

degrees of synergy or an additive effect against *H influenzae* in vitro.^{17,18} It is concentrated in tissues to a similar extent as roxithromycin and is taken up by human phagocytes. The clinical efficacy of clarithromycin has been confirmed against *H influenzae* and other pathogens causing a range of acute infections of the upper and lower respiratory tract acquired in the community, and the adverse reactions reported so far have been minor.^{19,21} Its gastrointestinal side effects in particular seem less than those with erythromycin as judged by the results of double blind comparative trials.¹⁹

What is the place of these new macrolides? The improved range of activity of clarithromycin, its twice daily administration, and its lower frequency of gastrointestinal symptoms, suggest that it may be a suitable alternative to erythromycin for monotherapy of many respiratory infections acquired in the community. Further comparative studies against the widely prescribed β -lactam drugs such as co-amoxiclav and the new oral cephalosporins are, however, needed before the optimal treatment can be determined for infections caused by *H influenzae*. The therapeutic consequences of the tissue penetration of compounds such as azithromycin also need elucidating. A decision on whether these new macrolides represent an important advance in the treatment of respiratory infections must therefore await the results of further studies.

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Improving survival after large bowel cancer

Surgeons should look for the occult

Hepatic metastases are present in up to one third of patients who undergo apparently curative excision of primary disease.¹ Excision of these "occult" hepatic metastases, made possible by recent developments in hepatic imaging and resection, may substantially improve survival after surgery for the primary disease.

Little is known about the natural course of colorectal metastases. The differing ages of colorectal hepatic and extrahepatic metastases in the same patient and their prevalences in different organs suggest that dissemination to extrahepatic sites such as lung and bone is often by secondary metastasis from metastases that have already developed within the liver.² Colorectal hepatic metastases are present for an average of four years before a patient's death.³ Neither conventional imaging^{4,5} nor the surgeon's hand at laparotomy⁶ is likely to detect metastases until they have reached a diameter of 2 cm—by which time three of their four years of growth will have elapsed.

Detecting hepatic metastases so late is not invariably hopeless as dissemination from the liver may occur very late in their history. That a primary large bowel cancer has already metastasised to the liver suggests that cells within hepatic metastases can metastasise. Despite this ability and the long interval that elapses before hepatic metastases become detectable, excision of the primary tumour and hepatic metastases

cures about 3% of patients with metastases detected by conventional methods.⁷ Several years may elapse between metastasis of large bowel cancer to the liver and secondary metastasis from the liver.

One reason for this late dissemination may be trapping within the liver of metastatic cells as they embolise from the primary tumour in the portal circulation. Experimental tumour studies suggest that successful metastasis will occur in only one in 10⁵ "attempts."⁸ This may explain some of the delay before metastasis from the liver to extrahepatic sites is successful.

Detecting "occult" hepatic metastases at primary surgery would reduce by about 16 months the three years that usually elapse before metastases become detectable by conventional means.⁹ During this three years secondary metastasis from the liver becomes more likely as metastatic volume doubles about five times, with cell numbers within an average metastasis increasing from about 10⁷ to 10⁹.³ More patients with large bowel cancer might be cured if more liver metastases were detected when the primary tumour was diagnosed, before secondary metastasis from the liver had occurred.

New techniques of hepatic imaging, particularly intra-operative ultrasonography¹⁰⁻¹⁴ and magnetic resonance imaging,¹⁵ can show small metastases—as small as 4 mm in diameter in the case of intraoperative ultrasonography.

Studies suggest that intraoperative ultrasonography can identify most patients with colorectal hepatic metastases at the time of surgery for the primary tumour.

Preliminary experience with intraoperative ultrasonography (A K Olsen, personal communication) suggests that resectable hepatic metastases will be found in about one in 10 patients undergoing apparently curative resection of primary large bowel cancer and that these can be excised by recently developed techniques for segmental resection.⁶ A further two in 10 patients will have unresectable hepatic disease because of too many deposits. Resection of conventionally detected hepatic metastases, which are apparently confined to the liver, produces long term survival in about one in four patients.⁶ Survival after resection of lesions detected by intraoperative ultrasonography may be better than after resection of the much larger tumours detected by conventional techniques—which have had longer to spread.

Patients in whom deposits detected by intraoperative ultrasonography are excised may also have hepatic metastases that are too small for detection by ultrasonography and may be missed by surgical resection. Thus detection of hepatic metastases by intraoperative ultrasonography may be more valuable in identifying patients in whom hepatic metastasis has occurred than in localising every deposit. Adjuvant intrahepatic infusion of fluorouracil has shown some survival advantage in large bowel cancer¹⁶—presumably the benefit is in patients with occult hepatic metastases—and advanced colorectal hepatic metastases respond to intrahepatic infusion of fluorodeoxyuridine.¹⁷ Resection of hepatic metastases detected by intraoperative ultrasonography should therefore be followed by intrahepatic infusion of either fluorouracil or fluorodeoxyuridine to maximise the possibility of eradicating any microscopic foci of disease remaining within the liver in these “high risk” patients.

Randomised trials are needed in patients undergoing apparently curative resection of primary large bowel cancer to compare long term survival after conventional management with survival after intraoperative ultrasonography, resection of hepatic metastases, and intrahepatic infusion of either fluorouracil or fluorodeoxyuridine. As well as revealing any survival benefit, these trials will test our understanding of the biology of metastasis in large bowel cancer.

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Fibrinogen

An independent risk factor for cardiovascular disease

Since the Northwick Park heart study showed that fibrinogen concentration was an independent risk factor for myocardial infarction¹ five further epidemiological studies have produced prospective data on fibrinogen and cardiovascular events.³⁻⁷ All measured fibrinogen concentrations in large random samples of the population and related them to cardiovascular events several years later. From these studies fibrinogen concentration has emerged as an important and independent risk factor for stroke and myocardial infarction. In the most recent trial fibrinogen concentration, leucocyte count, and plasma viscosity were at least as predictive of coronary events as cholesterol concentration, diastolic blood pressure, and body mass index.⁷

That the fibrinogen concentration is raised after stroke⁸ and myocardial infarction⁹ has been known for many years, although interpreting these findings is difficult given that fibrinogen is an acute phase protein and therefore likely to increase with inflammation or tissue necrosis. Recent work, however, suggests that fibrinogen concentration is raised before such events—for example, in patients with transient ischaemic attacks (p 605)^{10 11} and with angina pectoris.¹² More importantly perhaps, fibrinogen strongly predicts cardiovascular events in people with coronary heart disease⁹ and

peripheral vascular disease¹³ and in survivors of a first stroke.¹⁴ It also predicts the progression of atherosclerotic carotid stenoses.¹⁵

This may be explained by fibrinogen concentration's positive correlation with nearly all other cardiovascular risk factors: age, hypertension, hyperlipoproteinaemia, smoking, diabetes, body mass index, stress, and lack of physical activity.¹⁶ Also relevant to an understanding of the links between fibrinogen concentration and cardiovascular disease are the findings that oral contraceptives increase the concentration of fibrinogen¹⁷ while moderate alcohol intake decreases it.¹⁸ Despite these associations fibrinogen concentration has emerged as an independent risk factor for cardiovascular disease. More than that, an increased fibrinogen concentration may be a common mechanism by which several major risk factors promote coronary artery disease.¹⁹

If this is so, how does fibrinogen damage the circulatory system? Several possibilities exist. It may promote a hypercoagulable state favouring the deposition of thrombus on atheromatous plaques,¹² and it is an important determinant of blood rheology.¹⁶ Fibrinogen also links to platelet receptors, which is a precondition for platelet aggregation.²⁰ Multiple mechanisms exist whereby fibrinogen and its metabolites