent drop in total serum cholesterol.

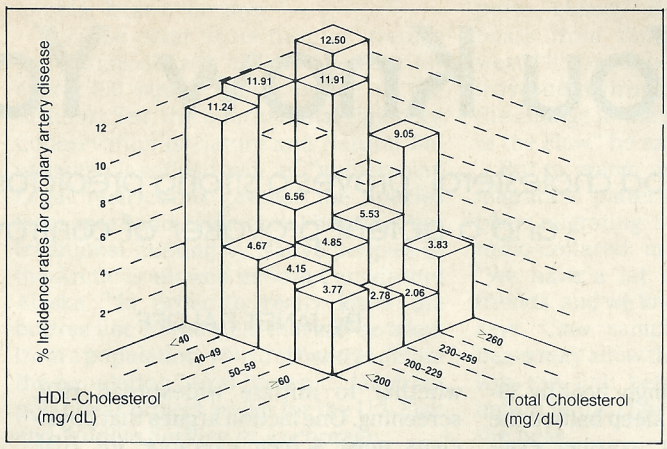
What's *not* often cited is the finding that only the men with HDL cholesterol levels of at least 35 mg/dl experienced a risk reduction, says Antonio M. Gotto Jr., an atherosclerosis researcher at the Baylor College of Medicine in Houston, one of the centers in the trial. Men whose HDL cholesterol remained under 35 mg/dl experienced "no significant decrease" in heart disease risk, he says, "even though they experienced the same degree of reduction in [total] cholesterol and LDLs as did other individuals who did benefit." Those who benefited most from total cholesterol reductions were men who maintained HDL levels above 50 mg/dl.

Women, compared with men of the same age, seldom develop significant coronary disease before menopause. A growing body of data now suggests women's lower risk springs from their relatively higher HDL levels, says Gerd Assmann, director of clinical chemistry and laboratory medicine at Westfalian-Wilhelms University in Münster, West Germany. "Estrogen, for some reason, is one of the best available rearrangers of blood fats. It raises HDL," he says.

Though women's estrogen levels normally drop after menopause, Assmann says several studies of postmenopausal women have demonstrated that estrogen supplementation can elevate their HDL cholesterol *above* premenopausal levels. Moreover, he notes, women receiving estrogen supplements show a "startlingly lower risk of dying from coronary heart disease—just one-third the risk of women not taking this hormone replacement therapy." Assmann says estrogen's protective effect appears to result largely from its role in raising HDL levels — a factor independent of the hormone's ability to lower LDL levels.

However, he adds, Framingham data indicate "the positive effects of estrogen on heart disease are not observed in smoking women." In fact, estrogen replacement therapy, for reasons unknown, can actually diminish HDL levels in smoking females, he says.

Assmann and others have shown that cigarette smoking—a significant elevator of coronary disease risk—lowers HDL. In fact, although "moderate" alcohol consumption can raise HDL levels (SN: 11/28/87, p.348), Assmann notes that many smokers also drink heavily. But his data indicate that because "the fall in HDL attributable to cigarette smoking is relatively large" — about 5 percent — it outweighs any possible beneficial HDL effect from alcohol.



Adapted by ILIB from 1986 data by Castelli *et al.*

These data, from Framingham patients aged 48 to 83, show that for people with HDL levels below 40 mg/dl, a total cholesterol level under 200 mg/dl corresponds to about the same coronary artery disease risk as having total cholesterol over 260 mg/dl — a level NCEP would classify as very risky.

Physical activity can also affect HDLs, according to several studies, including the ongoing West German PROCAM, which includes roughly 20,000 men and women aged 20 to 65. Assmann, who directs PROCAM, says that within each age group examined, "couch potatoes" have lower HDL levels than physically active individuals. Obesity presents a similar — and apparently independent — correlation. All other things being equal, PROCAM shows that "the more people weigh, the lower their HDL," observes Assmann.

But the most incriminating data linking heart disease to low HDL levels comes from the ongoing Helsinki Heart Study, begun in 1981. This placebo-controlled, double-blind drug trial in Finland is examining the lipoprotein-altering impacts of gemfibrozil (Lopid) on heart attack rates in 4,081 apparently healthy men aged 40 to 55. Gemfibrozil is a cholesterol-lowering drug marketed in the United States since 1981.

In the Aug. 5, 1988 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, Vesa Manninen of the University of Helsinki and his colleagues reported initial findings showing that gemfibrozil lowered risks of heart attack and sudden cardiac death 34 percent. All the men began the study with non-HDL serum cholesterol levels of 200 mg/dl or higher. Overall, compared with men on a placebo, those taking gemfibrozil twice daily showed a 10 percent drop in serum cholesterol, an 11 percent drop in LDL, a 35 percent drop in triglycerides and an 11 percent increase in HDL.

Analysis of the findings revealed that lipoprotein changes — far more than any drop in triglycerides—reduced the risk of heart attack. In fact, men entering the study with low HDL levels benefited more from drug treatment than those with elevated LDL levels.

Not only do the Helsinki data suggest that low HDL levels predict the degree of heart attack risk better than do elevated LDLs, Manninen says, but "we found that raising HDL alone contributed to [heart attack] risk reductions of 23 percent"—or two-thirds of the drug treatment's efficacy in reducing risks.

And last November, researchers at the Johns Hopkins University in Baltimore reported that among 288 patients with normal total cholesterol levels but with symptoms of heart problems — such as chest pain—71 percent of the men and 39 percent of the women indeed had artery-clogging coronary disease (SN: 11/26/88, p.348). Among the men, says Hopkins cardiologist Michael Miller, two out of every three with coronary disease (as diagnosed by angiography) had HDL cholesterol levels below 35 mg/dl.

These and other findings published over the past year prompt Gotto, Castelli, Assmann, Manninen and Miller to recommend that physicians begin using total-to-HDL cholesterol ratios to screen for heart attack risk. Assmann goes so far as to suggest physicians consider screening patients for this ratio during every office visit — much as they routinely monitor blood pressure. Says Manninen, "I'm already doing that."

Not everyone shares their view. W. Virgil Brown, medical director of Medlantic Research Foundation in Washington, D.C., argues that ideal HDL values have not been established. Vegetarians, he notes, often have HDLs in the 30s range, yet they run a very low heart attack risk. On the other hand, he says, though heavy drinking raises HDLs, it also can raise a person's heart attack risk. For this reason, Brown thinks the protective effect associated with high levels of HDL cholesterol may depend on how a person sustains those levels.

Castelli agrees with the point about vegetarians (a group he has studied) but says Brown's argument merely points out why HDL levels are less useful by themselves than as part of a total-to-HDL cholesterol ratio. In vegetarians, such