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The failure of antibiotics to prevent heart attacks

It's not necessarily the end of the road

Two recent trials have shed important light on the theory that the respiratory pathogen *Chlamydia pneumoniae* might cause atherosclerotic cardiovascular disease.[1 2] The first, by Grayston et al, was a trial of azithromycin or placebo taken each week for one year by 4012 patients with stable coronary artery disease who were followed up for four years. The second, by Cannon et al, was a trial of gatifloxacin or placebo taken for 10 days each month for two years by 4162 patients who were in hospital with an acute coronary syndrome. In neither trial did the antibiotic therapy reduce the occurrence of serious cardiovascular events, confirming the conclusion of an earlier meta-analysis of smaller studies.[3]

Three facts are beyond question in the relation between *C pneumoniae* and atherosclerosis. Firstly, *C pneumoniae* DNA and/or antigen have been detected, mainly by polymerase chain reaction technology, in 40% or more of atherosclerotic plaques of patients in various parts of the world, detection being recorded from about the age of 15 onwards.[4] Secondly, mice and rabbits inoculated with *C pneumoniae* have developed inflammatory lesions in arteries,[4] although, admittedly, these models may not mimic faithfully what happens in humans. Thirdly, antibiotics do not reduce cardiovascular events among patients who are already at risk.

Early reports of the benefit of short courses of antibiotics for patients who had experienced an acute coronary event[5 6] have not been borne out by the new large trials of long duration.[1 2] Moreover, the early promise that treatment with antibiotics might inhibit the development of abdominal aortic aneurysms and thickening of the carotid artery, both of which are associated with the presence of *C pneumoniae,* does not seem to have been fulfilled by prospective trials,[7 8] although this aspect of research warrants further exploration.

Thus, although *C pneumoniae* organisms, whole or in part, often exist in diseased arteries, antibiotics with antichlamydial activity have no protective effect. Why might this be? Human atherosclerosis develops progressively from an early age. Taking antibiotics too late in the inflammatory process is unlikely to have an effect, a point acknowledged by the authors of the two recent trials.[1 2] Detection of viable or metabolically active organisms in atherosclerotic lesions has proved to be difficult and achieved rarely.[4] By inference, it would seem likely that such organisms are sparse in plaques so that antibiotics—however active and for whatever duration taken—may have no chance of having a discernable effect on the occurrence of cardiovascular events.

Furthermore, *C pneumoniae* or at least its DNA is probably carried from the respiratory tract to atherosclerotic lesions by peripheral blood mononuclear cells. The presence of *C pneumoniae* DNA in these cells has been associated with cardiovascular disease,[9] but more studies are required to validate the notion that such bacterium carrying cells can be considered as a specific marker for the presence of *C pneumoniae* in atherosclerotic plaques. This would add weight and greater meaning to using the polymerase chain reaction to detect *C pneumoniae* in these cells[10] in order to identify infected patients in trials and to measure the effect of antichlamydial treatment. In one study, however, azithromycin or rifampicin did not inhibit chlamydial carriage in peripheral blood mononuclear cells, an observation that undoubtedly needs confirmation.[11]

The result of a trial of clarithromycin in patients waiting for coronary artery bypass surgery is also discouraging because the antibiotic did not reduce the prevalence of the main outer protein of *C pneumoniae* in vascular tissue taken at surgery (although the value of this finding is weakened because *C pneumoniae* was not detected by a polymerase chain reaction technique).[12] Lastly, not even the most avid proponent of a role for *C pneumoniae* in atherosclerosis would claim that it is the only factor involved. Factors unaffected by antibiotics are likely to cloud any beneficial antichlamydial effect if, indeed, it exists.

So, is this the end of the road? It is unless a different tack is taken. Certainly, the same kind of antibiotic trials have no future and, as said before, animal modelling is too remote from human reality. Danesh proposes that prospective epidemiological studies based on serology should help to better distinguish cause from consequence.[13] We are sceptical that this will help to determine whether *C pneumoniae* has any role in causing coronary heart disease. The odds certainly seem stacked against such a possibility, but it is too early to draw a final conclusion while the current evidence only concerns the late stages of disease. In this context, it is a sobering thought that the role of *Treponema pallidum* in tertiary syphilis is not questioned despite the fact that antibiotic therapy does not alter the pathological changes at the late stage of disease.

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Although large advances in dealing with heart disease may come in the future from gene therapy and stem cell research, it will still be important to determine beyond question whether antibiotic therapy can or cannot reduce *C pneumoniae* carriage by peripheral blood mononuclear cells. A finding that carriage can be greatly reduced or abolished significantly would provide a logical basis for trials of antibiotic treatment, not in patients with myocardial infarcts, but in young people without well established atherosclerosis. Of course, vaccination of the young against *C pneumoniae*, although hard to contemplate at the moment, is another avenue that could be taken. Such kinds of research will undoubtedly prove difficult but without implementation, the role, if any, of *C pneumoniae* in cardiovascular disease will remain shrouded in mystery for many years to come.

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Combing and combating head lice

Choose between four successive combings or two applications of pediculicide

You have to take your hat off to the head louse. Described in ancient Egyptian and Greek medical texts, it has been a source of irritation and disgust for thousands of years. Today, with a search on Google yielding 699 000 hits, the mostly harmless head louse has developed into an apparently fearsome pest. During the past 2000 years, a wide range of treatments for head louse infestation has been proposed. Not one has worked sufficiently for it to be regarded as a panacea. The comparison of effectiveness of comb and pediculicide, as reported in a paper in this week's *BMJ*, is certainly not new.[1]

Hill et al (p 384) report this week the most complete assessment of the non pharmacological approach "Bug Buster," testing it against pediculicides available over the counter in the United Kingdom.[2] This paper is particularly relevant and timely in the northern hemisphere because the school year starts again in a few weeks' time and, once again, health professionals are going to be asked for advice on the "best" treatment.

This paper by Hill et al seems to show that Bug Buster—a kit comprising four fine-toothed combs with instruction to use them with conditioner four times over two weeks—is more effective in eradicating infestation than a single treatment of a pediculicide available over the counter (malathion or permethrin) with cure rates of 57% versus 13%. The cure rate for treatment with pediculicides is surprisingly low compared with rates in other trials (generally in the range 70-80%).[3 4] Why was treatment with the pediculicides in this trial so much less effective than in other studies?[5] For example, a recent trial in the *BMJ* by Burgess et al testing phenophrin against dimethicone found cure rates of 75% and 70%, respectively.[6]

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The participants in both studies were children and young adults.[2 6] They responded to advertisements in the press to take part in the trial by Burgess and colleagues, whereas in the trial by Hill et al they were asked by their general practitioners to participate or responded to posters and information sheets in local pharmacies and primary schools. These different methods of recruitment may have yielded different types of participant.

The general practitioners recruiting patients in the Bug Buster trial were all given the randomisation list and could see, therefore, who would be allocated to which treatment before even talking to each patient about joining the study. The selection bias that could have arisen from this might, in turn, have led to as much as a 30% increase in the apparent efficacy of bug busting[7] compared with a trial with adequate concealment of randomisation. It is also possible that, despite using the randomisation list, some general practitioners used only one form of treatment because

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