able to give full informed consent when prescribed transurethral resection for prostatic hypertrophy. Are they being denied the information that such an approach carries certain disadvantages, or would full disclosures of this kind be reserved only for patients randomised into clinical trials? If so, this suggests that a double standard exists already and that ethical committees, instead of merely scrutinising the protocols of randomised controlled trials, should also be scrutinising the amount of information that patients are being given outside clinical trials. To deny a patient the knowledge of an appreciable and perhaps avoidable risk of mortality by the uncritical adoption of transurethral resection also raises important ethical issues.

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Sponsored training for overseas doctors

SIR,—We are pleased that the royal colleges' new sponsorship schemes have stimulated discussion on standards of training for overseas doctors.¹ It is correct that in the past many have been dissatisfied with the waste of their qualifications and their employment in poor quality NHS posts.^{2,3} The new system introduced by *Achieving a Balance*,⁴ in which visiting doctors will fill the vacancies created by reductions in career registrar posts, may provide an opportunity to improve their training.

We are concerned, however, that potential pitfalls have not been adequately addressed. *Achieving a Balance* was formulated in the light of the United Kingdom's new immigration laws, under which doctors from overseas nations will be allowed to stay for a maximum of four years. Have the royal colleges considered whether their training, academic as well as clinical, will be appropriate to the needs of the overseas doctors for practice in their countries of origin? The *BMJ* editorial by Mr C H W Bullough underlines this problem⁵: he points out that work in obstetrics in the developed world does not prepare overseas doctors for their future work on return to their own countries. Similar worries have been expressed with regard to psychiatry.⁶

Up until now the Professional and Linguistic Assessment Board examination has been considered vital to ensure suitability to practise in the United Kingdom. But doctors on the new sponsorship schemes are exempt from this. Language difficulties may lead to major problems for the doctors and their patients, and this would certainly bring the new schemes into disrepute.

It remains to be seen whether the royal colleges' new schemes really will lead to improved training for overseas doctors. In our opinion there is a danger that visiting doctors could once again be exploited as "cannon fodder in the service wars,"⁷ as has so often been the case in the past. This may be avoided if there is open discussion of the new training schemes accompanied by formal continuing evaluation. The medical profession in the United Kingdom has international as well as national responsibilities, and these include making every possible effort to provide training appropriate for junior doctors' future practice.

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Improving clinical effectiveness in the NHS

SIR,—I do not regard Ms Lois Quam's "alternative" for improving clinical effectiveness¹ as an alternative at all but a complementary element of the government's general strategy for reforming the National Health Service.

Ms Quam argues that the white paper is built on three fundamental assumptions. These are assumptions that I do not recognise and do not believe to hold true.

The first wrongly attributed assumption is that "price in medical care effectively reflects value." There is no such statement in the white paper, and it has been made abundantly clear in subsequent guidance that price is only one of a number of aspects that purchasers will be expected to take into account. Indeed, the government has explicitly stated that "the balance between quality and price is a judgment that has to be made by the DHA [district health authority] or GP [general practitioner] acting on behalf of the patient."²

What is proposed is not a free market but managed competition between providers. The buyers will be well informed district health authorities and general practitioners charged with securing equitable and appropriate access to comprehensive health care for the population and the patients they serve. Suppliers will be expected to cooperate with buyers in developing the information necessary to make these judgments. Buyers will in any case have incentives to consider both quality and cost when negotiating contracts for hospital services. For example, health authorities will be forced to bear the cost of poor initial treatment in repeat visits and higher readmission rates.

The second assumption attributed to the white paper is that patient throughput measures such as performance indicators effectively measure health care performance despite the absence of measures of patient outcome. This is simply not true. The government fully accepts that there is a need to supplement the present measures of activity and efficiency with measures of health outcome and quality of care. This is a complex area, but we are exploring how best to develop and publish indicators of hospital performance that cover the quality as well as efficiency of the services provided. Similarly, one of the reasons why we are working closely with the medical profession on introducing a national system of medical audit is that we recognise the need to develop a comprehensive set of measures of the outcome of much of the work of individual services and doctors.

These are not just long term plans: in recent guidance the government has stated that "as a minimum" contracts will be expected to specify measures of quality "relating to both the process and outcome of treatment."³ And we have already committed £2 million to develop medical audit this financial year.

In Lois Quam's third point the white paper is accused of truncating "the definition of quality of care into one of patient choice." Again, it does not. Certainly patient choice is an important element of the improvements we want to see in the health service, and the white paper includes many pro-

posals to increase the information available to health authorities, general practitioners, and their patients so that they can make better informed choices. In addition, I think we all need to recognise that patients' expectations, attitudes, and needs are evolving. But what we are not suggesting is that patient choice is a substitute for quality of care. The two should go together.

So let me state my view of the three fundamental themes running through the white paper. Quite simply, the reforms are designed to make sure that the NHS is more responsive to each individual patient, provides an even better quality of care to all, and gets the most out of the huge amount of public money that is concerned. These are goals that we should all be working towards.

Lois Quam puts forward an alternative reform of the NHS directed at improving the effectiveness and efficiency of clinical care. But this is not incompatible with *Working for Patients*, it is an integral part of it. The white paper's particular emphasis on the quality of care and medical audit (including measurements of clinical effectiveness and patient outcomes) has exactly the same aims. I am confident that we all agree with them.

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Drug Points

Methotrexate induced skin necrosis: a drug interaction with amiodarone?

Dr N J REYNOLDS, Dr S K JONES, Mr J CROSSLEY, and Dr R R M HARMAN (Departments of Dermatology and Pharmacy, Bristol Royal Infirmary, Bristol BS2 8HW) write: Several drugs interact with methotrexate, including non-steroidal anti-inflammatory drugs, phenytoin, and co-trimoxazole, sometimes resulting in life threatening complications.¹ Proposed mechanisms of interaction have included decreased renal secretion of methotrexate and displacement of methotrexate or its principal extracellular metabolite, 7-hydroxymethotrexate, from serum and tissue binding sites.² We describe a patient maintained on methotrexate for severe psoriasis who developed ulcerated skin lesions shortly after the introduction of amiodarone.

A 79 year old woman started taking oral methotrexate in August 1986 for recalcitrant psoriasis. The dosage was gradually increased to 20 mg/week with good effect and then titrated against the severity of the psoriasis. In November 1988 she was admitted with worsening psoriasis and episodes of prolonged palpitations associated with dizziness and breathlessness despite taking methotrexate 17.5 mg/week, frusemide 120 mg/day, amiloride 15 mg/day, isosorbide mononitrate 20 mg/day, digoxin 0.25 mg/day, and dothiepin 75 mg/day. Physical examination showed widespread psoriatic plaques, atrial fibrillation with a ventricular rate of 140 beats/min, and signs of mild left ventricular failure. Laboratory investigations showed normal blood count; urea, electrolyte, and serum creatinine concentrations; and liver and thyroid function. The digoxin value was in the therapeutic range and the creatinine clearance 32 ml/min/m² (normal 40-80). The electrocardiogram showed atrial fibrillation with inverted T waves in the inferior leads, and a chest radiograph confirmed mild left ventricular failure. Her psoriasis was treated with dithranol in zinc and salicylic acid paste (0.05%), tar baths, and ultraviolet B. Methotrexate was continued with no change in dosage. Her heart failure responded to

an increase in diuretic dosage (frusemide 160 mg and amiloride 20 mg daily), but atrial fibrillation was uncontrolled and after cardiological advice amiodarone was introduced, with a loading dose of 200 mg three times a day for one week, 200 mg twice a day for a further week, and a maintenance dose of 200 mg/day. Two weeks later many psoriatic plaques became tender, red, and subsequently eroded together with an area on the right inguinal region previously affected by ultraviolet B induced erythema. Methotrexate was stopped and amiodarone continued, and the superficial erosions rapidly healed. There were no other features of methotrexate toxicity.

Ulceration of psoriatic plaques is a rare complication of methotrexate treatment, which may be the only clinical evidence of toxicity.¹ Such ulceration usually occurs shortly after starting methotrexate and may be due to an interaction between methotrexate and drugs that the patient is already taking.¹ The reaction in our patient occurred on a stable dose two years after the introduction of methotrexate. Reactivation of erythema by methotrexate¹ probably accounted for the ulceration in our patient's right inguinal region but was unlikely to have explained the multiple erosions of psoriatic plaques. Amiodarone had been introduced two weeks earlier, and, although there are no reports of a pharmacokinetic interaction between amiodarone and methotrexate, several possible mechanisms exist. Amiodarone interacts with several drugs, including digoxin, warfarin, quinine, and procainamide.² Decreased renal clearance, plasma protein and tissue binding site displacement, altered volume of distribution, and decreased liver metabolism have all been implicated.³ Any of these could have contributed to our patient's skin ulceration, although displacement of methotrexate or 7-hydroxymethotrexate from plasma proteins is unlikely as amiodarone is a basic drug whereas methotrexate is an acidic drug. The increase in frusemide dosage may also have interfered with the tubular excretion of methotrexate in someone with impaired renal function as a toxic reaction to methotrexate after the introduction of penicillin and frusemide has been reported.⁷ This possibility is perhaps less likely in view of the timing of events and the relatively modest increase in frusemide dosage. Fortunately, our patient's skin erosions healed rapidly when methotrexate was stopped, but this case illustrates the care needed when prescribing additional drugs to a patient receiving methotrexate.

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Captopril and lymphocytic alveolitis

Dr JOSEPH C KIDNEY, Dr DOMHNALL J O'HALLORAN, and Professor MUIRIS X FITZGERALD (St Vincent's Hospital, Dublin 4) write: Cough is a side effect of angiotensin converting enzyme inhibitors.^{1,2} Abnormal bronchial responses have been proposed,^{1,3} and eosinophilic lung infiltration has been described.⁴ We report a case of cough caused by an intense lymphocytic alveolitis that occurred during captopril treatment.

A 68 year old hypertensive smoker presented with a cerebral infarct. He had no respiratory

symptoms and his chest radiograph was normal. Treatment comprised bendrofluzide K 2.5 mg/day, nifedipine 20 mg three times a day, captopril 50 mg three times a day, and dexamethasone 4 mg three times a day to reduce perinfarction oedema. He was discharged, well, after 14 days.

Seven weeks later he had a cough, fever, and dyspnoea. Pulmonary basal crackles were heard. Serial chest radiographs showed an infiltrate, progressing from the right base to affect both lungs diffusely. No evidence of bacterial or viral infection, aspiration, or cardiac failure was found. Nifedipine, bendrofluzide K, and dexamethasone were stopped and captopril continued for two weeks.

Function tests showed marked restriction with a forced vital capacity of 1.9 l (predicted 4.15 l), and a forced expiratory volume in one second of 1.6 l (predicted 3.0 l). Diffusing capacity for lung carbon dioxide was not measured. Bronchoalveolar lavage showed an intense alveolitis with 59.4% T lymphocytes (helper:suppressor ratio 2.4). Captopril was withdrawn. Nifedipine and bendrofluzide K were reintroduced. Considerable clinical and radiographic improvement occurred within a week.

Subsequent bronchoalveolar lavage eight weeks and six months later showed the T lymphocytes falling to 37% and 2% respectively. At six months he had a forced expiratory volume in one second of 1.8 l, forced vital capacity of 3.0 l, and carbon dioxide diffusing capacity 65% of predicted; at one year these values were 2.4 l, 3.6 l, and 83% respectively. Rechallenge with captopril was refused.

There were no chest symptoms or radiographic abnormalities before captopril. Cough, dyspnoea, lung restriction, and lymphocytic infiltration all occurred during captopril treatment. Once the drug was withdrawn these abnormalities improved significantly. Thiazide induced pulmonary oedema⁵ was excluded as our patient improved despite rechallenge with bendrofluzide. This report suggests that in some patients cough associated with angiotensin converting enzyme inhibitors may be due to a diffuse lymphocytic alveolitis.

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Neutropenia and metolazone

Dr K L DONOVAN (Department of Medicine, Cardiff Royal Infirmary, Cardiff CF2 1SZ) writes:

Metolazone is a commonly used diuretic in the treatment of resistant oedema and often in combination with loop diuretics. We describe a case of neutropenia induced by this drug.

A 58 year old woman who had been treated for six weeks with frusemide 120 mg, spironolactone 600 mg, and digoxin 0.125 mg for severe heart failure and oedema had metolazone 5 mg daily added to augment her diuresis. Within 10 days a profound leucopenia was noted (see figure). Bone marrow aspiration showed considerable suppression of granulopoiesis, typical of a drug reaction. No other abnormalities were seen. Suspected of being the cause, metolazone was withdrawn. Her neutropenia persisted for another 10 days, after which there was a rebound neutrophilia. Eosinophil, monocyte, and lymphocyte counts were all unaltered. Haemoglobin concentration and platelet count also remained normal (figure). The datasheet states that leucopenia may occur with metolazone. Reports are, however, rare and none have been published. Several companies now make and market metolazone all over the world. In the United Kingdom Hoechst have received only one report of neutropenia associated with metolazone. Likewise in the United States Fisons have only one case of severe neutropenia on their files. Agranulocytosis, hypoplastic anaemia, and aplastic anaemia have also been reported (Fisons, Searle, data on file), but in these cases other drugs may also have been implicated. There is one published report of hypoplastic anaemia possibly related to metolazone but in this case the white cell count was unaffected.²

The warning in the datasheet seems to be based on the fact that metolazone is structurally and pharmacologically related to both the thiazide diuretics¹ and the sulphonamides,⁴ both of which may cause leucopenia and agranulocytosis.^{1,6}

In our patient there was a very strong temporal relation between starting metolazone and neutropenia. We observed a 10 day latent period before neutropenia occurred, which corresponds to the 14 days seen in the Hoechst case and the eight days in the Fisons case. The neutropenia persisted for 10, seven, and an unspecified number of days respectively after withdrawal of the drug. The theoretical risk of neutropenia with metolazone is a rare reality, and early withdrawal of the drug in suspected cases should lead to a full recovery of bone marrow.

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Cell counts before, during, and after metolazone treatment