# Rheumatoid Arthritis Treated with Small Doses of Penicillamine

by Dr J R Golding, Dr A T Day,
Dr M R Tomlinson, Dr R M Brown,
Dr M O Hassan and Miss S R Langstaff
*(St James Hospital, Leeds and Royal Bath Hospital, Harrogate, Yorkshire)*

Our early work on penicillamine in rheumatoid arthritis, using a starting dose of 250 mg base and increasing to 1500 mg or 2 g daily over about eight weeks, resulted in an improvement in many patients, but with an unacceptable pattern of adverse reaction in about one-third (Golding *et al.* 1970). Some two years ago we considered the possibility of using penicillamine at an earlier stage of the disease and in a lower dosage. Such an application of the drug might be effective and we hoped that the incidence of side-effects would be lowered (Day *et al.* 1974).

*Material and Methods*

We report the results of 127 patients with definite or classical rheumatoid disease, treated for one year with a small dose of penicillamine. All patients had the disease for at least six months before treatment was started, all had progressive disease and had been uncontrolled by anti-inflammatory drugs and a three months' course of antimalarial drugs. All were treated as outpatients.

Penicillamine was started in a dose of 125 mg base daily, and the patients were reviewed at monthly intervals. Early in the trial the dose was increased by 125 mg daily at monthly intervals, but we soon found that it was possible for patients to improve on only 125 mg daily. Our policy now is to hold the dose at 125 mg daily for three months.

The blood and urine were checked weekly for the first month and thereafter at fortnightly intervals. If the patient failed to respond to 500 mg of penicillamine daily he was removed from the trial.

Eighteen patients were lost from the trial by failure to respond to a maximum dose of 500 mg of penicillamine daily. Fifteen patients were lost from toxic reactions.

*Results*

One hundred and nine patients who received penicillamine were analysed. As we included those who had adverse reactions, the balance is against rather than for penicillamine. Clinical analysis was made in the following ways:

*Early morning stiffness:* Table 1 shows the duration of early morning stiffness before starting penicillamine and after one year. Early morning stiffness before starting penicillamine was almost 90 minutes and after one year on penicillamine 15 minutes. This was of dramatic benefit to the patient.

*Table 1*

**Variations in morning stiffness, ESR and hæmoglobin in 109 patients receiving D-penicillamine (DPA) in a dose of 500 mg/day or less for one year**

| | *Mean value* | | |
|---|---|---|---|
| | *Before penicillamine* | *After one year DPA* | *P* |
| Duration of morning stiffness (minutes) | 86.9 s.d. ±61.5 | 14.7 s.d. ±10.6 | < 0.005 |
| ESR (mm in 1 h) (Westergren) | 55.4 s.d. 39.4 | 21.1 s.d. ±15.0 | < 0.0005 |
| Hb (g/dl) | 12.6 s.d. ±0.81 | 13.1 s.d. ±0.93 | < 0.2 (NS) |

*The Steinbroker grade:* Table 2 shows the remarkable improvement in the Steinbroker grade following penicillamine. No patients deteriorated.

Above all, and this cannot be shown in a Table, was the improvement in the patients' sense of well-being. Dr J M Walshe said earlier that the most important clinical question regarding any patient was whether he felt better as a result of the treatment or not. In almost every case our patients said that they felt improved.

*Table 2*

**Steinbroker classification of 109 patients before and after one year on penicillamine 500 mg or less daily**

| *Steinboker grade* | *Before penicillamine* | *After one year of penicillamine* |
|---|---|---|
| I | 0 | 85 |
| II | 96 | 85 |
| III | 13 | 2 |
| Total | 109 | 109 |

*Laboratory parameters – ESR:* The mean value of the ESR before penicillamine was 55 and after one year 21 (Table 1). Fig 1 shows how the ESR may fall after one year with 500 mg of penicillamine daily as compared with 1000 mg or 1500 mg of penicillamine daily, though it must be admitted that patients on the larger amounts probably had more longstanding and more severe disease.

*Hæmoglobin:* This showed only a marginal increase (Table 1). The fact that the mean hæmoglobin level before penicillamine was 12.6 g underlines that many of our patients had only early disease.

*Rose-Waaler test* (*Table* 3)*:* Of 76 patients whose Rose-Waaler test could improve by three tubes or more, 61 achieved this.

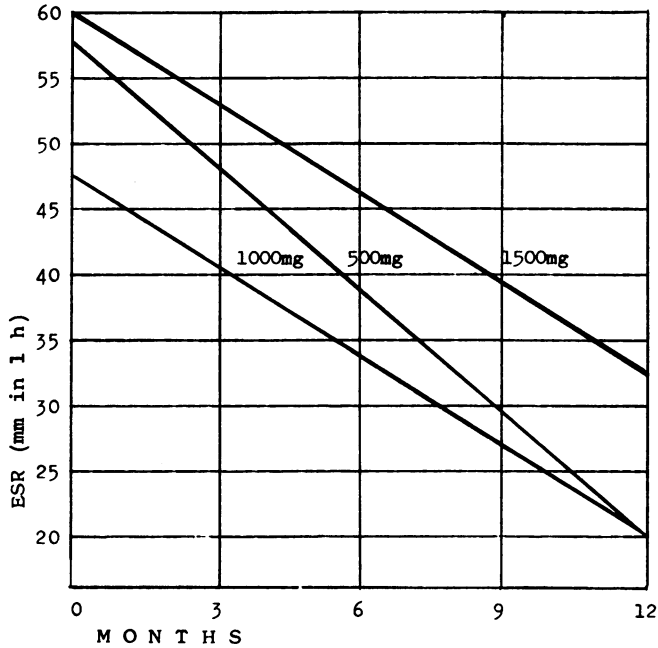


**Fig 1** *Mean ESR (Westergren) at 0 and 12 months in three series with daily doses of* D*-penicillamine 500 mg, 1000 mg, 1500 mg*

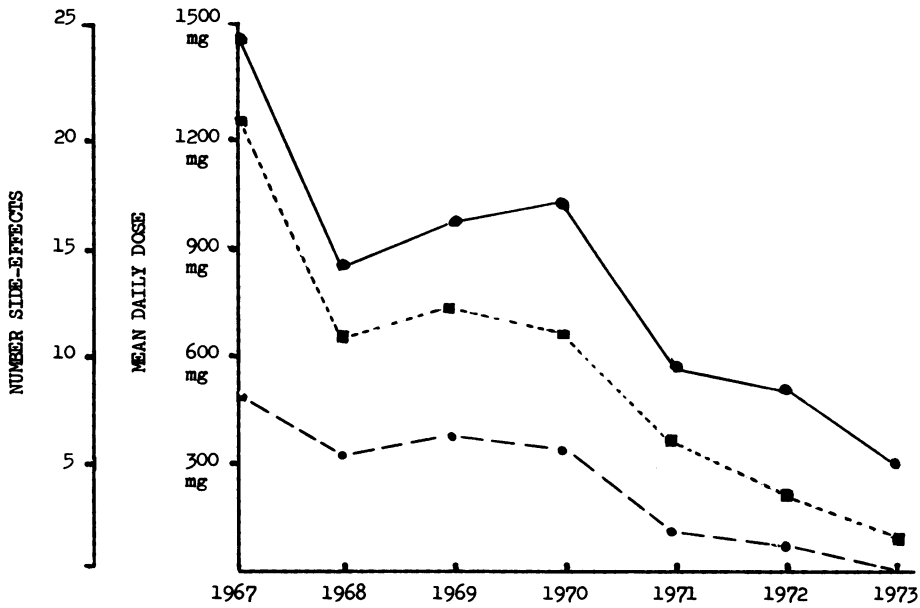


**Fig 2** *Correlation of mean daily dose of penicillamine with side-effects, by year.* ●–● *mean daily dose.* ■– – – ■ *total number of side-effects.* ●— —● *number of side-effects causing withdrawal of penicillamine (after Day* et al. *1974)*

*Table 3*

**Rose-Waaler test before and after one year on penicillamine (DPA) 500 mg/day or less (109 patients)**

| | *No. of patients* | |
|---|---|---|
| | *Positive* | *Negative* |
| Before DPA | 80 | 29 |
| After 1 year DPA | 32 | 77 |

Improvement of 3 tubes or more: 61 of 76 possible (80.2%), $P < 0.001$

*Radiology* (*Table 4*): X-rays of the hands at the beginning and end of one year's treatment were compared blind by a very experienced radiologist. Table 4 shows the results. Unfortunately some patients deteriorated, but this was less than could be expected had the patients not been on therapy.

*Table 4*

**Radiological observations (hands) on 109 patients before and after one year on D-penicillamine 500 mg/day or less**

| *Changes on radiology* | *No abnormality on X-ray* (%) | *No change after penicillamine* (%) | *Deteriorated* (%) | *Improved* (%) |
|---|---|---|---|---|
| Soft tissue swelling | 0 | 61 | 13 | 26 |
| Subarticular erosion | 15 | 39 | 36 | 9 |
| Joint erosion | 11 | 50 | 22 | 17 |
| Osteoporosis | 6 | 85 | 9 | 0 |

Results not significant

*Adverse Reactions*

Day *et al.* (1974) have already published their work regarding correlation of the mean daily dose of penicillamine with side-effects by years (Fig 2).

In the present study Table 5 shows that relatively few patients had side-effects, and of the total of 30 patients showing reactions, 15 were satisfactorily re-established on penicillamine. It is of interest that the 2 patients with low white cell counts could not be re-established, nor could the 5 patients showing albuminuria.

*Table 5*

**Adverse reactions among 109 patients ● on 500 mg/day penicillamine or less**

| *Adverse reaction* | *No. of reactions* | *Satisfactorily re-established on penicillamine* |
|---|---|---|
| Thrombocytopenia (< 100 000) | 15 | 9 |
| Neutropenia (< 2000) | 2 | 0 |
| Albuminuria (2 g/day or more) | 5 | 0 |
| Rash | 6 | 4 |
| Taste aberration | 2 | 2 |
| Total | 30 | 15 |

$P < 0.001$

●127 patients were initially admitted to study, but of these 18 failed to respond to a dose of 500 mg/day

*Discussion*

Our data suggest very strongly that penicillamine is a useful and relatively safe drug in the treatment of early active rheumatoid disease. One year is a short time in the progress of rheumatoid arthritis, but our studies are continuing.

REFERENCES

**Day A T, Golding J R, Lee P N & Butterworth A D** (1974) *British Medical Journal* i, 180

**Golding J R, Wilson J V & Day A T** (1970) *Postgraduate Medical Journal* 46, 599–605

DISCUSSION

**Dr A St J Dixon** (*Bath*): This, of course, is getting to the heart of the matter: how low a dose can be given and how early can treatment be started? First, something which came up strongly in the original ARC (formerly ERC) gold trial, was that when patients are taken into the study early in their disease we have to be sure that they have what would eventually be definite seropositive rheumatoid arthritis. Secondly, the few placebo-controlled clinical trials which have been published give no evidence yet that patients with consistently seronegative rheumatoid arthritis or, for that matter, examples of peripheral arthritis associated with spondylitis, Reiter's syndrome or psoriasis respond at all to penicillamine. It is possible that seropositivity for rheumatoid factor is a necessity for such response.

**Dr H Berry** (*London*): With regard to seropositivity, we have found no correlation between improvement on penicillamine and change in latex titres. Secondly, I do not believe that we will understand much more about side-effects until there is some way of investigating the concentration of penicillamine in blood and tissue. It has surprised me that in 15 years of using this drug unfortunately no one has yet produced such a method of investigation.

**Dr A G S Hill** (*Stoke Mandeville*): A brief and tentative thought about the radiographic changes:

judging from the control cases in a trial of synovectomy, the incidence and rate of deterioration may be very high in rheumatoid arthritis, and the radiographic changes in Dr Golding's patients *may* be being influenced, though clearly he cannot prove this without controls.

**Dr Golding:** In answer to Dr Dixon, I absolutely agree that some of these patients could have gone into remission anyway. With that in mind, as we saw these patients month by month, we tried to reduce the dose of penicillamine. We have not been able to do this in many patients, which means that the rheumatoid disease is still active. In 7 patients we were able to stop the drug completely, without any relapse of the rheumatoid arthritis. But the bulk of these patients were well stabilized on two, three or four tablets a day, and if we tried to reduce their dose the disease flared up.

**Dr F Dudley Hart** (*London*): How many patients in Dr Jaffe's and Dr Golding's series improved within the first fortnight? Are these placebo responders, or is there more to it?

**Dr Golding:** There was not one early responder.

**Dr Jaffe:** The earliest response was at 14 weeks. In reply to Dr Dixon, I agree with all that he has said. In our trial all patients are latex positive. I should like to emphasize that the kinds of patients represented in my small series of 6 were not the same as Dr Golding's – that is, they were not selected for early, mild disease, but some of them were quite advanced – the type we thought might not respond to D-penicillamine at any dosage, but they did, only they took a great deal longer to do so.

**Unidentified Speaker:** Can Dr Jaffe expand on his slightly enigmatic statements about the importance of not having had penicillamine previously, and not giving two tablets of 125 mg as opposed to one at 250 mg? There must be a hidden meaning which I have missed.

**Dr Jaffe:** My study was designed that way. We have experimental evidence based on penicillamine treatment of lymphocytes in tissue culture, which may have no relevance whatever to the disease in man; that things happen much more effectively if the cells are pulsed once daily with penicillamine than if the drug is given continually or on a twice-daily schedule. That is perhaps an irrelevant laboratory basis for a single daily dose, but clinically it works. The other point in your question about no previous treatment is based upon anecdotal clinical observations. I have never been successful in creeping down with the dose to any significant degree. Once an individual has 'seen' penicillamine, whether for immunological, biochemical, enzymatic degradation, or other reasons, it is much more difficult to reduce the level of the drug.

In contrast, when we start with a low dose 'creeping under the enemy radar' and never go very high, they seem to do better over the long haul. This is intuitive, based on uncontrolled observations. Thus, for this low dose trial, earlier treatment with penicillamine (which was at higher dosages of 750–1500 mg per day) was a basis for exclusion.

**Dr A M Freeman** (*Harlow*): Dr Jaffe said that on his low dose regimen patients took about twice as long to respond as on the higher dose. Did Dr Golding find this too? Did the patients take longer to respond than if they had received the higher dose more quickly?

**Dr Golding:** Yes they did.

**Dr F Wollheim** (*Malmö*): We have been giving our patients, whether they are on a low or a high dose, the whole daily dose in one nightly administration for about two years now, and it seems to work as well as giving divided doses.

**Dr H E Amos** (*Carshalton*): Dr Golding showed a few slides in which he did not seem to have much confidence. One slide was quite interesting, especially in relation to Dr Jaffe's comments about dose response relationships. In that slide there was a graph indicating that over a number of years the dose of penicillamine was being decreased and that the side-effects came down. Does he actually believe that is true?

**Dr Golding:** Yes I do.

**Dr Amos:** So there does seem to be some sort of dose response relationship.

**Dr R D Harkness** (*London*): On Dr Jaffe's one dose a day regime he puts in the dose just before the patient gives himself a dose of adrenal cortical hormone, does he not? There is a pulsing which goes on physiologically, and Dr Jaffe's pulse comes just before the adrenal cortical pulse. Can he comment on that, please?

**Dr Jaffe:** I think it is irrelevant. The diurnal variation does not help the sick rheumatoid patient. There is no synergy between a patient's own endogenous corticoid output and my penicillamine pulse. For reasons of convenience, 2 of my 6 patients preferred to take their daily dose

mid-morning, rather than at 9 p.m., and it apparently worked just as well.

**Dr J M M McKenzie** (*Peterborough*): It has taken me a long time to be convinced that a small dose of penicillamine is as effective as a large one. I will now state categorically that one can get a response on 250 mg just as well as on 1500 mg, which is the way I started.

I find that sometimes after a year of treatment, sometimes even after 18 months, for some reason or other the patients seem to escape from the drug. They suddenly begin to get worse, the ESR rises, but it is not the sort of ESR rise which occurs before the development of proteinuria. It does not seem to make much difference if the dose of penicillamine is increased – they just seem to escape from the drug.

**Dr Jaffe:** I have agonized about this escape phenomenon for years, as Dr Lyle knows. I think we are witnessing at least two events. Most of the escapes, I believe, are the result of what I discussed earlier, namely the accelerated inactivation of the penicillamine. Whether this is immunological, biochemical or by some adaptive enzyme which is induced, we do not know. I am inclined to think that with the low dose regime we may see less of this effect than when we continually increase the dose. Dr McKenzie may have experienced the reverse.

Secondly, a small number of these escapes are, undoubtedly, the superimposition of what we heard about earlier in this symposium – the polyarthritis due to the drug, which is the hypersensitivity phenomenon that we readily confuse with an exacerbation of the rheumatoid process. When the dose is raised the polyarthritis becomes if anything worse because more of the antigen is being given to the patient. That happens in a minority of the patients. Another speculation to explain the escapes is completely theoretical. If penicillamine requires a metal ion to 'do its thing' in rheumatoid arthritis, then depletion of that hypothetical trace metal caused by the chelating properties of the drug would perforce result in a secondary failure.

**Dr J M Walshe** (*Cambridge*): One of our Wilson's disease patients who developed what I am sure was a penicillamine-induced arthropathy, and who had a positive antinuclear factor and occasional LE cells, cured herself simply by pregnancy. She has had no more rheumatoid pains and her antinuclear factor has returned to normal. I believe I am right in saying that pregnancy is a well-known way of obtaining at least a temporary reversal of symptoms in rheumatoid arthritis.