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, quinidine, 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 bendrofluazide 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, bendrofluazide 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 bendrofluazide 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 bendrofluazide. 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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- 5 Mandell GL, Sande MA. Sulphonamides, trimethoprim-sulphamethoxazole and agents in urinary tract infections. In: Goodman LS, Gillman AG, Murad F, eds. *The pharmacological basis of therapeutics*. 7th ed. New York: Macmillan, 1985:1102.

Cell counts before, during, and after metolazone treatment