CHAPTER 3.1

SERUM CHOLESTEROL AND CORONARY HEART DISEASE IN THE SEVEN COUNTRIES STUDY

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In the past century cholesterol played a predominant role in research on the etiology of CHD. On the basis of largely experimental work in rabbits and on cross-cultural comparisons of serum cholesterol levels in humans, the hypothesis was formed that arteriosclerosis and its complications were associated with hypercholesterolemia (1). Cholesterol is transported in the blood in lipoprotein fractions. In the 1950s it was shown in clinical studies that the Low Density Lipoprotein (LDL) fraction in cardiac patients was higher, and the High Density Lipoprotein (HDL) fraction lower, when compared with controls (2). Advances in the genetics and cellular biology of cholesterol increased understanding about the role of mechanisms by which genes, hormones, and diet regulate serum cholesterol levels (3). Critical components of this system are lipoprotein receptors in the liver and extra-hepatic tissues that mediate the uptake and degradation of cholesterol-carrying lipoproteins.

By the 1960s, prospective epidemiological studies showed that serum total cholesterol levels were positively associated with CHD risk (4). In the 1970s epidemiological studies showed that HDL cholesterol levels were protective, in contrast to LDL cholesterol (5). This is because HDL is involved in reverse cholesterol transport from the peripheral tissues to the liver, where cholesterol is catabolized to bile acids. In the late 1980s, experimental work suggested that modified LDL, (e.g. oxidized LDL) could play a prominent role in the development of atherosclerosis (6). In summary, half a century of research on cholesterol has made clear that total cholesterol, as an indicator of LDL cholesterol levels, and HDL cholesterol play an important role in causing and predicting risk for CHD.

In this chapter, we will summarize the findings on total and HDL cholesterol from the Seven Countries Study. We also discuss trends in serum total cholesterol levels over a 35-year period, dietary determinants of serum total cholesterol, and serum total cholesterol levels and CHD risk from both cross-cultural and within-population perspectives. Finally, we will discuss the role of HDL cholesterol in CHD risk.

TRENDS IN SERUM CHOLESTEROL LEVELS OVER 35 YEARS

Determination of serum cholesterol level under field conditions was a major problem for the Seven Countries Study, and blood had to be collected in remote areas in northern and southern Europe. Valid cholesterol values were essential to cross-cultural comparisons. The Abell-Kendall method was used as the reference method. It provides similar cholesterol values to the enzymatic methods currently used (7,8). Anderson and Keys developed a simple method based on the Abell-Kendall method (9), and found that small samples (0.1 ml) of serum could be preserved for several months at temperatures of 25-30°C by air drying on filter paper. This allowed transportation to central laboratories in Minneapolis and Naples, where the dried serum samples were extracted from the filter paper by hydrolysis. This method was reproducible and valid compared to results of cholesterol determinations in fresh samples.

Standardization of serum cholesterol determinations was not always easy according to Keys in his memoirs (10). In a 1957 pilot study in Nicotera in southern Italy, the dried serum samples were sent for analysis to the University of Minnesota laboratory, where extremely high values were found in some samples. Keys wrote: “Detective work found the reason. Our Nicotera laboratory was full of flies and some of the filter paper samples showed flyspecks. We found that flyspecks contain