LETTERS TO THE EDITOR

Drugs and the elderly

Sir: I was interested to read the article by Bird¹ on drugs and the elderly. I agree that a substantial proportion of doctors will not understand pharmacokinetics. Unfortunately, their level of understanding will not be helped by some of the errors that have crept into this article.

For drugs which display first order kinetics the plasma half life and clearance are constant irrespective of the amount of drug available in the body for elimination. This is in contrast with a drug which displays zero order kinetics, where the clearance falls with increasing concentration as the elimination process becomes saturated. The definition of the volume of distribution of a drug is not, as stated in this paper, the amount of drug in the body available for elimination, but is the theoretical volume of fluid in which the drug is distributed if it existed in the same concentration elsewhere as it does in the plasma. This would be given by dividing the total amount of drug in the body by the plasma concentration. It is also incorrect to state that if the volume of distribution is reduced the peak plasma concentration will increase. This will be the case if the distribution process is rapid, but another major determinant of peak plasma concentration is the rate of absorption, and for a drug which is rapidly absorbed but slowly distributed, such as digoxin, volume of distribution will have a negligible effect on peak plasma concentration.

Finally, I find the term 'accumulation', as used here, confusing. Accumulation is not a phenomenon that depends upon the property of a drug, nor are there drugs which accumulate and drugs which do not accumulate. It depends upon the relation between the half life of the drug and the dosing interval and, by definition,² accumulation occurs if the drug is given at a dosage interval of less than 1.44 half lives. Thus, even in young patients, accumulation of piroxicam will occur and what we are speaking about in elderly subjects is relatively greater accumulation. It must also be stated that accumulation is not, in itself, a bad thing but is in fact necessary to produce fairly stable plasma concentrations.

T PULLAR
Clinical Pharmacology and Rheumatology Units
Department of Medicine
General Infirmary
Leeds LS1 3EX

1 Bird H A. Drugs and the elderly. *Ann Rheum Dis* 1990; 49: 1021-2.

2 Rowland M, Tozer T N. *Clinical pharmacokinetics: concepts and applications*. Philadelphia: Lea and Febiger, 1980: 173-94.

Sir: Dr Pullar's points are well taken, though such a detailed pharmacokinetic exposition was not available to me within the constraints on space imposed by a brief review article. Matters were rendered more ambiguous by the incorrect positioning of the term 'volume of distribution', which arose from my own transcribing error and for which I apologise. This allowed false conclusions to be drawn.

I remain less confused than Dr Pullar by the term 'accumulation', though accept that this

enjoys a precise definition and that 'relatively greater accumulation' is a more accurate description of what was being discussed. Although agreeing that accumulation may be beneficial in producing stable plasma concentrations, this benefit can only be reaped safely if the drug is relatively free from side effects.

H A BIRD
The University of Leeds
Royal Bath Hospital
Cornwall Road
Harrogate
North Yorkshire HG1 2PS

Cryptosporidial enteritis complicated by conjunctivitis

Sir: Shepherd *et al* recently reported two children with cryptosporidial enteritis complicated by reactive arthritis.¹

A 13 year old girl with a past history of epilepsy, asthma, and hypothyroidism presented with a two week history of profuse watery diarrhoea, colicky lower abdominal pains, lethargy, nausea, vomiting, scattered arthralgic and myalgic pains. She also had conjunctivitis in both eyes. The child was admitted and stool examination showed oocysts of *Cryptosporidia* spp. No other pathogens were uncovered, and she eventually made a spontaneous recovery; her conjunctivitis settled.

Reiter's syndrome may follow urethral infection or gastroenteritis, and the clinical features of the condition—namely, arthritis, conjunctivitis and urethritis, or gastroenteritis, are well known. Shepherd *et al* described two female paediatric cases (and referred to one adult male case described by others) where cryptosporidiosis was complicated by reactive arthritis¹; all these subjects were evidently immunocompetent. In addition, two potentially relevant cases positive for antibody to HIV have been described, one being a 27 year old homosexual man with diarrhoea, urethritis, conjunctivitis, arthritis, and cryptosporidial enteritis,² and the other a 4 year old child (sex unknown) with cryptosporidiosis who developed conjunctivitis as part of a more profound systemic illness (which was subsequently diagnosed as measles).³

Our patient had conjunctivitis and scattered arthralgic and myalgic pains associated with her gastroenteritic illness; accordingly, although the pathogenesis of cryptosporidial enteritis in immunocompetent subjects remains poorly understood, it is feasible that Reiter's syndrome may represent a potential clinical consequence of the condition. It may be pertinent to note that unlike the almost total male exclusivity of Reiter's syndrome associated with urethritis, among cases of Reiter's syndrome associated with gastroenteritis (of whatever underlying cause) a much larger proportion occur in women.⁴ In addition, the syndrome has been reported occurring in sexually inactive children.⁴

STEPHEN T GREEN
VIVIENNE SCOTT
JAMES McMENAMIN
DAVID J GOLDBERG
W CAMPBELL LOVE
Department of Infection and Tropical Medicine
and the Communicable Diseases (Scotland) Unit
Ruchill Hospital
Glasgow G20 9NB

1 Shepherd R C, Smail P J, Sinha G P. Reactive arthritis complicating cryptosporidial infection. *Arch Dis Child* 1989; 64: 743-4.

- Winchester R, Bernstein D H, Fischer H D, Enlow R, Solomon G. The co-occurrence of Reiter's syndrome and acquired immunodeficiency. *Ann Intern Med* 1987; 106: 19-26.
- Centers for Disease Control. Epidemiological notes and reports: measles in HIV-infected children. *MMWR* 1988; 37: 183-6.
- Rein M F. Reiter syndrome. In: Mandell G L, Douglas R G, Bennett J E, eds. *Principles and practice of infectious diseases*. 3rd ed. New York and Edinburgh: Churchill Livingstone, 1990: 949-52.

Raised plasma concentrations of endothelin-1 in systemic lupus erythematosus

Sir: Endothelin-1 is a newly described vasoconstrictor peptide produced and secreted by vascular endothelial cells.¹ It has potent and longlasting vasoconstrictive action and it may participate in the pathogenesis of hypertension and vascular spasm.

High plasma concentrations of endothelin-1 have been reported in acute and chronic renal failure,^{2,3} in subarachnoid haemorrhage with vasospasm,⁴ and in myocardial infarction.^{5,6}

Systemic lupus erythematosus is commonly associated with nephritis, hypertension, peripheral vasculitis, and vasospastic diseases like migraine and Raynaud's phenomenon.

In this study we measured venous plasma concentrations of endothelin-1 in 28 young female patients with systemic lupus erythematosus. All patients met at least four of the American Rheumatism Association's diagnostic criteria⁷ for systemic lupus erythematosus and were randomly chosen from a cohort of patients with systemic lupus erythematosus interviewed about their obstetric histories. Control subjects were healthy, young, mainly female laboratory personnel. Plasma endothelin-1 concentrations were measured by a specific radioimmunoassay.⁸ The endothelin-1 antiserum used showed less than 0.1% cross reaction with big endothelin-1: 1-38 and its fragment 22-38, and fragment 171-201 of preproendothelin-1. It cross reacted 100% with endothelin-2 and -3. Plasma endothelin-1, when analysed by high performance liquid chromatography, and endothelin-1 in fractions, coeluted with synthetic endothelin-1. No other peaks of immunoreactivity were detected. The small amount of endothelin-1 in plasma did not allow testing for bioactivity. The findings in this endothelin-1 assay were correlated with the clinical picture of systemic lupus erythematosus. We also measured anti-cardiolipin antibodies by an enzyme linked immunosorbent assay (ELISA). Lupus nephritis was verified by biopsy in 13 of the 15 patients, who at some time of their disease had had proteinuria of more than 0.5 g/day. The distribution of biopsy findings according to WHO classification was as follows: type II three patients, type III four, type IV five, and type V one patient. Biopsy was not done in two patients. Statistical analysis was by the χ^2 method.

Plasma concentrations of endothelin-1 were raised in 23 of 28 patients with systemic lupus erythematosus as compared with the normal range (mean 2 (SD)) in 66 healthy subjects (table). Raised plasma endothelin-1 concentration >5.3 pg/ml correlated with a history of nephritis ($p < 0.05$) but did not correlate significantly with hypertension, Raynaud's phenomenon (present in 8/28 (29%) of patients), migraine (present in 6/28 (21%)), thrombotic events, leg ulcers, creatinine clearance, or clinically evident peripheral vasculitis. Nine patients (32%) had positive anti-cardiolipin antibodies and eight of them had increased endothelin-1. This distribution did

Mean (SD) plasma endothelin-1 concentration in 28 patients with systemic lupus erythematosus: correlating factors (results given as number of patients)

Group	Endothelin-1 plasma concentration (pg/ml)	Nephritis†	Raynaud's phenomenon	Anticardiolipin antibodies
All patients (n=28)	10.8 (5.0)***	15	9	9
Normal endothelin-1 concentration‡ (n=5)	3.2 (2.0)	1	1	1
High endothelin-1 concentration§ (n=23)	12.4 (3.8)	14*	8	8
Healthy subjects (n=66)	2.9 (1.2)	0	0	Not done

*p<0.05 v patients with systemic lupus erythematosus with normal endothelin-1 concentrations;

***p<0.001 v healthy controls.

†Proteinuria >0.5 g/day during some period of the disease. Biopsy done in 13 patients (see text).

‡Plasma endothelin-1 concentration <5.3 pg/ml.

§Plasma endothelin-1 concentration >5.3 pg/ml.

not reach statistical significance, but is interesting. Anticardiolipin antibodies are directed against platelets⁹ and endothelial cells¹⁰ and may contribute to endothelial endothelin-1 production.

The increase of plasma endothelin-1 in patients with systemic lupus erythematosus found in this study suggests that endothelin-1 may play a part in the pathophysiology of systemic lupus erythematosus. The association with nephritis is intriguing, but needs further evaluation.

HEIKKI JULKUNEN
OUTI SAIJONMAA
CAROLA GRÖNHAGEN-RISKA
ANNA-MAIJA TEPPÖ
FREJ FYHRQUIST
Fourth Department of Medicine
Helsinki University Central Hospital
Unioninkatu 38
SF-00170 Helsinki, Finland

- 1 Yanagisawa M, Kurihara H, Kimura S, *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988; 332: 411-5.
- 2 Tomita K, Ujhie K, Nakanishi T, *et al.* Plasma endothelin levels in patients with acute renal failure. *N Engl J Med* 1989; 321: 1127.
- 3 Koyama H, Tabata T, Nishizawa Y, Inoue T, Morii H, Yamaji T. Plasma endothelin levels in patients with uraemia. *Lancet* 1989; i: 991-2.
- 4 Masaoka H, Suzuki R, Hirata Y, Emori T, Marumo F, Hirakawa K. Raised plasma endothelin in aneurysmal subarachnoid haemorrhage. *Lancet* 1989; ii: 1402.
- 5 Miauchi T, Yanagisawa M, Tomizawa T, *et al.* Increased plasma concentrations of endothelin-1 and big endothelin-1 in acute myocardial infarction. *Lancet* 1989; ii: 53-4.
- 6 Salminen K, Tikkanen I, Saijonmaa O, Nieminen M, Fyhrquist F, Frick M H. Modulation of coronary tone in acute myocardial infarction by endothelin. *Lancet* 1989; ii: 747.
- 7 Tan E M, Cohen A S, Fries J, *et al.* Criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
- 8 Fyhrquist F, Saijonmaa O, Metsärinne K, Tikkanen I, Rosenlöf K, Tikkanen T. Raised plasma endothelin-1 concentration following cold pressor test. *Biochem Biophys Res Commun* 1990; 169: 217-21.
- 9 Harris E N, Gharavi A E, Boey M L, *et al.* Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 1983; ii: 1211-4.
- 10 Carreras L O, Vermeylen J G. Lupus anticoagulant and thrombosis: possible role of inhibition of prostacyclin formation. *Thromb Haemost* 1982; 48: 28-40.

Mycoplasmas and human arthritis

Sir: The recent recovery of *Mycoplasma incognitus*¹⁻² and mycoplasmas from HIV infected patients draws attention again to the possible role of mycoplasmas in human disease.

The veterinarians have long known that animal mycoplasmas are a cause of joint symptoms, which sometime develop into a chronic stage.^{3,4} At least 13 mycoplasma species have been implicated.

In man, also, *Mycoplasma hominis*,⁵⁻⁸ *M. salivarium*,⁹ *M. pneumoniae*,¹⁰⁻¹⁴ and *Ureaplasma urealyticum*^{15,16} have been found in the joint fluid specimens from patients, some of them with hypogammaglobulinaemia. In one case ciprofloxacin and doxycycline seemed to be equally effective in producing a clinical response.⁸

M. arthritis strain Campo, previously called *M. hominis* type 2, was first isolated by Dienes in 1948 when he was studying urethral specimens from patients with polyarthritis.¹⁷ It was also found by Bartholomew in a synovial fluid specimen¹⁸ and by Brown *et al.* in pleural effusion of rheumatoid arthritis.¹⁹ In Finland this same mycoplasma species was found in synovial fluid and tissue specimens of several arthritic patients, whereas control specimens from traumatic joint lesions were negative.²⁰⁻²² In the polyacrylamide gel electrophoresis performed in our laboratory we found that the strain isolated earliest, 20-P, had a protein pattern similar to that of the *M. arthritis* strain PG 6 and, especially, strain Campo.

The possibility that mycoplasmas are aetiological triggers in human arthritis remains unresolved.

ELLI JANSSON
KATI HAKKARAINEN
ARI MIETTINEN
KARI KAITILA
MATTI KARPPÉLIN
University of Tampere
Department of Biomedical Sciences
Post Box 607
33101 Tampere
Finland

- 1 Lo S C, Shih J W, Newton P B III, *et al.* Virus-like infectious agent (VLIA) is a novel patho-

- genic mycoplasma: *Mycoplasma incognitus*. *Am J Trop Med Hyg* 1989; 41: 586-600.
- 2 Lo S C, Dawson M S, Wong D M, *et al.* Identification of *Mycoplasma incognitus* infection in patients with AIDS: an immunohistochemical, in situ hybridization and ultrastructural study. *Am J Trop Med Hyg* 1989; 41: 601-16.
- 3 Washburn L R, Ramsay J R. Experimental induction of arthritis in LEW rats and antibody response to four *Mycoplasma arthritis* strains. *Vet Microbiol* 1989; 21: 41-55.
- 4 Kirchhoff H, Binder A, Runge M, *et al.* Pathogenetic mechanisms in the *Mycoplasma arthritis* polyarthritis of rats. *Rheumatol Int* 1989; 9: 193-6.
- 5 Taylor-Robinson D, Thomas B J, Furr P M, *et al.* The association of *Mycoplasma hominis* with arthritis. *Sex Transm Dis* 1983; 10 (suppl 4): 341-4.
- 6 McDonald M I, Moore J O, Harrelson J M, *et al.* Septic arthritis due to *Mycoplasma hominis*. *Arthritis Rheum* 1983; 26: 1044-7.
- 7 Madoff S, Hooper D C. Nongonitourinary infections caused by *Mycoplasma hominis* in adults. *Rev Infect Dis* 1988; 10: 602-13.
- 8 Sneller M, Wellborne F, Barile M F. Prosthetic joint infection with *Mycoplasma hominis*. *J Infect Dis* 1986; 153: 174-5.
- 9 So A K L, Furr P M, Taylor-Robinson D, *et al.* Arthritis caused by *Mycoplasma salivarium* in hypogammaglobulinaemia. *BMJ* 1983; 286: 762-3.
- 10 Weinstein M P, Hall C B. *Mycoplasma pneumoniae* infection associated with migratory polyarthritis. *Am J Dis Child* 1974; 127: 125-6.
- 11 Taylor-Robinson D, Gumpel J M, Hill A, *et al.* Isolation of *Mycoplasma pneumoniae* from the synovial fluid of a hypogammaglobulinaemic patient in a survey of patients with inflammatory polyarthritis. *Ann Rheum Dis* 1978; 37: 180-2.
- 12 Johnston C L W, Webster A D B, Taylor-Robinson D, *et al.* Primary late-onset hypogammaglobulinaemia associated with inflammatory polyarthritis and septic arthritis due to *Mycoplasma pneumoniae*. *Ann Rheum Dis* 1983; 42: 108-10.
- 13 Davis C P, Cochran S, Lisse J, *et al.* Isolation of *Mycoplasma pneumoniae* from synovial fluid samples in a patient with pneumonia and polyarthritis. *Arch Intern Med* 1988; 148: 969-70.
- 14 Murray B J. Nonrespiratory complications of *M. pneumoniae* infection. *Am Fam Physician* 1988; 37: 127-30.
- 15 Stuckey M, Quinn P A, Gelfand E W. Identification of *Ureaplasma urealyticum* (T-strain mycoplasma) in a patient with polyarthritis. *Lancet* 1978; ii: 917-20.
- 16 Webster A D B, Taylor-Robinson D, Furr P M, *et al.* Mycoplasma (ureaplasma) septic arthritis in hypogammaglobulinaemia. *BMJ* 1978; i: 478-9.
- 17 Dienes L, Ropes M V, Smith W E, *et al.* The role of pleuropneumonia-like organisms in genitourinary and joint disease. *N Engl J Med* 1948; 238: 509-15.
- 18 Bartholomew L E. Characterization of mycoplasma strains and antibody studies from patients with rheumatoid arthritis. *Ann NY Acad Sci* 1967; 143: 522-34.
- 19 Brown T McP, Bailey J S, Clark H W. Mycoplasma in pleural effusion of rheumatoid arthritis. In: *International congress on rheumatology*. Vol XIII. Amsterdam: Elsevier/Excerpta Medica, 1973: 172. (International congress series No 299.)
- 20 Jansson E, Mäkisara P, Vainio K, *et al.* Further studies on mycoplasma in rheumatoid arthritis. *Acta Rheumatologica Scandinavica* 1971; 17: 227-35.
- 21 Jansson E, Miettinen A, Hakkarainen K, *et al.* Cultivation of fastidious mycoplasmas from human arthritis. *Z Rheumatol* 1983; 42: 66-9.
- 22 Jansson E, Backman A, Hakkarainen E, *et al.* Mycoplasmas and arthritis. *Z Rheumatol* 1983; 42: 315-9.