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several cases in clinical practice in which joint symptoms that developed during previous treatment with beta blockers (withdrawn because of these side effects) reappeared when the treatment was restarted.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 Proflex (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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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 $alpha_1$ adrenoceptor antagonists and calcium channel blockers, perhaps related to differential effects on peripheral $alpha_1$ and $alpha_2$ 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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**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,