year, however, and from these cumulative savings we could begin to afford the new expensive drugs. Placing hospitals on the same footing as their community counterparts, who do not pay value added tax on drugs, would release additional funds.

More rational ways of using the nation's resources should be sought, and as a national problem it requires a national solution. The long term benefits of a solution—both financial and in improved working relationships—would handsomely repay any short term infusion of resources.

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More macrolides

Some may be improvements on erythromycin

Almost 40 years have elapsed since the first reports of the use of the macrolide antibiotic erythromycin in the treatment of human infections.[1] During this period it has established itself as one of the safest antibiotics in current use and an effective alternative to penicillin for the treatment of and prophylaxis against Gram positive infections of the skin, soft tissues, and respiratory tract.[2] It has also become the favoured agent of choice for treating infections caused by *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Legionella* sp. Indeed, with doctors' increasing awareness of the role of intracellular pathogens such as mycoplasma, legionella, and *Chlamydia pneumoniae*,[3] not only in pneumonia[4] but also in milder respiratory illnesses of all types, erythromycin has become the first line treatment for many respiratory illnesses acquired in the community.[5]

Erythromycin does, however, have several drawbacks related to its pharmacokinetics, microbiological activity, and tolerability. Because of its instability at a low pH the concentrations achieved in the blood after oral administration are erratic. Various oral preparations of erythromycin have been formulated to overcome this poor bioavailability, but little convincing evidence exists that these modifications are accompanied by any improvement in clinical efficacy. The main microbiological drawback of erythromycin is its inadequate activity against *Haemophilus influenzae*. A recent survey found that one in six isolates of *H influenzae* from England and Scotland had high level resistance to erythromycin,[6] precluding sole reliance on erythromycin when *H influenzae* is a likely pathogen. Finally, compliance with erythromycin treatment is often poor. Part of the problem is that it is usually prescribed in a six hourly regimen; once or twice daily regimens are generally better adhered to.[7] An additional factor, however, is the frequent occurrence of nausea, epigastric discomfort, and other minor gastrointestinal symptoms, particularly in adults, after it is taken.[2]

Over the past decade the pharmaceutical industry has shown a resurgence of interest in the macrolides and a dozen or so derivatives have been undergoing development.[8] All these new macrolides are more stable in acid than erythromycin; many also have a longer half life or better microbiological activity, or both. The first of these new macrolides is now available in the United Kingdom and others may follow soon.

Roxithromycin is an ether oxime derivative of erythromycin and is already available in several European countries, although not in the United Kingdom. It has a long serum half life, allowing twice daily administration, but otherwise few advantages. What is gained by higher plasma concentrations is lost by lower in vitro antimicrobial activity than erythromycin against most organisms.[9] Flurithromycin has a similar range of activity but has only 25-50% the potency of erythromycin.[8] Dirithromycin is an oxazine derivative of erythromycin with a half life of over 24 hours and excellent tissue penetration. Its range of activity is similar to that of erythromycin but with less activity against Gram positive bacteria and somewhat better activity against Gram negative organisms. Clinical assessments are not yet available.

Azithromycin is the first of a new group of 15 membered ring macrolides referred to as the azalides. It, too, is less active against Gram positive bacteria but considerably more active against *H influenzae* than erythromycin.[10] It is also effective in vitro against *Toxoplasma gondii* and *Mycobacterium avium-intracellulare* and may be more effective against legionella than erythromycin.[11] It is more stable in acid than erythromycin. Its serum half life is eight to 16 times longer than that of erythromycin, and the tissue concentrations are considerably higher than the serum concentrations and persist for several days after dosing.[12]

The clinical importance of this divergence between serum and tissue concentrations needs clarification. The criteria on which to decide whether an organism is sensitive or resistant and the types of infection to treat are still uncertain. Some studies have suggested that for certain organisms the tissue concentrations are more important.[13] This may be particularly important in intracellular infections: one study suggests that a single dose of azithromycin may be effective in chlamydial urethritis.[14] This may not be the case for other infections: poor results were obtained against *H influenzae* in exacerbations of chronic bronchitis, for instance, despite high sputum concentrations,[15] and fears exist that the low serum concentrations may be detrimental in the treatment of infections such as pneumococcal pneumonia in which septicaemia is frequent.

Clarithromycin is a new, orally absorbed 6-*O*-methyl derivative with a similar range of activity to that of erythromycin. Launched in Ireland and Italy last year, it has now become the first of the new generation of macrolides to be introduced in the United Kingdom. After oral administration it is converted to a 14-hydroxy metabolite.[16] The parent compound has similar activity to that of erythromycin against *H influenzae*, but the metabolite is twice as active,[10 16] and combinations of clarithromycin and 14-hydroxy-clarithromycin, in ratios achievable in vivo, show varying

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-amoxyclav 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 laparotomy[6] 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 10^5 "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 10^7 to 10^9.[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 intraoperative ultrasonography[10-14] and magnetic resonance imaging,[15] can show small metastases—as small as 4 mm in diameter in the case of intraoperative ultrasonography.