digoxin measurements can be unreliable in this setting.

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History of the cholesterol hypothesis in Britain

Sir,

Dr Grimes\(^1\) accuses me of an error of scientific thought for believing that statins reduce coronary morbidity and mortality by virtue of their low-density lipoprotein (LDL) cholesterol-lowering action. Instead, he attributes these benefits to their so-called pleiotropic effects. He further states that co-administration of ezetimibe with a statin has a major effect on lowering serum cholesterol but is without clinical benefit. I question both of these assertions.

The pleiotropic effects of statins are thought to reflect cholesterol-independent actions (e.g. reduced prenylation of proteins) consequent upon inhibition of HMG-CoA (hydroxymethylglutaryl
co-enzyme A) reductase. Other means of lowering LDL cholesterol such as bile acid sequestrants and partial ileal bypass (which reduce absorption of bile acids) and ezetimibe (which blocks cholesterol absorption) up-regulate the HMG-CoA reductase pathway and hence cannot exert the pleiotropic effects attributed to statins. A recent meta-analysis\(^2\) investigated this issue and concluded that the reduction in coronary events seen in statin and non-statin trials did not differ and were consistent with a one-to-one relationship between LDL cholesterol lowering and coronary heart disease reduction. Thus, the effects of statins in reducing coronary events are explicable entirely on the basis of their cholesterol-lowering properties.

The ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial\(^3\) examined the effects on carotid intima-media thickness (IMT) of simvastatin alone versus simvastatin plus ezetimibe in patients with familial hypercholesterolaemia and found no difference between the treatment groups after 2 years. However, the design of the study was flawed inasmuch as the IMT was normal in both groups at baseline, reflecting years of previous statin therapy, and it remained so throughout the trial. The latter was not powered to examine the effect of ezetimibe on clinical events, but this is being tested in IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. \(\text{Am Heart J 2008; 156}:826–32.\)

I suggest to Dr Grimes that this strategy reflects an evidence-based rather than an evangelical approach to resolving this latest chapter of the cholesterol controversy.

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**Variability in the prevalence of radiographic stigmata and in their use for profiling disease severity makes comparisons more complicated**

Sir,

The fact that as many as 21% of the patients with a clinical diagnosis of community-acquired pneumonia (CAP) may have ‘negative’ chest radiographs on admission\(^1\) adds complexity to the validation of CAP by chest radiography,\(^2\) and also has the potential to complicate comparisons of profiles of disease severity,\(^3\) given the fact that, in some profiles, radiographic stigmata make a contribution to the eventual severity score,\(^4\) and in others they do not.\(^4\) Although the ‘reference standard to diagnose CAP is a new infiltrate on chest radiograph in the presence of recently acquired respiratory signs and symptoms’,\(^2\) patients who have negative chest radiographs on admission have clinical stigmata and disease severity comparable with their counterparts with positive chest radiographs.\(^1\) To complicate matters even further, although only a minority of chest radiograph-negative patients with clinical stigmata of CAP have been followed up with repeat imaging studies, in 44% of those instances of repeat imaging, an infiltrate was identified, which was not present in the initial chest radiograph.\(^1\) In terms of prognostic implications, useful analogies can be derived from similarities between chest radiograph-