tuberculous arthritis, to gout, or to a variant of the so-called seronegative peripheral arthritis as seen in Reiter's disease, arthritis associated with gastrointestinal disease, psoriasis, and ankylosing spondylitis. In all these conditions, however, the involvement of the proximal interphalangeal joint is uncommon, with exception of tuberculous arthritis where the tumor albus or spina ventosa are typical examples. Polyarthritis of the small hand joints was seen in four paintings. Polyarthritis was only present or visible in one hand and not with certainty in the other hand. The feet were only visible in one painting and there they were normal. So no convincing evidence of symmetrical rheumatoid arthritis is found. Except for one case, all observed arthritis cases were males, which is in contrast to the male/female ratio of rheumatoid arthritis.

Although I looked for arthritis in the work of Breughel, Vandenbosch, Rembrandt, Rubens, and other painters of the Renaissance, no such deformities were found.

Immunostimulant therapy for rheumatoid arthritis. E. C. Huskisson, P. A. Dieppe, Jane Scott, Jane Trapnell, H. W. Balme, and D. A. Willoughby (*St. Bartholomew's Hospital, London*)

If rheumatoid arthritis is a chronic inflammatory response maintained by a persistent antigen, it is as logical to stimulate the immune system in the hope of removing the antigen as it is to suppress it in the hope of stopping the reaction which follows. Therefore considerable interest has been shown in the possible use of levamisole and a report of its effectiveness in an uncontrolled study (Schuermans, 1975).

34 patients with active rheumatoid arthritis were studied. 12 received at least 3 months' treatment with levamisole (50 mg tds), 12 with penicillamine, and 10 with placebo; treatments were not identical. Before assessment, patients were stabilized on an analgesic and anti-inflammatory regimen which remained constant during the study. Measurements were carried out before and at 3-monthly intervals after the start of the treatment by a 'blind' observer who was unaware of the treatment and with whom the side effects were not discussed. Measurements included pain (visual analogue scale), duration of morning stiffness, articular index, and proximal interphalangeal joint circumference. Weekly measurements of pain relief were made by the patient. ESR, tests for rheumatoid factor, and immunoglobulins were measured at 3-monthly intervals. At these times

delayed hypersensitivity to tuberculin was assessed by skin tests and by leucocyte migration inhibition.

After 3 months' treatment there was significant pain relief in both penicillamine and levamisole groups compared to placebo, and both produced significant reduction in ESR (Table). Both drugs worked slowly. There was a trend towards enhancement of skin tests and greater leucocyte migration inhibition in patients on levamisole than in those on placebo. These changes showed a significant correlation with pain relief ($r=0.44$, $P<0.05$ for skin tests, $r=0.4$, $0.1>P>0.05$ for leucocyte migration inhibition). It is suggested that levamisole has activity of the type shown by penicillamine in rheumatoid arthritis.

Reference

SCHUERMANS, Y. (1975) *Lancet*, 1, 111

Penicillamine in rheumatoid arthritis: comparison of two dose schedules. A. G. S. Hill and H. F. H. Hill (*Stoke Mandeville Hospital*)

The UK controlled trial (Multi-centre Trial Group, 1973) proved the superiority of penicillamine over placebo in a group of patients with advanced persistently active rheumatoid arthritis. It did not attempt to define its use in rheumatological practice, either in terms of selection of patients or dose. Day *et al.* (1974) and Hill (1974) suggested that side effects were less common if the drug was introduced slowly and the maintenance dose was the lowest which produced a satisfactory response.

This study compared two dose regimens in patients with disease which had been persistently active for months or years. Penicillamine (base) was added to the existing anti-inflammatory regimen when the latter had failed to halt disease activity. All patients had poly-articular synovitis and raised sedimentation rate (ESR) and a positive test for C-reactive protein. Vasculitis in the form of skin lesions and peripheral neuropathy were present in some patients and were taken as an additional indication for treatment. Patients were aged between 32 and 67 and the duration of disease was from 9 months to 21 years.

Group 1 In 21 patients the regimen used in the controlled trial (Multi-centre Trial Group, 1973) was adopted, namely 250 mg penicillamine daily increased by 250 mg every 2 weeks until the dose was 1500 mg at which it was held for 6 months. Thereafter the dose was decreased by 250 mg not more often than every 2 months, the final maintenance dose being the lowest which maintained remission.

Group 2 In 22 patients the dose of penicillamine was increased more slowly from the same initial dose of 250 mg. Subsequent increments of 250 mg were made at monthly intervals until the dose was 750 mg at which it was held for a minimum of 3 months. Thereafter further increments of 250 mg were made if disease activity persisted, but always at intervals of not less than 3 months.

The duration of follow-up (October 1975) was 22–30 months in group 1, 12–24 months in group 2.

Table Changes in clinical measurements and ESR after 3 months' treatment with levamisole, penicillamine, and placebo

	Pain	DMS	Joint size	Articular index	ESR
Levamisole	+8.8*	+25.6	+11.3	+5.3	+27.3*
Penicillamine	+6.1*	+116.3*	+14.3*	+5.6	+35.2*
Placebo	+0.3	+10.0	+1.6	+3.4	–1.8

Positive figures indicate improvement. *Denotes statistically significant difference between active drug and placebo ($P<0.05$).

Group 1. Dose increments of 250 mg every 2 weeks to a maximum of 1500 mg daily

Of the 21 patients, 2 developed anorexia and stopped treatment before attaining a dose of 750 mg. Of the remaining 19, disease activity decreased in 18, the drug being ineffective in only 1 patient. 3 patients with vasculitis all improved, skin lesions disappeared, and the extent of the peripheral neuropathy decreased. One patient died from a cerebrovascular accident unrelated to treatment. Side effects were common, only 3 patients had none (Table). Only 8 patients continue, 2 maintained at 100 mg; 1 relapses if the dose is dropped below 1500 mg.

Group 2. Dose increments of 250 mg every 4 weeks to a maximum of 750 mg

The 22 patients on this regimen had fewer side effects, a total of 13 being recorded, but all 13 have been withdrawn (Table). Active synovitis has decreased in all these patients but the response has been less dramatic than in Group 1. 6 have been successfully maintained on 750 mg, but in 2 the maintenance dose is 1250 mg.

Six patients with vasculitis improved and skin lesions have disappeared or are less numerous, the extent of the peripheral neuropathy has decreased in 3 patients who had this additional manifestation of vasculitis. In particular gastrointestinal upsets have been rare, 1 patient reported mild vagaries of taste and 1 transient nausea with vomiting. Results in both groups are shown in the Figure and the Table.

Group 1

			Side-effects	
			present	none
43 patients	21 patients	→ 8 continue → 13 withdrawn	8	3
	22 patients	→ 8 continue → 15 withdrawn	13	10

Group 2**Table**

Side effects	Group 1 (21 patients)	with- drawn	Group 2 (22 patients)	with- drawn
Thrombocytopenia (platelets < 100 000 withdrawn if < 70 000)	6	3	2	1
WBC < 3000	1	1	0	0
Proteinuria (withdrawn when > 2g/24 h)	3	2	10	9
Rash				
Early (all temporarily with- drawn, all restarted without recurrence of rash)	1	1	0	0
Late	2	2	4	4
Oral ulcer	2	1	0	0
Recurrent nausea and diarrhoea	1	0	0	0
Severe anorexia	2	2	0	0
Transient nausea	0	0	1	0
Severe dyspepsia and recurrence of peptic ulcer	2	2	0	0

Penicillamine is a potentially hazardous drug and thrombocytopenia and proteinuria occur in a significant number of patients. Thrombocytopenia may occur in the early or late months of treatment but proteinuria has been more common after 6 or more months of therapy, hence continued vigilance is essential. Gastrointestinal side effects, some sufficiently severe to enforce withdrawal of penicillamine, were common in group 1 as were withdrawals for thrombocytopenia. The lower incidence of side effects in group 2 suggests that monthly increments are associated with fewer side effects, but the optimum maintenance dose must be found for each patient according to clinical and laboratory indices of activity.

References

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Trial comparing azathioprine and penicillamine in treatment of rheumatoid arthritis. H. Berry, S. Liyanage, R. Durance, C. G. Barnes, and L. Berger (*The London Hospital and St. Mary's Hospital, Colchester*)

A 'single blind' external observer trial has been carried out in two centres to compare penicillamine and azathioprine in the treatment of rheumatoid arthritis. One person supervised all patients in the trial and one 'blind' observer was employed in each centre. The length of the trial was 1 year.

65 outpatients were admitted to the trial. All had erosive, seropositive disease at a stage where gold therapy would conventionally be considered. If the patients were receiving corticosteroid therapy, a stable dosage for the previous 6 months without alteration during the trial was the accepted policy. The patients had to remain on constant anti-inflammatory-analgesic therapy, the only other drug allowed being paracetamol.

Azathioprine 2.5 mg/kg body weight dispensed on ordinary prescription as 50 mg tablets and penicillamine 250 mg tablets were similarly prescribed; penicillamine tablets were initially taken 1 a day, increasing by 1 tablet every 2 weeks to 1 g, i.e. 4 tablets a day. 33 patients received azathioprine, 32 penicillamine tablets.

Assessments were carried out on admission to the trial, then every 3 months. Articular index (Ritchie), early morning stiffness, 'Geigy' ring size, and grip strength were measured and pain was evaluated using the visual analogue scale (VAS) and the 4-point scale. Investigations included a full blood count, ESR, and weight. X-rays were taken on admission to the trial then at 3, 6, and 12 months. These were assessed by 2 'blind' observers, a clinician (C.G.B.), and a radiologist (L.B.). Toxic effects were sought by direct questioning; a check list was not used.

The initial values and change at 6 months (as a + or - figure) for each measure is as follows (a = azathioprine; p = penicillamine):