Some aspects of the prognosis of the eczema-asthma syndrome are discussed, with some observations on the use of tests of ventilatory function in the assessment of these children.

We thank Dr. R. Hall, who suggested this review, for his interest, Professor O. L. Wade for advice, and Dr. J. Jefferson for selecting the seborrhoeic and contact dermatitis cases. Dr. W. McDaniel reviewed this group of children in 1951, and his careful notes made our task much easier.

REFERENCES

- Bates, D. V. (1952). *Clin. Sci.*, **11**, 203.
 Brereton, E. M., Carpenter, R. G., Rook, A. J., and Tyser, P. A. (1959). *Med. Offr.*, **102**, 317.
 Engström, I., Escardó, F. E., Karlberg, P., and Kraepelien, S. (1959). *Acta Paediat. (Uppsala)*, **48**, 114.
 Gaensler, E. A. (1950). *Amer. Rev. Tuberc.*, **62**, 17.
 Ingram, J. T. (1955). *Aust. J. Derm.*, **3**, 5.
 Kennedy, M. C. S., Thursby-Pelham, D. C., and Oldham, P. D. (1957). *Arch. Dis. Childh.*, **32**, 347.
 Meenan, F. O. C. (1959). *Irish J. med. Sci.*, p. 79.
 Purdy, M. J. (1953). *Brit. med. J.*, **1**, 1366.
 Schnyder, U. W., and Klunker, W. (1957). *Hautarzt*, **8**, 510.
 Vowles, M., Warin, R. P., and Apley, J. (1955). *Brit. J. Derm.*, **67**, 53.

LONG-TERM USE OF PHENYLBUTAZONE IN RHEUMATOID ARTHRITIS*

BY

R. M. MASON, M.A., D.M., M.R.C.P.
Physician

AND

V. L. STEINBERG, M.B., M.R.C.P.Ed., D.Phys.Med.
Senior Registrar

Department of Physical Medicine and Regional Rheumatism
Centre, The London Hospital

It is now eight years since the first report on the clinical use of phenylbutazone ("butazolidin") appeared (Currie, 1951). Since then many papers have been published confirming its therapeutic effects, but the reported incidence of toxicity has varied widely. A survey of the American and British literature gives an overall incidence of toxic reactions of 30% (Mauer, 1955). Kuzell *et al.* (1953) give a figure of 15.1% of patients having to interrupt phenylbutazone therapy because of toxicity, while in a more recent series (Sperling, 1959) this was as low as 5.1%. Mason and Hayter (1958) found an overall toxicity rate of 34% in a series of 225 rheumatoid arthritic patients.

During this time very few long-term studies have been published. Gillhespy (1956) found the drug to be well tolerated over "prolonged periods" in the treatment of rheumatoid arthritis. Smyth and Clark (1957) followed up 49 patients on phenylbutazone for periods of between two and five years and found that in 39% it was a satisfactory long-term therapeutic agent. Sperling (1959), who treated a large series of various rheumatic disorders for periods up to three years, concluded that long-term therapy was effective and relatively safe.

The present study consists of an analysis of all the patients with rheumatoid arthritis who attended the Department of Physical Medicine and Regional Rheumatism Centre of the London Hospital between August, 1952, and December, 1954, for whom phenyl-

butazone was prescribed. These have been followed up in order to obtain information about the number of patients for whom the drug provided satisfactory symptomatic control, and who were able to tolerate the drug when given for months or years. Patients with rheumatoid arthritis were selected, since this is the only chronic disease for which long-term administration is likely to be useful and which is seen in sufficient numbers to provide adequate data. Except for some of the early cases in the series, the daily dose of phenylbutazone did not exceed 400 mg. A few cases were maintained on doses as low as 100 mg. daily, and 12 received short courses of 800-1,200 mg. a day; two of these developed intolerance (nausea, oedema). The frequency and time of development of various manifestations of intolerance have been recorded and are analysed. A total of 315 patients were available for study with a minimum of four years' possible continuous administration.

Overall Results

Table I shows the number of patients continuing to take the drug at the end of three months, six months, one year, two years, three years, and four years. Intolerance is, of course, only one of the reasons for stopping the drug, and the causes of withdrawal are analysed below. In 37.1% the drug was discontinued within three months, in 53.6% within six months, and in 67.6% in the first year. At two years 80% had stopped the drug, and by the end of four years only 12.1% of the original patients were still taking phenylbutazone. The percentage of the original patients being withdrawn fell off fairly rapidly with increasing time: 37.1% were withdrawn in the first three months, 16.5% in the second three months, and 14% between six months and one year, while only 2.2% were withdrawn in the fourth year. Of those entering each period, 27%-40% were withdrawn during this time up to the fourth year, when only 15.5% of those still continuing on the drug were withdrawn.

TABLE I.—Number of the Original 315 Patients Who Continued to Take Phenylbutazone After Increasing Intervals of Time

Period	No. of Patients Still on Drug at End of Period	% of Original Number Remaining on Drug
3 months	198	62.9
6 " " " " " "	146	46.4
1 year	102	32.4
2 years	62	19.7
3 " " " " " "	45	14.3
4 " " " " " "	38	12.1

Reasons for Discontinuing Administration During Specified Periods

The reasons for withdrawal of the drug were classified as follows: (1) intolerance; (2) remission of disease so that continued administration was no longer necessary; (3) drug considered ineffective or inadequate; and (4) miscellaneous causes—for example, intercurrent illness, symptoms of very doubtful drug toxicity, patient defaulted, or transferred elsewhere owing to change of domicile, etc.

In 50 of the 117 patients who were withdrawn at three months the cause of withdrawal was intolerance (Fig. 1). In 40 the drug was considered ineffective. Seven patients went into remission. Of the 198 who continued to take the drug after three months, 52 had withdrawn by six months, 21 of these owing to intolerance. In 10 the drug was ineffective and five patients remitted. During the next six months withdrawals amounted to 44, of

*Based on a paper read at the 4th European Rheumatological Congress in Istanbul in September, 1959.

FIG. 1.—Reasons for withdrawal of phenylbutazone.

which only 9 (20%) were due to intolerance. During the second year of the 102 patients entering this period still taking phenylbutazone, a further 40 were withdrawn, intolerance accounting for 5 (13%), remission for 8 (20%), and ineffectiveness for 17 (42%). In the third year there were 62 patients available, of whom 17 were withdrawn, intolerance accounting for 2 (12%), remission for 2 (12%), and ineffectiveness for 4 (24%). In the fourth year 45 patients entered the period; 7 were withdrawn, none due to intolerance or remission, but 3 due to ineffectiveness of the drug. The part played by intolerance in each specified period is illustrated in Tables II and III.

TABLE II.—Incidence of Intolerance

Period	No.	% of Original	% of Available	Total % Showing Intolerance
-3 months	50	15.9	15.9	15.9
-6 "	21	6.7	10.6	22.6
-1 year	9	2.9	6.2	25.5
-2 years	5	1.6	4.9	27.1
-3 "	2	0.6	3.2	27.7
-4 "	0	0	0	0

TABLE III.—Part Played by Various Factors in Causing Withdrawal of Phenylbutazone in 315 Patients at Increasing Periods of Time

Period	No. Withdrawn	Remission		Intolerance		Ineffective		Miscellaneous	
		No.	%	No.	%	No.	%	No.	%
-3 months	117	7	6	50	42	40	34	21	18
-6 "	52	5	10	21	40	10	18	17	32
-1 year	44	9	20	9	20	19	43	8	18
-2 years	40	8	20	5	13	17	42	10	25
-3 "	17	2	12	2	12	4	24	9	53
-4 "	7	0	0	0	0	3	43	4	57
Total	277	31		87		93		69	

N.B.—Where more than one cause operated—for example, intolerance and ineffective—these have been included under both headings (three cases).

It can be seen, therefore, that with increasing duration of administration intolerance plays a progressively decreasing part in causing withdrawal of phenylbutazone—a striking and important contrast to steroid therapy, which results in a constantly mounting incidence of side-effects. This confirms our view that the longer a patient continues on the drug the less likely is intolerance to develop in that patient. The fact that the drug has to be given for a long period is, other things being equal, therefore an indication for continuing with it rather than the reverse. These figures also confirm our view

that the intermittent administration of phenylbutazone for short periods in a chronic disease such as rheumatoid arthritis in an attempt to prevent intolerance serves no useful purpose. Remissions are most common between six months and two years after beginning its administration, but some remissions were observed up to three years. Although the incidence is small, nevertheless no fewer than 31 patients in this series remitted, so that it is clearly worth pursuing treatment for a considerable period in the hope of avoiding steroid therapy. Intolerance was not observed after three years, but the number of patients continuing on the drug after this period is small, and it seems that at this interval of time, in the large majority, either remission will have taken place or the decision will have been made to try other treatment.

Types of Intolerance Observed

Intolerance was categorized as follows: (1) gastro-intestinal; (2) rash; (3) buccal ulcers, stomatitis, sore throat; (4) oedema; (5) headache or vertigo; (6) blood dyscrasias; and (7) miscellaneous.

The frequency and time of development of these symptoms are shown in Fig. 2. In some patients more than one intolerance developed at the same time, in which case both are recorded if severe enough to warrant discontinuation of the drug had it occurred in isolation (this happened in three cases). We have already pointed out that, of the 277 patients withdrawn in the four years, intolerance accounted for only 87 (31.4%). With the exception of blood dyscrasias, which did not occur throughout the whole period of study, all categories of intolerance were observed during the first three months. Gastro-intestinal intolerance was the most common, accounting for one-third, but rash (20%), oedema, and headache and vertigo were all relatively frequent. One patient died from a generalized hypersensitivity reaction and has been recorded elsewhere (O'Brien and Storey, 1954). Many of the miscellaneous side-effects were probably of doubtful significance, and it has already been shown that over 20% of patients on a placebo will have "toxic" effects (Kerr and Davidson, 1958). Buccal ulceration played only a small part in causing withdrawal, thus confirming the view of Sperling (1959) that this is not a significant symptom.

During the second three months of administration gastro-intestinal side-effects formed an increasing

FIG. 2.—Manifestations of intolerance of phenylbutazone during specified periods in 87 patients.

proportion (60%), although the total numbers were diminishing. It was during this period that the one haematemesis occurred in a patient whose barium-meal examination revealed nothing abnormal. After one year the only toxic effects observed were gastro-intestinal although no proved peptic ulcers occurred. However, after the third year no further intolerance developed, although it must be remembered that only 38 of the original 315 patients were continuing to take the drug, and these must therefore represent a residue of highly tolerant patients. Rash, when it occurred, usually did so in the first three months of administration. None were seen after six months. Oedema, however, occurred at any time during the first year.

Summary

315 patients with rheumatoid arthritis treated with phenylbutazone in an average dose of 300 mg. a day have been studied over a period of at least four years; the reasons for withdrawal of the drug are analysed.

The overall intolerance rate was 27.7%, but this accounted for less than one-third (31.4%) of the cases in which the drug was withdrawn, the other important causes being inadequate relief (33.6%) and remission (11.2%).

Gastro-intestinal intolerance was the most frequently observed symptom of intolerance, and after more than one year of continuous administration it was the only form of intolerance seen.

38 patients (12.1%) continued to take phenylbutazone for over four years with satisfactory control of symptoms and without intolerance.

We are grateful to Dr. W. S. Tegner for allowing us to make use of the patients under his care.

REFERENCES

- Currie, J. P. (1951). *Proceedings of 2nd European Congress of Rheumatology, Barcelona*, p. 417.
 Gillhespy, R. O. (1956). *Contemporary Rheumatology: Proceedings of 3rd European Rheumatology Congress, The Hague, 1955*, p. 657, edited by J. Goslings and H. Van Swaay.
 Kerr, D. N. S., and Davidson, S. (1958). *Lancet*, **2**, 489.
 Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E., Gaudin, G., and Mankle, E. A. (1953). *A.M.A. Arch. intern. Med.*, **92**, 646.
 Mason, R. M., and Hayter, R. R. P. (1958). *Practitioner*, **181**, 23.
 Mauer, E. F. (1955). *New Engl. J. Med.*, **253**, 404.
 O'Brien, D. J., and Storey, G. (1954). *Brit. med. J.*, **1**, 792.
 Smyth, C. J., and Clark, G. M. (1957). *J. chron. Dis.*, **5**, 734.
 Sperling, I. L. (1959). *Arth. and Rheum.*, **2**, 203.

"Diagnosis in indigenous medical systems is aimed basically at discovering the occult agency responsible and seldom involves careful physical examination or history-taking as in scientific practice, but, particularly in Africa, is often based on divination by throwing cowrie shells, seeds, or bones, which may be carved out of wood or be genuine, as, for example, the talus bones of the lion and koodoo which are highly prized in parts of Rhodesia, or by using different forms of trance, crystal gazing, dream interpretation, or possession. Thus among the Fore people in the hinterland of New Guinea Gajdusek and Zigas record that divination to diagnose the sorcerer thought to be responsible for a case of kuru is based on the examination of end results of rats that have been roasted in bamboo cylinders." (D. B. Jelliffe and F. J. Bennett, "Indigenous Medical Systems and Child Health," *J. trop. Pediat.*, August, 1960.)

HYPERURICAEMIA DUE TO PYRAZINAMIDE

BY

J. SCHNEEWEISS, M.B., B.S.

Medical Registrar

AND

G. W. POOLE, M.B., M.R.C.P.

Assistant Chest Physician

From the Hammersmith Chest Clinic and the Postgraduate Medical School, Hammersmith Hospital, London

Streptomycin, isoniazid, and sodium P.A.S. are the three drugs most commonly employed in the treatment of tuberculosis, and their value and efficacy is well known. A number of second-line drugs are also available; their use is reserved for those situations where, for one reason or another, resistance has developed to two or all three of the above drugs, and for those cases where the development of toxic side-effects or the patient's refusal to continue taking one or more of these drugs makes their suspension necessary.

The additional drugs include viomycin, cycloserine, pyrazinamide, and 1314 TH (alpha-ethyl-thioisonicotinamide). Unfortunately, several of these have their usefulness limited by undesirable side-effects, and in some there is only a small margin, often difficult to calculate, between the therapeutic and a toxic dose.

Our attention was focused upon one aspect of pyrazinamide treatment when a man aged 55 under our care, who because of multiple resistances had been treated with a combination of pyrazinamide and 1314 TH for five months, developed pains in his feet and a small tophus-like lesion in the left ear in August, 1959. Investigations revealed an elevated serum uric acid. It was subsequently shown that his symptoms and signs were in fact unrelated to this hyperuricaemia, and the earlier suspicion of a gouty diathesis was not confirmed. After the discovery of hyperuricaemia in this patient, a number of other patients, also under treatment with pyrazinamide, were investigated from this aspect.

Chemistry and History of Pyrazinamide

In 1945 nicotinamide was found to have tuberculo-static activity in guinea-pigs and mice, and in 1947 there followed the investigation of many allied drugs. In 1952 an analogue of nicotinamide—pyrazinamide—was found to be more active in mice, and the first clinical trial of it was reported (Yeager *et al.*, 1952).

Pyrazinamide (pyrazinoic acid amide) is a diazine carboxamide chemically related to nicotinic acid and has the following structural formula:

It is an odourless, white crystalline powder stable indefinitely at ordinary temperatures. It is soluble in water (15 mg./ml. at 25° C.) to form a neutral colourless solution stable at room temperature.

Pyrazinamide is hydrolysed in the body, the primary product being pyrazinoic acid, which reacts with ferrous