symptom-free relatives of patients with terminal renal disease have an extremely high incidence of underlying renal disease themselves.[25 26] If such be the case then potential female donors should be investigated rigorously, and some aspect of proximal tubular function should be determined.

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Azathioprine and penicillamine in treatment of rheumatoid arthritis: a controlled trial

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Summary

Sixty-five patients, 33 receiving azathioprine and 32 receiving penicillamine, took part in a one-year, single-blind external-observer trial designed to compare the efficacy and toxicity of these two drugs in the treatment of rheumatoid arthritis. By six months there was a significantly greater rise in haemoglobin and fall in erythrocyte sedimentation rate among those receiving penicillamine, and by one year this difference remained only in the increase in haemoglobin levels. Fifteen patients, 10 on azathioprine and 5 on penicillamine, had to stop treatment because of side effects; 90 single side effects occurred, 48 in those on penicillamine and 42 in those on azathioprine. After one year both drugs were similar in efficacy and toxicity, but longer-term trials are needed. Both drugs were effective.

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Introduction

Azathioprine has a steroid-sparing effect in rheumatoid arthritis[1] that has been shown to be greater than that obtained with gold.[2] Less progression in joint erosions was also reported in patients treated with azathioprine.[1 2]

Penicillamine, introduced by Jaffe[3 4] for treating severe rheumatoid arthritis, was later confirmed as an effective agent in a multicentre trial.[5] Subsequently Huskisson *et al*[6] reported that results with penicillamine were comparable to those obtained with gold.

Our trial was designed to determine whether there is any demonstrable difference between azathioprine and penicillamine in efficacy or toxicity in the treatment of rheumatoid arthritis.

Methods

A single-blind external-observer trial was performed at the London Hospital, Notley Hospital, and St Mary's Hospital, Colchester. The trial supervisor (HB), who was aware of the treatment allocation, was responsible for routine management, checking blood tests and urine analysis results, and listing unwanted effects described by the patients. Two blind observers assessed the severity of the disease, the same observer always assessing the same patients (SPL at the London Hospital and RAD at the other centres). In an initial pilot study, their assessments on the same patients correlated closely.

Patient selection—Outpatients at the three centres were admitted to the trial if they were over 18 years old and had definite or classical rheumatoid arthritis,[7] including a positive latex test result (titre of 1/80 or more) and erosive changes on *x*-ray pictures of the hands or feet, or both. The disease had to be severe enough for the clinician to conventionally consider the use of gold. Those patients already receiving systemic corticosteroids were admitted only when the dosage had been constant for at least six months. Criteria for exclusion were: (*a*) previous treatment at any time with azathioprine or penicillamine or with gold salts in the previous six months; (*b*) an abnormally low white cell or platelet count at any time; (*c*) evidence of renal impairment (raised blood urea or serum creatinine concentrations); and (*d*) risk of pregnancy. Informed consent was obtained from all patients at the beginning of the trial.

Drugs—Azathioprine 2·5 mg/kg body weight/day in divided doses was compared with penicillamine 1 g/day reached by 250-mg increments every two weeks. Patients were randomly allocated to either treatment but were stratified for sex and age (45 and under, and over 45) and current corticosteroid treatment. In addition to the trial drugs and corticosteroids (see above) patients continued receiving a regular dose of the anti-inflammatory or analgesic drugs that they had been taking before the trial, the dose of which had to have been unchanged for at least a month. Only paracetamol was allowed in addition. All medication was issued through normal outpatient prescribing channels. Phenylbutazone was not allowed in view of its potential effect on the bone marrow.

Assessments—The following indices were assessed at the beginning of the trial and at three, six, nine, and 12 months: (*a*) pain using the visual analogue scale (VAS)[8]; (*b*) pain using the 4-point scale (1 = nil, 2 = mild, 3 = moderate, 4 = severe); (*c*) articular index[9]; (*d*) ring size (using Geigy ring size measuring device); (*e*) grip strength (bag inflated to 30 mm Hg, repeated three times and taking the sum of the last two readings for each hand); (*f*) early morning stiffness (assessed by the patients in minutes).

Laboratory investigations—Blood counts and erythrocyte sedimentation rates (ESR) were measured at least every three weeks throughout the trial (this included total and differential white counts and platelet counts). Patients were given regular supplies of Albustix to test their urine daily if on penicillamine. They were told to report any abnormality, which was then checked by a midstream specimen of urine, and, when indicated, a 24-hour urine was estimated for protein count. Titred latex tests were performed every three months.

X-ray pictures were taken of the hands and feet on admission to the trial and then at three, six, and 12 months. These were evaluated by two blind observers—namely, a rheumatologist and a radiologist. They assessed the overall condition as severe, moderate, or mild (3, 2, or 1) at the beginning of the trial and at 12 months, and any change in the patient's condition (1 = worse, 2 = much worse, +1 = better, +2 = much better) between 0 and 3 months, 3 and 6 months, and 6 and 12 months.

Procedure—Each patient was seen at least every three weeks throughout the trial by the supervisor. Azathioprine or penicillamine was stopped if the blood count or platelet count fell below the lower limit of the laboratory normal values (platelets 150×10^9/l (150 000/mm^3), white cells 4×10^9/l (4000/mm^3), or neutrophils 2×10^9/l (2000/mm^3)). On recovery the drug was gradually reintroduced and increased to the initial dose. If the unwanted effect recurred the patient was withdrawn from the trial. Withdrawal from the trial occurred when the supervisor thought continuation of treatment represented an unreasonable risk to the patient.

Results

Sixty-five patients were admitted to the trial; 33 received azathioprine (26 women) and 32 received penicillamine (25 women). Fifty completed the trial at 52 weeks (23 on azathioprine, 27 on penicillamine). Four (two on penicillamine, two on azathioprine) were withdrawn because of an increase in disease activity and 11 (three on penicillamine, eight on azathioprine) because of toxic effects. The mean age of all the patients in the trial was 53 years and mean disease duration was 9·7 years (range 6 months to 27 years). There were no significant differences between treatment groups in any measurement at the start of the trial. No significant differences were found between stratification groups in initial measurements or in response to treatment, and this stratification will not be further considered.

All indices in both treatment groups had improved at the end of the trial compared with initial values (the statistics carried out were either paired or grouped *t* tests throughout, as appropriate) (table I).

At nine months six of the patients in the penicillamine group had a flare of disease activity, compared with observations at six months. This was defined as a subjective increase in pain and stiffness which was confirmed objectively by the trial observer as increased inflammatory activity in two or more joints. None had a similar flare on azathioprine treatment. This represented a significant difference between the treatment groups ($\chi^2 = 6{\cdot}91$; $P < 0{\cdot}05$). In the penicillamine group pain was reduced at six months by one unit on the 4-point scale, but there was a significant increase between 6 and 9 months so that by 12 months the two treatments were comparable (fig 1).

Intergroup analysis showed that the improvement in haemoglobin levels and fall in latex titre and ESR were significantly greater in the penicillamine group at six months, but by 12 months only the improvement in haemoglobin levels remained superior on penicillamine (table II and fig 2). Ring size was reduced in both groups by three months. This fall continued on penicillamine throughout the year but no further improvement occurred in the azathioprine-treated patients, although there were no significant differences between the groups (fig 3). Latex titres fell on both treatments (table II), but this fall correlated poorly with other measurements of disease activity, the only significant correlation being with increased grip strength and fall in ESR at six months ($P = 0{\cdot}05$).

X-ray examination in both groups showed deterioration, but there was no difference between treatment groups.

Withdrawals—Ten patients were withdrawn from azathioprine treatment and five from penicillamine treatment (fig 4). Nausea early in the course of the trial was a major cause of withdrawal. This was more of a problem in the azathioprine-treated patients because it was more severe and was not controlled by antiemetics (such as chlorpromazine).

All side effects—Ninety side effects occurred during the study; one patient on penicillamine had five, and one on each treatment had four. There was no significant difference between the treatment groups. Early transient proteinuria occurred in seven patients treated with penicillamine, but no patients developed "late" proteinuria in this

TABLE I—*Clinical results and statistical comparisons between treatments*

	Azathioprine (A)	Penicillamine (P)	Statistics (P values)		
			A*v*P	A *v* initial value	P *v* initial value
		Pain (4 point)			
Initially ..	3·09	3·43	NS		
3 months ..	2·97	2·81	NS	NS	<0·01
6 months ..	2·88	2·53	NS	NS	<0·01
9 months ..	2·75	2·72	NS	NS	<0·01
1 year ..	2·40	2·63	NS	<0·05	<0·01
		Pain (VAS)			
Initially ..	11·30	12·13	NS		
3 months ..	8·93	8·58	NS	0·01	<0·01
6 months ..	8·58	6·17	NS	NS	<0·01
9 months ..	6·83	7·37	NS	<0·01	<0·01
1 year ..	6·04	6·40	NS	<0·01	<0·01
		Articular index			
Initially ..	15·88	14·03	NS		
3 months ..	13·96	11·55	NS	NS	NS
6 months ..	9·88	8·24	NS	<0·01	<0·01
9 months ..	9·29	7·75	NS	<0·01	<0·01
1 year ..	8·22	7·00	NS	<0·01	<0·01
		Ring size (mm)			
Initially ..	593·2	595·9	NS		
3 months ..	583·8	588·2	NS	<0·01	<0·01
6 months ..	583·6	578·0	NS	<0·01	<0·01
9 months ..	579·2	570·7	NS	<0·01	<0·01
1 year ..	581·2	567·2	NS	<0·01	<0·01
		Grip strength (mm Hg)			
Initially ..	464·1	416·6	NS		
3 months ..	505·3	457·6	NS	NS	<0·01
6 months ..	547·2	511·5	NS	<0·01	<0·01
9 months ..	536·8	530·9	NS	<0·05	<0·01
1 year ..	583·9	555·6	NS	<0·01	<0·01
		Morning stiffness (min)			
Initially ..	119·9	113·9	NS		
3 months ..	94·6	49·8	NS	NS	<0·01
6 months ..	81·3	28·8	NS	NS	<0·01
9 months ..	60·9	32·1	NS	<0·05	<0·01
1 year ..	63·2	39·9	NS	NS	<0·01

NS = Not significant.

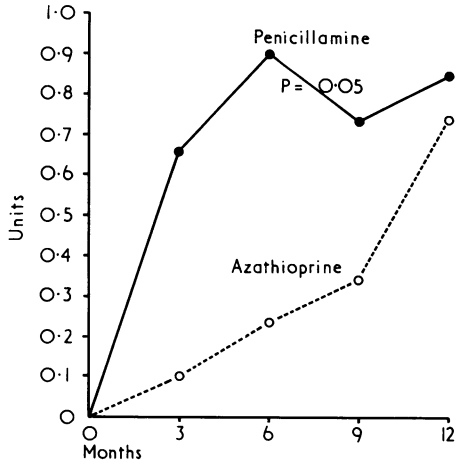

FIG 1—Mean pain relief on both drugs.

TABLE II—*Laboratory results and statistical comparisons between treatments*

	Azathioprine (A)	Penicillamine (P)	Statistics (P values)		
			A *v* P	A *v* initial value	P *v* initial value
		Haemoglobin (g/dl)			
Initially ..	11·89	11·91	NS		
3 months ..	12·08	12·50	NS	NS	0·01
6 months ..	12·25	13·10	<0·05	NS	<0·01
9 months ..	12·49	13·31	0·05	<0·05	<0·01
1 year ..	12·31	13·13	0·05	NS	<0·01
		Latex (titres)			
Initially ..	6·58	6·71	NS		
3 months ..	6·03	5·77	NS	<0·01	<0·01
6 months ..	5·96	4·92	NS	<0·01	<0·01
9 months ..	4·75	4·18	NS	<0·01	<0·01
1 year ..	5·10	3·95	NS	<0·01	<0·01
		ESR (mm in 1 h)			
Initially ..	57·5	57·7	NS		
3 months ..	49·3	39·6	NS	NS	<0·01
6 months ..	44·5	30·1	<0·05	0·01	<0·01
9 months ..	42·2	32·1	NS	<0·01	<0·01
1 year ..	40·6	33·2	NS	0·01	<0·01

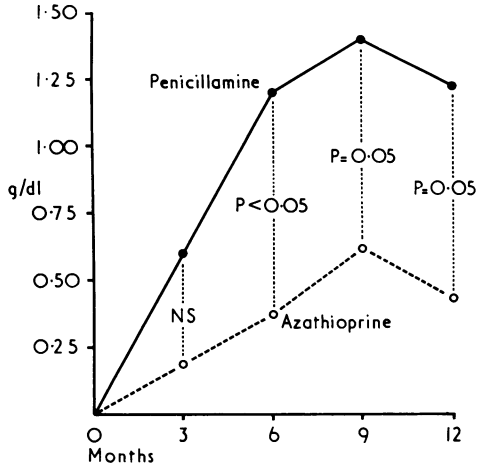

FIG 2—Improvement in haemoglobin concentrations.

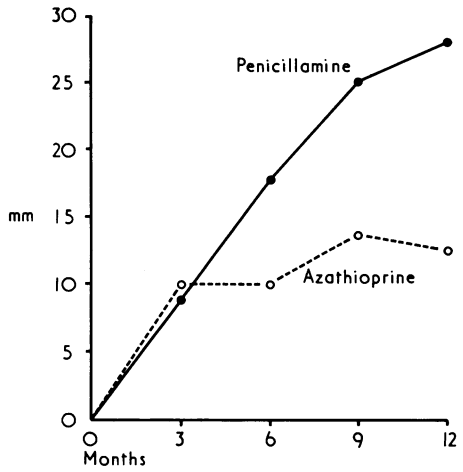

FIG 3—Mean reduction in ring size.

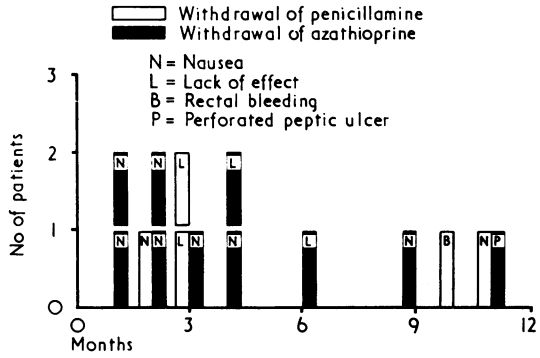

FIG 4—Times of and reasons for withdrawal.

TABLE III—*Numbers of side effects in both groups*

	Azathioprine	Penicillamine
Nausea	16	9
Indigestion	5	3
Abdominal pain	1	4
Sore throat	1	0
Taste loss	0	10
Diarrhoea	2	4
Proteinuria (transient)	0	7
Thrombocytopenia	3	2
Neutropenia	4	0
Rash	2	4
Irritation	3	1
Mouth ulcers	2	3
Sore tongue	1	0
Breast enlargement	1	0
Angio-oedema	1	1
Total* ..	42	48

*Azathioprine *v* penicillamine: $\chi^2 = 2{\cdot}17$; not significant.

trial at nine months. Ten patients on penicillamine transiently lost their sense of taste. One woman developed breast enlargement on azathioprine, and a rash in one patient on penicillamine was pemphigoid in nature (table III).

Discussion

When all patients had completed six months penicillamine seemed to have the greater advantage, but there were large standard deviations in all measurements, which indicated a wide variation in response. A few patients receiving penicillamine showed an increase in disease activity between six and nine months. This had also been noticed by Jaffe.[10] By one year the patients in both treatment groups showed comparable improvement.

The finding that both drugs are equally effective and have similar toxic effects indicates the need for long-term studies into dosage and toxicity. Dixon *et al*[11] suggest that 600 mg penicillamine is as effective as 1200 mg and less toxic. Urowitz *et al*[12] have indicated that azathioprine 1·1 mg/kg body weight/day may be as effective as 2·2 mg/kg/day.

This study confirmed the incidence of toxic effects on both drugs, although such unwanted effects as did occur were of nuisance value and resolved spontaneously on stopping the drug. Nausea was a common problem in this study, particularly on azathioprine, and seemed to be more common than in other studies. We did not encounter heavy proteinuria in the penicillamine-treated patients.

The fear of malignancy in patients receiving cytotoxic drugs has not yet been dispelled,[13] and, if confirmed, may be found to be related to length of exposure. In the long term the study organised by Kinlen[14] should provide the answer.

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