putative inhibitor brought about by volume depletion. We would, however, question the criticisms of our study. We did not use verapamil in view of quoted evidence for actions other than calcium channel blockade.

We are uncertain of the relevance of the study of Pang and Sperelakis, which showed that cell uptake of nifedipine was lower than that of verapamil over 120 minutes. Our study was based on subjects exposed to the drug for three months. There is no more reason to believe that the effects of nifedipine are "dependent on a continued presence in the extracellular fluid" than are the effects of verapamil: until more direct evidence is available their suggestion must remain purely speculative.

We were aware of problems over degradation of nifedipine when exposed to ultraviolet light. There is controversy about the rapidity with which this occurs: it seems that nifedipine is stable in plasma under fluorescent light for 60 minutes.² Nevertheless, we took the precaution of studying subjects taking nifedipine entirely under a sodium light source to see if this influenced results. There was no difference in efflux rate constants under fluorescent light and sodium light (mean efflux rate constant (1 h): total 1.86 v 1.81; ouabain sensitive 1.23 v 1.13; ouabain insensitive 0.63 v 0.68).

Although the unpublished *in vitro* studies of Dr Gray and others may throw a new light on the changes in leucocyte transport, they do not in any way affect our conclusion that inhibition of the leucocyte sodium pump is not a manifestation of a necessary pathogenetic abnormality in essential hypertension.

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Metabolism of narcotics

SIR,—The reports (5 February, p 438; 10 September, p 751) and correspondence (19 November, p 1547) on prolonged narcosis due to dihydrocodeine overdose expose a fundamental misconception about the metabolism of some narcotics. For morphine, codeine, and dihydrocodeine it is generally considered that a plasma clearance approaching the hepatic blood flow (21 ml/min/kg) means that these compounds are mainly metabolised by the liver and that drug removal by other organs is relatively insignificant.¹ There is little real evidence for this in man.

Taking morphine as typical, reported values for plasma clearance can vary from very low (4 ml/min/kg)² to very high (33 ml/min/kg)³ values; this defies a simple classification of morphine as a high clearance drug. Indeed the assumptions implicit in high clearance—that hepatic extraction is 70% and that liver failure will result in reduced plasma clearance—have both been shown to be wrong. In a study of patients with cirrhosis compared with volunteers with normal liver function Patwardhan and colleagues showed that moderate or severe cirrhosis made no difference

to the kinetics of morphine.⁴ This agrees with evidence in animal studies that hepatic extraction of morphine is low except at very high plasma morphine concentrations.⁵ Moreover, oral availability of 10 mg doses in man can approach 100%, which is far in excess of the maximum of 30% expected with high hepatic extraction.⁶

Morphine glucuronidation in human liver is optimal at concentrations of 1 mmol/l,⁷ orders of magnitude above usual plasma concentrations. So where is the morphine metabolised? The kidney is an obvious candidate, and indeed rabbit tubule can both accumulate and glucuronidate morphine at concentrations below 700 nmol/l,⁸ in the range of concentrations observed during morphine treatment in man. The human kidney also plays a part in morphine metabolism. During and after transplantation of a kidney from a live related donor, plasma morphine concentrations remain on a plateau for up to six hours and do not fall until the transplanted kidney begins to excrete creatinine after a period of cold ischaemia.²

The prolonged narcosis with dihydrocodeine overdose in renal failure can therefore be explained without invoking any hepatic dysfunction. Therapeutic overdosage should be expected with drugs in the morphine series when a fixed dose interval is used in the presence of renal insufficiency.

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The pathogenesis of cutaneous malignant melanoma

SIR,—Professor Rona M MacKie's leading article on the pathogenesis of cutaneous malignant melanoma (26 November, p 1568) cites a study in England and Wales that "detected clear jumps in incidence two years after a particularly warm summer."¹ That study also showed a considerably higher incidence of malignant melanoma in the south western region for both sexes as compared with Wessex, despite identical hours of sunshine in these two regions. Subsequent correspondence in your columns speculated that the high incidence in south west England might be explained, at least in part, by the geochemical distribution of arsenic.^{2,3} It was suggested that a more detailed epidemiological survey of melanoma and other skin cancers should be undertaken in this area.²

Arsenic combines with sulphhydryl groups in

body tissues and interferes with pyruvate-oxidase activity. It is associated with cancers of the skin.⁴ With the help of the South Western Regional Health Authority cancer registry, we have recently looked for evidence of geographical clustering for the incidence of cutaneous malignant melanoma associated with the geochemical distribution of arsenic. Geographical clustering of male cases was found at local authority district level and was positively associated with the geochemical distribution of arsenic within the South Western region.⁵ No such association was found for female cases. These findings suggest that there could be sex specific differences in the aetiology of malignant melanoma or, if arsenic is a causative factor, that there may be differences between the sexes for total body exposure to arsenic.

We have used the same method to study cases of squamous cell cancer of the skin in the South Western region. For both sexes squamous cell cancers showed differences in geographical and body site distributions as compared with malignant melanoma. The distributions suggested that exposure to sunshine was likely to be the principal causative factor.

We are planning a case-control study in an attempt to clarify the role of arsenic.

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Arthropathy induced by beta blockade

SIR,—Dr Jaakko Savola (29 October, p 1256) describes 18 patients who developed an arthropathy that was ascribed to treatment with beta blockers. The criteria used to identify cases thought to be caused by treatment were the occurrence of joint symptoms during administration of some beta blocking agent and the disappearance of these symptoms on discontinuation of the drug. In addition, other causes of arthropathy were excluded by radiology and serological tests for rheumatoid disease.

The development of an illness resembling idiopathic systemic lupus erythematosus may be induced by beta blocking agents.¹⁻³ Despite the fact that Raynaud's phenomenon and symptoms of sicca syndrome were common in Dr Savola's patients, no specific mention was made of the incidence of positive anti-nuclear antibodies in his patients. The article also fails to mention the time lapse between withdrawal of the drug and disappearance of the symptoms. Furthermore, there are no data concerning rechallenge of the patients with the original agent; this ideally should be done in a double blind fashion.

In the absence of these pieces of vital information it is perhaps unwise to draw any definite conclusions on the role of beta blocking agents in the transient arthropathies in these patients.

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* *The author replies below.—Ed, *BMJ*.

SIR,—Antinuclear antibodies were tested for in one third of the patients; all results were negative.

In arthropathy induced by beta blocker the symptoms disappeared within four to 14 days of stopping all treatment with beta blockers. In connection with a study like this I do not think that I can submit my patients to a rechallenge with the original agent, which I believe causes severe adverse reactions. I have already observed several cases in clinical practice in which joint symptoms that developed during previous treatment with beta blockers (withdrawn because of these side effects) reappeared when the treatment was restarted.

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Colitis associated with non-steroidal anti-inflammatory drugs

SIR,—Further to the report of Mr R I Hall and others (22 October, p 1182) and the subsequent correspondence (26 November, p 1626) we report a case of colitis associated with ingestion of a non-steroidal anti-inflammatory drug. The patient was a 26 year old man with a six year history of ulcerative colitis who developed bloody diarrhoea one day after taking six Proflax (ibuprofen 200 mg) tablets for arthritis.

The growing volume of anecdotal reports linking relapse of ulcerative colitis with ingestion of analgesics suggests, but does not prove, that these drugs may in some way be harmful to the colonic mucosa. There seem to be two patterns of association between non-steroidal anti-inflammatory drugs and colitis. The onset of diarrhoea seen in patients without prior colitis who take mefenamic acid seems to occur after several months' ingestion. By contrast, the apparent precipitation of relapse of pre-existing ulcerative colitis by non-steroidal anti-inflammatory drugs may occur rapidly.¹ Before it is concluded that both are due to the same mechanism, and that this entails inhibition of prostaglandin synthesis, it is worth recalling that paracetamol is one of the few individual drugs ingestion of which has been associated both with relapse of ulcerative colitis and with the development of upper gastrointestinal bleeding.^{2,3} In neither case is it likely that inhibition of prostaglandin synthesis is involved, as paracetamol is not a recognised inhibitor of gastrointestinal mucosal prostaglandin synthesis, and in both cases the

ingestion may represent a consequence rather than a cause of the disease.

Finally, these observations are at variance with the preliminary report of the efficacy of flufenamic acid in the treatment of ulcerative colitis, reported by Rachmilewitz and his colleagues,⁴ and it would be valuable to know the final results of their trial.

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¹ Rampton DS, Sladen GE. Relapse of ulcerative proctocolitis during treatment with non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1981;57:297-9.

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Acute hypotensive response to nifedipine added to prazosin

SIR,—Although we agree with Dr L D Jee and Professor L H Opie (19 November, p 1514) that use of prazosin and nifedipine in combination should be carefully monitored, we wish to make the following observations.

It is not clear from the report whether the doses of prazosin were single or part of a continuing regimen. If the prazosin was administered as a single dose then its maximum effect would occur after about three hours, particularly in the standing position,¹ and it alone may have produced an acute postural hypotensive response whether or not nifedipine was added during this time. If prazosin was part of a steady state antihypertensive regimen, which included, in case 1, atenolol and a thiazide diuretic, it is surely not possible to selectively incriminate prazosin.

Similarly, in case 2, it appears that two separate doses of 2 mg prazosin were given, but blood pressure was recorded only in the supine position. It does not seem surprising that the subsequent addition of nifedipine in a large sublingual dose resulted in a dramatic reduction in blood pressure.

We believe that concurrent administration of calcium antagonists and alpha receptor antagonists may be rational combinations that have useful therapeutic activity in some patients with hypertension. The combination of prazosin (1 mg) with another calcium antagonist, verapamil (160 mg), given acutely has a considerably greater hypotensive effect than either drug given alone. The reduction in blood pressure is not as dramatic as that described by Dr Jee and Professor Opie but is greater than a simple additive effect of the two agents given separately. In normotensive subjects the mean arterial pressure (mm Hg) (mean (SD)) over an eight hour study period was as follows—supine, 84 (2) with placebo, 84 (2) with verapamil, 82 (3) with prazosin, and 78 (4) with the combination: standing 91 (2) with placebo, 93 (3) with verapamil, 86 (6) with prazosin, and 79 (7) with the combination.

Although there may be pharmacodynamic factors underlying an interaction between alpha₁ adrenoceptor antagonists and calcium channel blockers, perhaps related to differential effects on peripheral alpha₁ and alpha₂

receptors in vascular smooth muscle,² or to interference with compensatory reflex mechanisms, it is important to exclude a pharmacokinetic interaction. Both nifedipine and verapamil, like prazosin, are extensively metabolised in the liver and subject to considerable and variable first pass metabolism. In our study of normotensives we found that the area under the concentration time curve for prazosin was increased by more than half when verapamil was administered concurrently, indicating a substantial increase in the systemic availability of prazosin and thus higher plasma prazosin concentrations and a greater hypotensive effect.¹ A similar pharmacokinetic explanation may underlie the hypotensive responses in the patients described by Dr Jee and Professor Opie.

Whatever the underlying mechanism, the combination of a calcium antagonist with prazosin has pronounced antihypertensive activity that may be useful in patients not controlled on simple regimens. We suggest that the combination has potentially useful antihypertensive activity and warrants further controlled evaluation.

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¹ Elliott HL, McLean K, Sumner DJ, Meredith PA, Reid JL. Immediate cardiovascular responses to oral prazosin—effects of concurrent beta-blockers. *Clin Pharmacol Ther* 1981;29:303-9.

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* *The authors reply below.—Ed, *BMJ*.

SIR,—We thank Dr Elliott and his colleagues for their instructive comments. Due to limitations of space, not all clinical details could be included in our report.

In case 1 prazosin (10 mg twice daily), atenolol (100 mg daily), and thiazide (one Moduretic tablet daily) formed a continuing regimen that failed to control the patient's blood pressure adequately. As mentioned in the text, a similar response was also seen after atenolol had been removed for six weeks, thus excluding the possibility of an interaction of beta blockade and nifedipine. An interaction between nifedipine and the thiazide diuretic is also unlikely, as after the first episode of severe hypotension, the patient was treated for a month on a regimen of atenolol, thiazide, and nifedipine, which also failed to control his blood pressure until prazosin was re-introduced, when the postural hypotension resulted and led to the series of drug challenges given in our report.

In case 2, although the dose of nifedipine was relatively large (20 mg twice daily), the patient had been taking this dose twice daily for some months before his admission. Before that he had received prazosin 5 mg twice daily also for months, again without any hypotensive reaction. Only when prazosin and nifedipine were introduced together did a serious drop in blood pressure occur.

As all our acute doses of nifedipine were administered sublingually, and prazosin orally, it is unlikely that any meaningful hepatic pharmacokinetic interactions were at play. The sublingual route may, however, have resulted in greater systemic availability of nifedipine,