A recent review¹ has suggested that reports of gold salts being inhibitory to adjuvant arthritis following parenteral administration may be explained by counterirritancy. While we cannot completely preclude this possibility, the following points seem relevant. The injection sites were examined daily and no signs of irritation or necrosis were observed, the animals were not distressed, and there were no adverse effects on bodyweight gain. NATM had no effect on the acute indomethacin-sensitive inflammation at day 3, but the secondary arthritis was inhibited in a dose-dependent manner, with the activity being maintained for 14 days after cessation of dosing. Finally, the systemic non-inflammatory disease was modified, with NATM reversing the thymic regression and splenic hypertrophy seen in adjuvant arthritic rats.

These results are similar to those obtained by Walz *et al.*,⁴ who in addition showed a correlation between antiarthritic activity and serum gold levels. It appears that under certain conditions adjuvant-induced arthritis in the rat can be used to evaluate the efficacy of gold salts.

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Hypogammaglobulinaemia associated with gold therapy

SIR, The recent report of two patients with hypogammaglobulinaemia associated with gold therapy¹ prompts me to report the case of a man with seronegative rheumatoid arthritis who developed hypogammaglobulinaemia while on gold therapy. The development of hypogammaglobulinaemia coincided with a complete clinical remission. His immunoglobulin levels have returned to normal, and he has remained in remission for nearly five years.

The patient was well until 1976 when at age 46 he developed a symmetrical polyarthritis. The latex fixation test was negative. In April 1978 despite salicylate therapy and naproxen 250 mg twice a day, he still had persistent

Table 1 Serum immunoglobulins

Date	Serum			Total dose of gold (mg)
	IgG	IgA	IgM	
4 May 1978	20.98	2.11	1.17	60
8 Aug 1978	12.91	1.12	0.61	735
6 Dec 1978	6.1	0.26	0.19	1200
4 Jan 1980	3.52	0.20	0.10	1540
27 Feb 1980	4.11	0.82	0.32	
19 Nov 1980	6.91	0.63	0.53	
16 Oct 1984	8.64	1.98	1.03	
Normal (g/l)	5.6-15.12	1.04-4.48	0.66-3.52	(by nephelometer)

active synovitis of the wrists, metacarpophalangeal joints, proximal interphalangeal joints, knees, and metatarsophalangeal (MTP) joints. The latex test was again negative. Radiographs of the hands were normal, but the feet showed small erosions of the right third and left fifth MTP joints. The serum IgG level was raised, and serial levels are shown in Table 1. He was started on sodium aurothiomalate 50 mg intramuscularly (IM) weekly, and by December 1978 he was markedly improved with only synovitis of both wrists. However, serum levels of IgA and IgM had fallen below normal levels. He was continued on gold 25 mg IM monthly and was seen again in January 1980 when he was in complete remission. However, his serum IgG level had fallen below normal. Gold was discontinued as were the salicylates and naproxen, and his immunoglobulin levels returned to normal. No infections occurred during the course of his illness. He remains in clinical remission, and radiographs of his hands and feet remain unchanged.

It is interesting to speculate whether there is a relationship between the development of hypogammaglobulinaemia and the excellent response to gold seen in this patient.

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Non-steroidal anti-inflammatory drugs and adverse renal effects

SIR, We read with interest the report by Sellars *et al.* of the induction of nephrotic syndrome and renal impairment

associated with fenclofenac.¹ Apart from the well known gastrointestinal adverse reactions of the non-steroidal anti-inflammatory drugs it has become increasingly apparent that these agents can cause a number of adverse renal effects, for example, acute renal failure, chronic renal damage, nephrotic syndrome and interstitial nephritis, and also abnormalities of water, sodium, and potassium homeostasis.²

We would like to report our experience with a 66-year-old male patient suffering from rheumatoid arthritis for three years who was taking piroxicam for his arthritis and Moduretic for ankle oedema. As his arthritis was deteriorating piroxicam was stopped and instead he was started on diclofenac 50 mg three times a day and also penicillamine 125 mg a day. Before introduction of these drugs the laboratory investigations showed: white cell count $9.5 \times 10^9/l$, haemoglobin 10.9 g/dl, erythrocyte sedimentation rate 108 mm/h, serum urea 10.3 mmol/l, serum creatinine 96 $\mu\text{mol/l}$, electrolytes and bicarbonate within normal limits. About 10 days later the patient complained of nausea and malaise and his urinary output fell to 500 ml in 24 hours. Investigations revealed normal urinary microscopy, no proteinuria, serum urea 22.3 mmol/l, serum creatinine 160 $\mu\text{mol/l}$, and serum potassium 5.2 mmol/l, but the other electrolytes were within normal limits. A straight x-ray of the abdomen showed no abnormality of the renal outlines. Both penicillamine and diclofenac were stopped, after which the serum urea, creatinine, and potassium gradually fell and returned to normal levels in five days.

Our patient developed uraemia after only 10 days' treatment with diclofenac and penicillamine. Adverse reactions on the kidneys due to penicillamine are usually late events and appear initially with proteinuria.³ We cannot absolutely rule out penicillamine as the offending drug in our patient, but it seems unlikely. A more obvious suspect is diclofenac, as a number of non-steroidal anti-inflammatory drugs have now been reported to cause renal impairment believed due to inhibition of prostaglandins' action in the kidneys.² In any patient who develops unexplained uraemia, especially in the presence of previous renal impairment or during the use of diuretics, a full drug history should be taken, and any non-steroidal anti-inflammatory drug should be withdrawn for a period to see if renal impairment improves, before resorting to further renal work up which may be necessary. Due caution should be exercised in prescribing these drugs to patients who may be liable to renal complications, in particular patients with chronic renal insufficiency, hepatic cirrhosis, cardiac failure, and intravascular volume contraction as a result of either nephrotic syndrome or the use of diuretics.

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Free thiomalate levels in rheumatoid arthritis

SIR, With reference to the recent article by Rudge *et al.*¹ we wish to raise the following points:

- (1) The concluding paragraph states that the methodology devised and employed by us for measuring D-penicillamine is 'unsuitable for human studies'. We have and still are using this method on a routine basis in a large study measuring plasma concentrations of D-penicillamine in patients with rheumatoid arthritis to assess whether any correlations exist between plasma concentration, efficacy, and toxicity. The assay is relatively simple, and on an average day a single person can assay nine samples in duplicate with appropriate standards. To our knowledge this method is the only type that permits such a throughput of samples.
- (2) We feel it is more appropriate to measure total D-penicillamine or indeed any other drug (thiomalate, captopril) of this type rather than the free, reduced form since (a) it is unclear which is the pharmacologically active form(s) of the drug, and (b) even if the free reduced form of penicillamine is the active moiety, the sulphhydryl oxidation reactions which this type of drug undergoes (plasma protein binding, disulphide formation/exchange) are reversible. Hence all forms of the drug and not just the free reduced form are potentially available for pharmacological activity.

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Reference

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SIR, In reply to the above letter from Notarianni *et al.* we entirely agree and have stated previously¹ that studies on the metabolism and pharmacology of thiol-containing drugs should attempt to quantify all individual metabolites. Unlike D-penicillamine where detailed work over two decades by many workers²⁻³ has identified four metabolites, comparable metabolic data for sodium aurothiomalate do not as yet exist. In the paper under discussion we predict that similar metabolites for thiomalate are likely. At present, work is in hand to synthesise these metabolites and develop methods for their chromatographic separation and quantification.