in contact with the patient's serum for one hour. Tests were carried out on admission, when the Donath-Landsteiner titre was 32, and were repeated when the titre had fallen to 2. Results are shown in Table I. The indirect antiglobulin test was negative when carried out on serum which had been inactivated at 56° C. for 30 minutes. The direct antiglobulin test was carried out on red cells when the serum titre was 32. As gross haemolysis of the blood occurred at room temperature, the red cells were separated at 37° C. and washed in saline warmed to 37° C. The test was then weakly positive at an antiglobulin serum dilution of 1 in 10 but negative at a 1 in 20 dilution.

Mumps antibody levels were measured on six specimens of serum taken at intervals. The results were consistent with a recent attack of mumps. There appeared to be some correlation between haemolysin titre and mumps antibody levels. Results are shown in Table II.

TABLE II.—*Mumps Antibody Levels*

Date	Donath-Landsteiner Titre	Mumps, Soluble	Mumps, Viral
2 May ..	32	40	320
21 June ..	16	10	80
26 July ..	8	<10	40
9 August ..	2	<10	40
23 „ ..	2	<10	20
6 September	2	<10	10

No treatment was given in hospital apart from keeping the patient warm. He was discharged from hospital after five weeks, having had no further attacks of haemoglobinuria except for two which were induced by immersing his hand in cold water. The haemolysin titre was then still 16 but active only up to 15° C. As it was then mid-June the risk of further attacks seemed small so long as reasonable precautions against cold were taken. After 22 weeks the haemolysin was no longer detectable, there had been no further attacks, and the patient was very well. The only treatment given during this time was a prophylactic injection of gamma-globulin during a measles epidemic.

DISCUSSION

Paroxysmal cold haemoglobinuria may be classified into syphilitic chronic types, and non-syphilitic types which may be acute or chronic (Dacie, 1962). Those non-syphilitic cases secondary to some other disorder such as viral infection are usually acute and clear up spontaneously, although serological evidence may persist for some months, as in the present case. It seems reasonable to assume that in the present case the development of paroxysmal haemoglobinuria resulted from mumps. It is possible that the formation of cold antibodies may have been initiated during the previous six months by a series of acute infections of possible viral origin. The cold antibody associated with viral pneumonia, however, is serologically quite different from the Donath-Landsteiner antibody.

Serologically the above case was exceptional in that the haemolysin was active at a temperature as high as 24° C. This appears to be a feature of those non-syphilitic cases associated with an acute febrile illness. The case following measles described by Dacie (1954) also had a high thermal range of activity up to 25° C. Schubothe and Haenle (1961) also describe a case developing in a child during the course of a febrile illness, in which the haemolysin was active up to 25° C. They suggest that, owing to this wider thermal range, the haemolysin in these cases is potentially more dangerous than in syphilitic cases. The haemolysin in the present case was not destroyed by heating at 56° C. for 30 minutes, but thermolabile constituents of complement appeared to be necessary for fixation of the antibody in the cold, as the Donath-Landsteiner test was negative using inactivated serum.

I wish to thank Dr. E. M. Belton, under whose care the patient was admitted, for permission to publish this report; Professor J. V. Dacie for confirming the diagnosis, for advice regarding treatment and prognosis, and for reading the manuscript; Dr. G. T. Cook, of the Public Health Laboratory, Guildford, for estimation of mumps antibody titres; and Dr. A. E. Wilkinson, of the Venereal Diseases Reference Laboratory, for the treponemal immobilization test and other serological tests for syphilis.

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Trial of Nifenazone ("Thylin")

Brit. med. J., 1964, **1**, 1553–1554

The pyrazole drugs, phenylbutazone and oxyphenbutazone, are in regular everyday use in the treatment of a variety of rheumatic disorders. One of us (F.D.H.) has been particularly interested in this group of drugs since phenylbutazone was first used 12 years ago in this country by Currie (1952). We were therefore pleased to note the advent of a newcomer, nifenazone (2:3-dimethyl-4-nicotinamido-1-phenylpyrazol-5-one; "thylin") which claimed to be ten times less toxic than phenylbutazone. As no clinical trials appeared to have been done in this country with this substance prior to its introduction, it seemed important to find out if it was in any way as efficient as phenylbutazone; if so, the claims on its behalf could be substantiated regarding non-toxicity. No other analogues tried in the past have proved as potent as phenylbutazone; the only other one available, oxyphenbutazone, appearing to be rather less effective, though perhaps slightly less toxic than phenylbutazone (Hart and Burley, 1959).

A group of 26 patients, all of whom suffered from persistently painful rheumatic disorders, were given nifenazone for 14 days, having previously been on phenylbutazone or oxyphenbutazone 100–300 mg. daily, or salicylates. Of 20 patients with rheumatoid arthritis, the sheep-cell agglutination titre was positive in 13, between 1/64 and 1/2,048. Five patients suffered from osteoarthritis and one had long-standing ankylosing spondylitis. Fourteen patients received nifenazone 750 mg. daily, nine received 1,000 mg. daily, two received 1,500 mg. daily, and one was given 2,000 mg. daily, orally in divided dosage. Marked symptomatic deterioration ensued in eight patients, and in a further 10 less marked deterioration was noted. In seven patients there was a mild reduction in pain and stiffness, though less than with the previous therapy, but three of these showed no deterioration on cessation of therapy and were therefore classed as inconclusive. One patient noted symptomatic improvement comparable to that obtained from phenylbutazone 300 mg. daily. Serial recordings of grip strength, joint tenderness, and joint size, as measured by standard jewellers' rings, were made in four of these patients and no significant change occurred.

The Chart shows the progress of the one patient with rheumatoid arthritis who was admitted to hospital. There

was steady improvement in symptoms and signs while he received phenylbutazone 300 mg. daily for 14 days. Nifenazone 500 mg. q.d.s. was then substituted for the phenylbutazone and there was an immediate dramatic deterioration. The reintroduction of phenylbutazone 300 mg. daily did not check this deterioration and the dose had to be raised to 400 mg. daily before there was improvement.

Side-effects occurred in eight patients, five of whom received 750 mg. daily and three had 1,000 mg. daily. Three patients experienced dyspepsia, two of whom were intolerant of phenylbutazone and the other of soluble aspirin, and two patients complained of nausea while on nifenazone. One patient felt devoid of energy while on nifenazone. One complained of painful mouth ulceration, and one developed a rash on the legs.

In addition to these relatively uncontrolled studies, a double-blind trial was organized in which 10 patients with rheumatoid arthritis received nifenazone 500 mg. t.d.s. for 14 days and identical inactive placebo tablets for the same period. Nifenazone was given to five patients for the first 14 days and placebo to five for the same period, therapy then being changed to the other preparation for the second fortnight. Assessment of symptoms, joint size, grip strength, and joint tenderness had been previously made at fortnightly intervals until a steady baseline had been obtained. Nifenazone or placebo was introduced, and after further assessment,

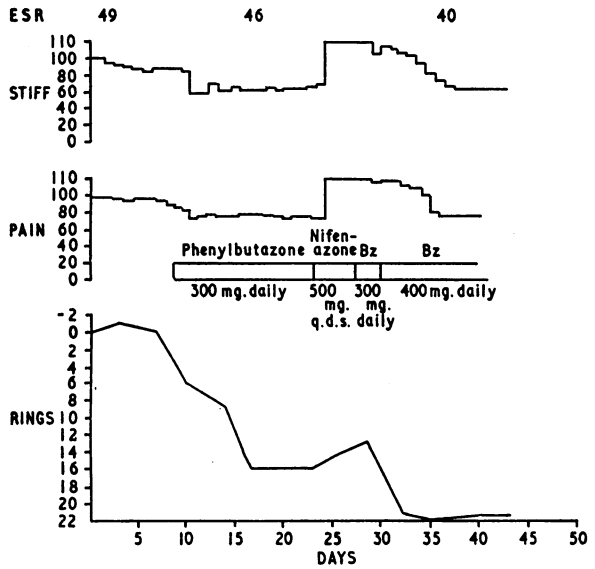

Chart showing the progress during a period of 45 days of a man aged 40 with rheumatoid arthritis (Rose-Waaler titre 1/512) treated with phenylbutazone and nifenazone ("thylin"). Pain, stiffness, erythrocyte sedimentation rate (Westergren), and joint size, measured by standard jeweller's rings, are recorded.

14 days later, the other preparation was substituted. No other change was made in treatment or activity during the trial period.

Two patients withdrew from the trial—one as a result of dyspepsia and the other owing to a feeling of weakness—both while on nifenazone. Of the eight who completed the trial, seven noted no change and one experienced mild symptomatic improvement while on nifenazone. There was no significant change in the objective criteria.

The results of treatment on 62 patients who received nifenazone for rheumatic disorders were reported by Zwerenz (1959). He recorded subjective improvement in almost all of the patients, but they were receiving simultaneous spa therapy and he does not mention the use of identical inactive tablets which might have been given to eliminate placebo response. Likewise, some of his patients may have simply shown a non-specific improvement due to the general effect of spa therapy. Hartert (1959), who studied the effect of short courses of nifenazone on 565 patients with assorted painful disorders, does not mention the use of control tablets. The same criticism applies to the paper by Dziuba (1961). Schmidt and Pape (1961) treated 918 tuberculous patients and divided their results into groups. Again there is no mention of a control series. None of their patients suffered from gastric irritation—a remarkable finding in such a large series, particularly because one group of over 300 patients received the drug in combination with prednisone, admittedly, in low dosage. Spath (1961) treated eight patients with nifenazone while they received antituberculous therapy. Improvement, in the absence of controls, may have resulted from natural remission of the associated rheumatic disorder, or better health as a result of anti-tuberculous therapy.

Results obtained in our first 26 patients suggested that a short course of nifenazone did not induce symptomatic improvement and that most of them deteriorated when transferred from phenylbutazone or oxyphenbutazone. The occurrence of side-effects in 8 out of 26 patients was unexpected. Dyspepsia occurred in three patients, two of whom had experienced similar symptoms while on phenylbutazone and one on soluble aspirin. The patient who developed an irritating rash on the legs while on nifenazone (which disappeared within a few days of cessation of therapy) had had a similar reaction to phenylbutazone after a few weeks of treatment. The result of the double-blind trial was that in seven out of eight patients there was no detectable difference between the effect of nifenazone and that of placebo.

It is with reluctance that we suggest that nifenazone is not of significant value in the therapy of the chronic rheumatic disorders and that side-effects may be expected to occur, particularly in those patients who give a history of abnormal reactions to phenylbutazone and oxyphenbutazone.

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