Organisation's projections suggest that 1 in every 1000 people in India will be infected by 2000.² An Indian news magazine recently highlighted the problem of cross border trafficking by prostitutes from Nepal.³ Commercial sex is an important route of transmission of HIV in Asian countries.

At the heart of this problem is the complacency shown by the central government in New Delhi. It is astonishing that, while the numbers of cases of HIV infection and AIDS are rising, the programme budget remains underspent.¹ There is no coherent national strategy on conducting safe sex campaigns. Government departments shy away from giving explicit information about the spread of HIV. Campaigns through leaflets will have no role in rural areas owing to low literacy rates. But it is not too late to reverse the rising number of cases. Satellite television is now reaching the most remote parts of India. Both the government and voluntary organisations should be keen on using this in their fight against HIV infection and AIDS.

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Ciprofloxacin in general practice

EDITOR,—The Lesson of the week by Roland J Körner and colleagues highlighted the dangers of fluoroquinolones.¹ We have also noted that patients with chest infections have been treated with ciprofloxacin in general practice; the slower resolution of their *Streptococcus pneumoniae* infection required a change of antimicrobial agent, and one patient died.

We understand, however, that ciprofloxacin is not promoted as first line treatment in general practice for community acquired chest infections, but some general practitioners in our area have provided promotional material that does. This material contains data showing that 14.4% of bacterial pathogens in acute exacerbations of chronic bronchitis are *S pneumoniae*.

Bantz and colleagues (some of whom worked for Bayer) are cited in Bayer's promotional leaflet for Ciproxin; they mentioned a >95% resolution rate but compared only doxycycline with ciprofloxacin and made no reference to bacterial pathogens. In the same supplement to the *American Journal of Medicine*, however, other papers gave less favourable views—for example, "the activity of ciprofloxacin against *Streptococci* and *Enterococci* is marginal, at best."²

The only other reference concerning efficacy that is cited in Bayer's promotional leaflet is a study of just 34 patients.⁴ Those with *Haemophilus influenzae* rapidly recovered, and these organisms were not culturable beyond three days. Of those with *S pneumoniae* infection, five still had positive results after three days, five after 11 days, and one after 25 days. Five patients had a relapse and were then treated with either amoxycillin or cotrimoxazole and clinically recovered. Six patients acquired *S pneumoniae* infection during or after treatment, and three required treatment. Two patients had rising minimum inhibitory concentrations to ciprofloxacin in *S pneumoniae*, with organisms being isolated further into ciprofloxacin treatment.

In the same issue of the *Journal of Antimicrobial Chemotherapy* a leading article on quinolones in chest infections, concludes that there is little reason for optimism about the role of quinolones in

chest infections mainly because of problems with resistance, recurrence, and reinfection with *Pseudomonas aeruginosa* and *S pneumoniae*.⁵

Clearly, ciprofloxacin is not a suitable agent for use in general practice for the blind initial treatment of chest infections and should not be so promoted.

We believe that there are major discrepancies between the promoted image and the clinically interpreted usefulness of ciprofloxacin. We hope that this sort of problem is not widespread in the pharmaceutical industry but wonder how extensive it is considering the gamut of drugs being actively promoted, often to those without the time or resources to easily and critically interpret the data presented to them.

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Fluoroquinolones in chronic obstructive pulmonary disease

EDITOR,—In their editorial Harold Hosker and colleagues suggest that fluoroquinolones are suitable second line antibiotics for infective exacerbations of chronic obstructive pulmonary disease.¹ We report two cases that illustrate our reservations about this suggestion.

Case 1—A 75 year old woman was admitted complaining of severe shortness of breath and right sided pleuritic chest pain. She had been admitted several times before with exacerbation of chronic obstructive pulmonary disease. Before this admission she had taken ciprofloxacin 500 mg twice daily and prednisolone for six days. On examination she had signs of right lower lobe pneumonia, which was confirmed on chest radiography. She was hypoxic (oxygen pressure 6.8 kPa, carbon dioxide pressure 5.21 kPa) and had a white cell count of $23 \times 10^9/l$, with 84% neutrophils. *Streptococcus pneumoniae* capsular type 4 was isolated from blood cultures, with a minimum inhibitory concentration for ciprofloxacin of 4 mg/l and for benzylpenicillin of 0.125 mg/l. She responded to amoxycillin and was discharged after seven days.

Case 2—A 72 year old man with a 30 year history of chronic obstructive pulmonary disease was admitted with severe shortness of breath. Before admission he had been treated with ciprofloxacin 250 mg twice daily and prednisolone. On examination he was afebrile, breathless, and cyanosed. There were widespread crackles and wheezes in the chest but no focal abnormality in the chest radiograph. *S pneumoniae* capsular type 15 was isolated from sputum taken after admission. The minimum inhibitory concentration for ciprofloxacin was >8 mg/l and for penicillin 0.125 mg/l. He was treated with amoxycillin and erythromycin and discharged after 22 days.

S pneumoniae is the pathogen most commonly identified in pneumonia acquired in the community and in lower respiratory tract infection seen in general practice; it is frequently isolated in chronic obstructive pulmonary disease.² Fluoroquinolones such as ciprofloxacin and ofloxacin

are not particularly active against it. Serum bactericidal concentrations after oral or intravenous dosage are minimal,³ which may lead to antimicrobial resistance. Fluoroquinolones are highly active against *Haemophilus influenzae* and some of the bacteria causing atypical chest infections, which may contribute to infective exacerbations of chronic obstructive pulmonary disease.

Failure of treatment with fluoroquinolones in respiratory tract infection has been reported.⁴ The datasheets for fluoroquinolones indicate that the drugs are not predictably active against *S pneumoniae*, yet some are heavily promoted for the treatment of chronic bronchitis in general practice. We believe that fluoroquinolones should not be used alone for blind treatment of respiratory tract infections, including exacerbations of chronic obstructive pulmonary disease. An agent effective against pneumococcus should always be included until a microbiological diagnosis is made.

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Safety of thalidomide

EDITOR,—Use of thalidomide only on a named patient basis does not necessarily mean that patients are protected from its side effects, as implied by Baroness Cumberlege, the junior health minister.¹ According to Sir William Asscher, the former chairman of the Committee on the Safety of Medicines, "the companies who supply a drug for named patient use are not required by law to provide warnings about the use of the drug" and, furthermore, "the information provided with the supplies of thalidomide [to patients with leprosy in the United Kingdom] does not specifically mention peripheral neuropathy as a side effect" (personal communication). Until 1979 patients with leprosy were not warned that the drug could cause loss of sensation in the extremities (M F R Waters, personal communication). Requests to find out whether they have now been warned have not been answered by Sir William. Early recognition of thalidomide neuropathy with immediate withdrawal offers the best chance of recovery, but this option is being denied to patients with leprosy. Even worse, the patients will assume that any loss of sensation occurring during treatment will be due to the disease.

Electrophysiological studies, particularly the recording of sural nerve action potentials, have proved valuable in detecting thalidomide neuropathy at an early stage,² but these have not been

used in patients with leprosy. When thalidomide has been used to treat non-leprosy disorders the frequency of neuropathy is at least 21%.³ Waters accepts this figure but claims that "the nerves [of patients with lepromatous leprosy] are relatively insusceptible to thalidomide-induced peripheral neuropathy."⁴ Without application of the already mentioned safeguards, plus details of the clinical neurological findings, this assertion cannot be sustained. Because of the failure of leprologists to take thalidomide neuropathy seriously the drug has been distributed widely in developing countries, culminating in the disaster in Brazil, where to date 47 children have been born deformed after their mothers took thalidomide during pregnancy.⁵

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Supervised administration of methadone by pharmacists

EDITOR,—The Advisory Council on the Misuse of Drugs recently concluded that structured methadone maintenance programmes should be developed throughout Britain.¹ Putting this recommendation into practice is not free from controversy. In the debate on the place of prescribing for drug misusers a criticism commonly made concerns "street leakage," whereby some or all of the prescribed drug is diverted by various means from the patient for whom it is intended towards illicit users.²

In an attempt to minimise the possibility of such street leakage several doctors in Glasgow have arranged with several pharmacists for methadone to be administered under the pharmacists' supervision in community pharmacies (P Wilson, personal communication). This frequent, often daily contact with patients by the pharmacist thus offers the opportunity for an increased contribution towards the patients' care. This is in keeping with a report on the future role of community pharmacies in Britain, which notes that pharmacists should aim to provide a full service to drug misusers, particularly those receiving a maintenance prescription.³

In order to assess the pharmacists' current role in dispensing methadone a questionnaire was distributed to all community pharmacies in the area covered by Greater Glasgow Health Board (n=214). This questionnaire formed part of a letter introducing the newly established Glasgow drug problem service. The letter was sent out after discussion with the board's area pharmaceutical committee, which had given its support to the supervised administration of methadone. The response rate to the questionnaire was 63% (n=135).

Of the 97 pharmacies currently dispensing methadone, 43 supervised its administration. An additional 38 would be willing to do so if given guidance from the drug problem service. Of the 38 not dispensing methadone during the survey, 15 expressed a similar view. Thus 96 of those that returned the questionnaire were either already supervising the administration of methadone or prepared to do so. This represents a quite remarkable total of 45% of all community pharmacies in Glasgow.

Some respondents expressed concerns about the security of their stock, staff, and other customers. There were also anxieties about the possibility of being overwhelmed by requests for this service should substitute prescribing of methadone substantially increase in the city. Additional collaboration among general practitioners, the Glasgow drug problem service, the area pharmaceutical committee, and individual pharmacists will seek to resolve these problems, while further studies will examine in greater detail the relation between the patients' health and behaviour and supervised administration of methadone.

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Safety of tamoxifen

EDITOR,—Rivalry among pharmaceutical companies and their products is a fact of modern life. But Gary M Williams overstates concerns about tamoxifen, and, in suggesting that toremifene, an antioestrogen that is not yet approved for treating advanced breast cancer in Britain or the United States, should be substituted for tamoxifen in prevention studies, he is suggesting the use of a drug whose long term toxicological effects in women are unknown.¹ The rationale for his recommendation is that large doses of tamoxifen cause liver tumours in rats but toremifene does not.² Had I found that tamoxifen was producing liver tumours in rats two decades ago I would not have advocated long term adjuvant tamoxifen treatment for node positive or node negative breast cancer. The risks of introducing a dangerous drug would have been too great. Thousands of women would have lost their lives prematurely if tamoxifen had not been developed.³

It is of concern that excessive doses of tamoxifen produce liver tumours in rats, but it is lifetime high dose, not short term low dose, tamoxifen treatment that does so. Rats require 40 times the daily human dose of tamoxifen to produce the tumours.² No liver tumours have been reported in women taking 20 mg of tamoxifen daily for five years. The fact that blood concentrations of the drug in rats and humans are similar^{1,2} is irrelevant because 40 times the drug is being processed by the rat liver, inducing unknown metabolic pathways peculiar to the overdosing schedule. An effective daily dose for tamoxifen to produce antimammary cancer effects in rats is 250 µg/kg⁴—almost identical with the human experience. This dose does not produce liver tumours in rats.

In prevention trials tamoxifen is given for only five years—that is, less than 6% of a life span. No one has reported the effects of tamoxifen for an equivalent duration of treatment in rats. Similarly, Williams refers to the formation of adducts in mice and hamsters,¹ but no evidence is presented that tamoxifen causes liver tumours in these species when given for short periods at appropriate, or even excessive, doses. Large doses of tamoxifen may invoke carcinogenic pathways unique to the rat liver, but whether the results of extensive laboratory studies counterbalance the more than

five million woman years of experience recorded in the clinic is questionable.

In contrast, there is up to a 10-fold increase in the risk of hepatocellular carcinoma in women who use oral contraceptives for more than five years.⁵ The mechanism of action of oral contraceptives as liver carcinogens is not relevant.¹ The only relevant fact is that society (that is, drug regulatory authorities) accepts the increased risk of a xenobiotic that does not treat or prevent a fatal disease. To be relevant, the particular risk of hepatocellular carcinoma with tamoxifen must exceed the 10-fold increase established for oral contraceptives.

I believe that recruitment to prevention trials must continue. No alternative strategies wait in the wings to replace tamoxifen tomorrow. The view that middle aged women can prevent breast cancer by reducing their fat intake for several years¹ is not supported by the disappointing results of the nurses health study.⁶ The calculations of benefits, safety, and toxicity used for the tamoxifen prevention study, however, are essentially unchanged from the original projection. Tamoxifen is not for everyone. The risk and benefits are being assessed in a well monitored group of volunteers who have chosen to contribute to clinical research. Without the clinical trials mechanism there will be no answers to any questions.

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The scandal of poor medical research

EDITOR,—Douglas G Altman and most of the correspondents writing in response to his editorial equate better research—a fine aspiration—with less research.^{1,2} We also aspire to better football, cricket, tennis, athletics, industry, writing, and drama (to mention a few activities). To achieve these goals seems to require more and earlier participation and constant practice. Competition is deemed essential to raise performance. Is research different? I believe not.

To get more good research we need to tolerate, indeed encourage, the work of the novice and the enthusiast so that talent can be spotted and developed. The price to pay is more supervision, close peer review, and, when peer review fails, publication of unsatisfactory work. The (elitist) alternative is to foster the view that doing and publishing research are the responsibility only of the talented. Their approach may lead to the extinction of research.

Altman's goals are correct, but his remedy is too stringent. In my view neither the quantity of research done nor the motivation behind it is relevant. (Like Altman I deplore the fact that some doctors are forced into research to achieve clinical career goals.) Two things matter: identifying,