with a ductus arteriosus of over 4 mm should be considered candidates for surgery.

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Does change in serum cholesterol of a population influence coronary heart disease mortality?

See page 566 for the article to which this Editorial refers

Serum total cholesterol levels predict the outcome of future coronary heart disease in individuals independently of other risk factors. This has been shown in many prospective epidemiological studies in countries with high and low incidence of coronary heart disease. Several primary and secondary prevention randomized trials have demonstrated that a reduction in total cholesterol is followed by a significant decrease in coronary heart disease mortality in men. The order of magnitude is an approximately 2% reduction in mortality for a 1% reduction in serum cholesterol. Law et al estimated that the benefit of coronary heart disease reduction with cholesterol lowering decreases with age. A 0-6 mmol.1^{-1} reduction in cholesterol produces a reduction in coronary heart disease from 50% at age 40 years, down to 20% at age 70 years. Angiographic studies in coronary patients have also shown slower progression of coronary atherosclerosis following lipid reduction.

The frequency of coronary heart disease differs among developed countries. Where average total serum cholesterol is lower than 5-2 mmol.1^{-1} there are no high mortality rates from coronary heart disease. Strong evidence for this came from the Seven Countries study led by Ancel Keys. In this multinational study, 16 small cohorts of 12763 men aged 40-59 years from U.S.A., Finland, The Netherlands, Italy, Greece, Japan and the former Yugoslavia (i.e. Croatia and Serbia), were examined and followed up for 25 years. Baseline mean serum cholesterol levels during the 1950s ranged from 4-2 mmol.1^{-1} in Serbia and Japan to 6-9 mmol.1^{-1} in East Finland. Both median serum total cholesterol and the average percent of energy intake from saturated fatty acids in the diet were highly and significantly correlated (r=0-80 and 0-84) with 10 year coronary heart disease mortality, in a between-cohort (ecological) analysis. These results were confirmed recently using 25-year mortality follow-up and adjusting for smoking, blood pressure, body mass index and physical activity at work. These correlations were close to those found by Law and Wald for men of the same age, with data from surveys from 17 countries, and to those found in other studies. The international Atherosclerosis Project collected and analysed data on 21302 autopsies from 14 countries. It showed that the ranking of atherosclerotic lesions
corresponded well to the ranking of mean serum cholesterol \((r=0.76)^{[10]}\) and with coronary heart disease mortality rates\(^{[11]}\). Knuiman et al.\(^{[12]}\) found a correlation of 0.86 between coronary mortality and blood cholesterol measured in a central laboratory in small samples of employed men aged 33-48 years from 13 countries. It is remarkable that the correlations in all these studies are so similar, despite the different time lags and the fact that most of them, unlike the Seven Countries, used indirect data and consequently were not so well standardized.

A different question is whether changes in average cholesterol levels in the population as a whole, are followed by changes in mortality rates from coronary heart disease. A secular shift in serum cholesterol levels, should, in theory, with other risk factors held constant, be followed by a change in coronary heart disease mortality rates. The WHO-MONICA Project was set up in the 1980s. It studies 38 populations from 21, mostly European, countries, in well defined\(^{[14]}\) geographical areas. It tries to find out how much population changes in risk factors and in medical care influence trends in coronary heart disease and stroke incidence. Although the Seven Countries and the WHO-MONICA studies are similar, there are fundamental differences. The former is a longitudinal follow-up observation of coronary heart disease in 16 different small cohorts of men aged 40-59 years.

MONICA is not a cohort study. It studies the trends in risk factors in independent surveys of random samples of the general population (men and women) aged 35-64 years and will relate these changes to trends in coronary heart disease incidence of the population as a whole from where the samples are taken. Seven Countries used an uncommon epidemiological definition of coronary heart disease which also included heart failure and arrhythmias. MONICA is studying mainly acute myocardial infarction with a very strict definition criteria.

While we await MONICA's main results, which will not be available before the end of 1998, in this issue Menotti et al.\(^{[15]}\) present interesting data based on the 25 year mortality of the Seven Countries Study. The authors split the follow-up into two periods, the first 10 and the subsequent 15 years. They found that the correlation between baseline mean serum cholesterol with coronary heart disease mortality across the 16 cohorts was lower during the second period than during the first 10 years of follow-up. This weakening of the correlation was mostly because coronary heart disease mortality in two of the Serbian cohorts was much higher in the second period, shifting their ranking of mortality from the lower-intermediate to a high position. Originally these populations had the lowest initial cholesterol levels, but experienced the largest increase in cholesterol during the first 10 years of follow-up\(^{[17]}\). Menotti et al.\(^{[15]}\) then repeated the analysis, taking the 10-year change in cholesterol and its relationship to baseline levels into account in the statistical model. The correlation coefficient for the second period increased from 0.56 to 0.84. Furthermore, this model explained three quarters of the differences in 25-year coronary heart disease mortality between the cohorts, taking into account for initial blood pressure and smoking. The change in cholesterol also explained almost half of the variance of the ratio of coronary heart disease mortality between the years 5 and 25.

Although this is not the first time that Menotti et al. have reported on this issue\(^{[16]}\) this is probably the only study showing increases in serum cholesterol followed by increases in coronary heart disease mortality. This 'natural experiment' closes the loop of epidemiological causal proof. Increases in cholesterol levels were also observed in the Italian and Greek cohorts. However, the greatest increase was observed in Serbia\(^{[7]}\). In the Japanese cohorts, as in the whole of Japan, increases in cholesterol have been observed more recently, although the mean was still 4.8 mmol.1\(^{-1}\)\(^{[17]}\), somewhat lower than in the country as a whole\(^{[18]}\). However, Japanese coronary heart disease mortality rates are low and decreasing nationwide\(^{[19]}\). The few published studies looking at the dynamics of coronary heart disease mortality and risk factors have reported on associated declines. For example, in Finland coronary heart disease mortality in men aged 35-64, decreased by 55% between 1972 and 1992. Approximately three quarters of this decline was predicted by the changes in smoking, cholesterol and diastolic blood pressure, but almost half of the decline was associated with the decrease in serum cholesterol alone. This change in cholesterol accompanied changes in diet and food consumption. Similar data are available for a small number of countries\(^{[20]}\) and for the Framingham study\(^{[21]}\).

The increase in coronary heart disease mortality in the Serbian cohorts of the Seven Countries Study in Menotti's paper\(^{[15]}\) may have been due to a detection bias, i.e. a higher chance of being diagnosed with coronary heart disease. Hospital renovation was underway in the study areas during this period\(^{[22]}\). However, this is probably unlikely because total mortality in both the Serbian and the Slavonian cohorts is also the highest of the study. Furthermore, vital statistics for the whole of ex-Yugoslavia show a similar international ranking to
that found in Menotti's paper, for acute myocardial infarction mortality rates in men aged 65–74 years during the mid 1980s. Deaths from tuberculosis were more frequently centrally coded in Yugoslavian death records than in those of other cohorts. This suggests that a real epidemiological transition occurred during these 25 years in ex-Yugoslavia, changing from malnutrition-related diseases. Measurement bias in cholesterol seems unlikely since analyses were centralized in Minneapolis for all countries except Japan, and an Anderson modified version of the Abel Kendall method was used in all examinations. It could be argued that other social or environmental factors might have affected mortality in Zrenjanin, Serbia, as this was an occupational cohort. But this would not explain why the nationwide coronary mortality was also high.

At variance with the results of the Seven Countries study and other studies is an interim analysis of the WHO-MONICA Project which failed to find a significant correlation between serum cholesterol and coronary heart disease mortality during the mid 1980s. Several reasons could explain the lack of significant correlation in this case, including a narrower range of cholesterol, the use of proportions instead of means, no accounting for sampling variance, the short lag time used and others. But most importantly, the MONICA analysis included data from French, Spanish, and some Swiss and Italian populations which have intermediate levels of total serum cholesterol but low mortality rates from coronary heart disease. Explanations for the so-called 'French paradox' (high saturated fat intake, but low coronary heart disease mortality) include the low consumption of dairy products (rich in saturated myristic acid) and a high consumption of foods rich in antioxidants (fruits, vegetables and seed oils). MONICA has shown that plasma antioxidants, such as alfatoxocopherol, explain a good part of the variability in coronary heart disease mortality in European countries with long-established market economies. Other studies also showed a good correlation between coronary heart disease mortality and the alfatoxocopherol content of country food supplies. Not only is this consistent with knowledge about oxidized LDL, but vitamin E might be important in reducing platelet aggregability. Thus, serum cholesterol alone is not the whole story.

Coronary heart disease mortality is increasing in Central and Eastern Europe and to a less extent in some Southern European countries. This is a challenge of considerable importance to public health.

Population exposure to elevated levels of atherogenic lipoproteins should be of sufficient magnitude and duration to translate into massive coronary heart disease. On the other hand, a full reduction in coronary risk is achieved, on average, in 5 years of cholesterol reduction. Rapid changes in coronary heart disease mortality are probably more related to changes in thrombogenic rather than to atherogenic factors. It is crucial that, beyond the Seven Countries Study, research on the cardiovascular effects of long-chain dietary fatty acids, other than those on serum cholesterol, advances. Monitoring of risk factors, coronary heart disease and the atherogeneity of thrombogenicity indexes of the diet must also continue.

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Relationship between coronary lesion morphology and inducible wall motion abnormalities

See page 596 for which this Editorial refers

Assessing the functional severity of a coronary artery stenosis is one of the major goals of diagnostic cardiology. However, when selecting a new interventional approach the cost of any new therapy has to be taken into account.

Patients who have suffered a myocardial infarction are a group for whom defining optional treatment is difficult. To find out which akinesis consists of a scar, which of hibernating myocardium, which stenosis may lead to an adverse prognosis, and which can be treated conservatively, becomes more and more important in the face of cost effectiveness on the one hand and the possibility of restenosis on the other.

A large number of studies have shown that stress echocardiography has the potential to differentiate between hibernation, stunning and scar has been shown.

In this issue, Dr Lu and co-workers publish their experience with coronary lesion morphology and the dipyridamole echocardiography test in the chronic state after myocardial infarction[11]. Their previous investigations were in patients with single-vessel disease without prior infarction[2]. In the present study[11] they showed that induced wall motion abnormalities were observed more often in patients with a complex culprit lesion morphology after myocardial infarction. Interestingly, it was possible to demonstrate that the period up to the development of new wall motion abnormalities was shorter in patients with complex culprit lesions than in patients with angiographically simple lesions. Furthermore ischaemic reactions were observed with low dose dipyridamole in 73% of patients with complex lesions compared to only 22% with simple lesions. No