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Science's Next Wave

Editor: John Benditt

EDITORIAL

Heart Attacks: Gone with the Century?

This issue of *Science* highlights the progress and promise of research in cardiovascular disease, the most frequent cause of death in men over age 35 and women over age 65 in the United States. Heart attacks were recognized as a public health problem only in this century. They are likely to lose this notoriety early in the next. The reason? Four decades of progress in understanding cholesterol and the lipoproteins that carry it in blood plasma.

Atherosclerosis begins when plasma lipoproteins of intermediate and low density (here called LDL) are deposited in artery walls. Evidence for the causative role of LDL comes from three sources. (i) Experimental: Animals with low levels of LDL have no atherosclerosis, and manipulations that raise LDL universally cause the disease. (ii) Epidemiologic: Human populations with low LDL levels have very little atherosclerosis; the disease increases in proportion to LDL in all populations studied. (iii) Genetic: Mutations that impair the receptor-mediated removal of LDL from plasma cause fulminant atherosclerosis. The final (therapeutic) line of evidence has now been supplied by three clinical trials, all completed in the past 18 months.

All three trials used drugs called statins, which inhibit 3-hydroxy-3-methyl glutaryl CoA reductase, a key enzyme of cholesterol synthesis. Statins slow cholesterol production and enhance receptor-mediated removal of LDL from plasma. The three studies followed 15,198 people for 5 years. The studies from Scandinavia (4S)* and from North America (CARE)† enlisted patients with coronary disease. The study from Scotland‡ enrolled asymptomatic individuals with high cholesterol. All studies yielded similar results: Plasma levels of LDL fell by 26 to 35% and heart attacks declined by 25 to 31%. In the 4S study, heart attack deaths were reduced by 42% and deaths from all causes fell by 30%. We believe that the results would be even more striking if cholesterol were lowered further and earlier.

The 4S and CARE studies found that coronary events were reduced in patients with "normal" plasma cholesterol levels around 210 mg/dl. This is not surprising, as a cholesterol level of 210 mg/dl, which is near the median in the United States and Europe, is above the 90th percentile for the human species worldwide. Individuals with such levels who develop atherosclerosis have arteries that are unusually susceptible to LDL. As cholesterol rises above 210 mg/dl, the incidence of atherosclerosis increases; and at very high levels, atherosclerosis is rampant even when patients are not especially susceptible.

Well-documented susceptibility factors include smoking, hypertension, diabetes, a lipoprotein called Lp(a), and low levels of high density lipoproteins. More recently discovered are genetic polymorphisms that raise blood homocysteine or disrupt regulation of blood clotting. All of these should be treated when possible, but the therapeutic trials tell us that atherosclerotic events can be reduced by lowering of LDL even when these factors are present.

Statins are effective, but are they safe? In the three trials, statins were taken by 7500 people for 5 years without a significant increase in deaths from noncardiac diseases. These studies are reassuring but brief. Will some hidden toxicity emerge when individuals take these drugs for most of their adult lives? Long-term studies are needed.

In middle-aged people with cholesterol levels greater than 240 mg/dl, the potential for coronary heart disease warrants aggressive cholesterol lowering with diet and drugs. People with normal cholesterol levels of 210 mg/dl have a lower relative risk, but their absolute numbers are greater. If we wait for susceptible individuals to develop symptoms before deciding to treat, the earliest symptom is often sudden death. The challenge is to develop noninvasive screening methods to detect coronary atherosclerosis in its earliest stages. Exploitation of recent breakthroughs—proof of the cholesterol hypothesis, discovery of effective drugs, and better definition of genetic susceptibility factors—may well end coronary disease as a major public health problem early in the next century.

Michael S. Brown and Joseph L. Goldstein

The authors are professors of molecular genetics at the University of Texas Southwestern Medical Center in Dallas, TX, USA.

*Scandinavian Simvastatin Survival Study Group, *Lancet* **344**, 1383 (1994). †The CARE Trial, paper presented at the annual meeting of the American College of Cardiology, Orlando, FL, USA, 26 March 1996. ‡J. Shepard et al., *N. Engl. J. Med.* **333**, 1301 (1995).