600 mg weekly, and zidovudine 600 mg daily. Previous treatment with penicillin, clindamycin, trimethoprim, and erythromycin on various occasions over the past year had precipitated generalised rash and fever. Acid-fast bacilli were demonstrated on sputum smear, and pyrazinamide, rifampicin, isoniazid, and ethambutol were started. He became afebrile within 48 h and remained so until the 7th day when his temperature rose to 39·5°C, associated with a maculopapular rash. The anti-tuberculous medications were stopped and the temperature and rash settled within 24 h. He has since been challenged individually with rifampicin, isoniazid, pyrazinamide, ethambutol, prothionamide, streptomycin, and clofazimine—all of which precipitated fever, rigor, and maculopapular rash within 24–48 h.

We are not aware of any reports of such multiple drug hypersensitivity in patients with AIDS, and management of tuberculosis in this patient is proving to be a therapeutic challenge. Small doses (a tenth) of each drug—rifampicin, isoniazid, pyrazinamide, and ethambutol—are being used with prednisolone to desensitise the patient. We would be interested to know whether other clinicians have such experience and what immunologists think the underlying mechanisms might be.

Regional Department of Infectious Diseases and Tropical Medicine, University of Manchester School of Medicine, Monsall Hospital, Manchester M10 8WR

E. L. C. ONG
B. K. MANDAL

1 Jaffe HS, Abrams DI, Amman AJ, Lewis BJ, Golden JA. Complications of co-trimoxazole in treatment of AIDS-associated *Pneumocystis carinii* in homosexual men *Lancet* 1983; ii: 1109–11.
2. Mitsuyasu R, Groopman J, Volberding P. Cutaneous reaction to trimethoprim-sulphamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308:** 1535–36.
3. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulphamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **100:** 495–99.

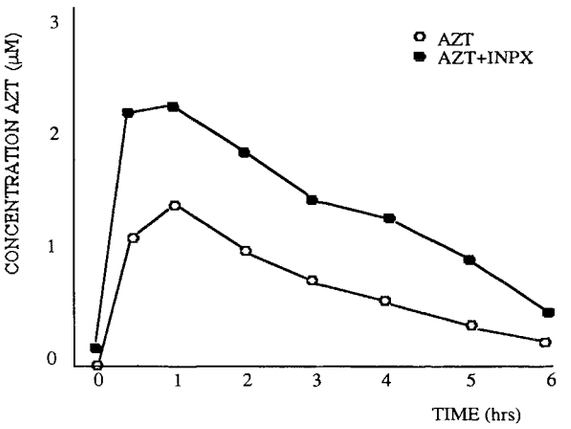
INOSINE PRANOBEX AND ZIDOVUDINE METABOLISM

SIR,—Dr Kornhauser and colleagues (Aug 26, p 473) suggest the use of probenecid, an inhibitor of glucuronidation, to extend the interval between zidovudine doses and reduce the daily requirement for the drug. We arrived at a similar result with inosine pranobex (INPX; 'Viruxan', Sigma Tau, Italy) whose *p*-acetoamidobenzoic acid moiety is glucuronidated in the liver.[1] INPX is a virtually non-toxic drug which inhibits HIV reverse transcriptase and has an immunopotentiating activity on HIV-infected lymphocytes. INPX does not enhance HIV yield when used alone or in combination with zidovudine in peripheral blood mononuclear cells, and it seems to be effective in reducing opportunistic infections in HIV-infected patients.[2-5]

We studied eight patients with AIDS (group IVC) who had bone marrow toxicity while on 200 mg zidovudine 4-hourly and also when maintained for 2 months on only 800 mg daily. They were then given zidovudine 100 mg every 6 h (one-third of the currently recommended dosage) by mouth for 7 days, followed by 100 mg zidovudine plus 1 g INPX every 6 h for a further 7 days. The patients weighed 47·3–63·2 kg. No other drug thought to affect hepatic glucuronidation was administered. On days 7 and 14 blood was taken over a 6 h dosing interval for measurement of zidovudine by a specific radioimmunoassay ('ZDVTRAC'; Incstar, USA).[6] To validate the assay zidovudine was also measured by reverse-phase high-performance liquid chromotography (HPLC).[7]

On day 7 (patients not on INPX) the peak plasma level of zidovudine averaged 1·44 μmol/l (SD 0·71, range 0·06–2·54) and the nadir was 0·25 μmol/l (SD 0·19, range 0·06–0·7). On day 14 (patients on INPX and zidovudine) peak plasma levels averaged 2·25 μmol/l (SD 1·6 range 0·14–4·7) and the nadir was 0·48 μmol/l (SD 0·28, range 0·14–0·88). At time zero (ie, before zidovudine was taken) the drug concentration was consistently higher in patients taking INPX (0·21 *vs* 0·015 μmol/l) and the half-life for the elimination phase was significantly shorter (44 *vs* 70 min) when zidovudine alone was taken.

Values obtained by HPLC were within 20% of the mean of RIA estimates. Chromotographic studies (not shown) revealed that both



Mean plasma concentrations of zidovudine (AZT) after 100 mg was given orally to eight patients every 6 h.

the *p*-acetamidobenzoic acid and zidovudine are metabolised, suggesting that the increase in serum concentration and half-life could be due to metabolic competition. Whether INPX acts as an inhibitor of an enzyme responsible for metabolism or as competing substrate for that enzyme remains to be elucidated.

The advantages of adding INPX are lower doses of zidovudine, a longer interval between doses, and reduced costs; furthermore there is the potential of enhancing the host's immunological response via INPX treatment.

Departments of Infectious Diseases and Experimental Medicine, Università degli Studi dell'Aquila degli Abruzzi, 67100 L'Aquila, Italy

CLAUDIO DE SIMONE
SONIA TZANTZOGLOU
VINCENZO VULLO
SALVATORE CATANIA
VITO TRINCHIERI

Infectious Diseases Clinic, Università La Sapienza, Rome

1. Campoli-Richards DM, Sorkin EM, Heel CR. Inosine pranobex· A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1986; **32:** 383–424.
2. Pompidou A, Zagury D, Gallo RC, Sun D, Thornton A, Sarin PS. In-vitro inhibition of LAV-HTLVIII infected lymphocytes by dithiocarb and inosine pranobex. *Lancet* 1985; ii: 1423.
3. Schinazi RF, Cannon DL, Arnold BH. Interaction of Isoprinosine with 3'-azido-3'-deoxythymidine (AZT) in HIV-1 infected human peripheral blood mononuclear (PBM) cells and in FMuLV/SFFV infected BALB/C mice. IV International Conference on AIDS (June 12–16, 1988, Stockholm); abstr 3635.
4. De Simone C, Albertini F, Almaviva M, et al. Clinical and immunological assessment in HIV + subjects receiving inosine-pranobex: a randomised, multicentric study. *Med Oncol Tumor Pharmacother* 1989; **1:** 63–67.
5. The Scandinavian Isoprinosine Study Group Isoprinosine reduced clinical progression in HIV infected patients in a double blind placebo controlled study. V International Conference on AIDS (June 4–9, 1989, Montreal); abstr ThB 0.46.
6. Puckett LD, Orf BS, Hostager CR, Goldensoph JE. Characteristics of a two hour RIA for assessment of the levels of AZT in serum. IV International Conference on AIDS (June 12–16, 1988, Stockholm); abstr 3642.
7. Langtry HD, Campoli-Richards D. Zidovudine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1989; **37:** 408–50.

FEMALE-TO-MALE TRANSMISSION OF HIV-1

SIR,—Dr Cameron and colleagues (Aug 19, p 403) present intriguing evidence to support the importance of genital ulcer disease and lack of male circumcision as risk factors for female-to-male transmission of HIV-1. There is a potential source of bias in the reported estimates of effect. In sexually transmitted HIV-1 infection a long time may elapse between exposure and seroconversion.[1,2] The factors which determine the length of this period are not known, but seroconversion probably happens only after a threshold of HIV-1 replication in the blood has been crossed. Since the mean serological follow-up from reported sexual exposure was only 14 weeks in Cameron's study (and men with follow-up for as little as 2 weeks were included) a significant proportion of infected men probably had not seroconverted. Although based on few seroconversions, the data in fig 1 suggest that the interval between exposure and seroconversion may have been much shorter for uncircumcised men who presented with genital ulcer disease than for men with fewer risk factors. If so, the aetiological fraction of