possibility of constitutional factors, as illustrated by a family tree which shows that four members of a family received fatal damage to their kidneys in connexion with medication against migraine.

REFERENCES

Ask-Upmark, E. (1929). *Acta path. microbiol. scand.*, **6**, 383.
—— (1953). *Acta med. scand.*, **147**, 191.
—— (1957). Life, Death, and Disease in Sweden. Almqvist and Wiksell, Stockholm.
Dahmen, H. (1958). *Münch. med. Wschr.*, **100**, 1846.
Essen-Möller, E. (1956). *Social-med. T.*, **33**, 271.
Jasiński, B., and Wuhrmann, F. (1958). *Schweiz. med. Wschr.*, **88**, 1290.
Lindeneg, O., Fischer, S., Pedersen, J., and Nissen, N. I. (1959). *Acta med. scand.*, **165**, 321.
Moolten, S. E., and Smith, I. B. (1960). *Amer. J. Med.*, **28**, 127.
Sarre, H., Mönch, and Kluthe (1958). *Phenacetinabusus und Nieren-schädigung*. Thieme, Stuttgart.
Spühler, O., and Zollinger, H. U. (1953). *Z. klin. Med.*, **151**, 1.
Studer, A., and Zbinden, G., Schärer, K., and Fust, B. (1958). *Bull. schweiz. Akad. med. Wiss.*, **14**, 154.

PROGNOSIS OF THE ECZEMA-ASTHMA SYNDROME

BY

D. BURROWS, M.D.

Senior Registrar, Skin Department, Royal Victoria Hospital, Belfast

AND

R. W. B. PENMAN, M.B., M.R.C.P., M.R.C.P.Ed.

Senior Tutor and Senior Registrar, Department of Therapeutics and Pharmacology, Queen's University of Belfast

The parents of children suffering from infantile eczema are naturally anxious to know the long-term prospects for the child's health. At present there is no definite answer to this question. Numerous investigators have examined various aspects of the prognosis of infantile eczema. Most of these have dealt with groups of children who were referred to hospital. For example, Vowles *et al.* (1955) showed that 55% of such children will still have eczema at the age of 13 years and 50% will have asthma. Purdy (1953) states that a similar percentage will still be affected at the age of 20. Meenan's (1959) investigations of older subjects showed that about 30% of the skin lesions never clear up

We have had an opportunity of assessing a group of children who were admitted some years ago to the skin department of the Belfast City Hospital suffering from infantile eczema. We were interested in the outlook for these children, through the years, from both the skin and the respiratory viewpoint.

Methods

The records of the skin department for the years 1947–50 were searched, and 43 cases of infantile eczema were found. Similar criteria to those of Purdy (1953) were used in the selection of cases: (1) the diagnosis must have been either infantile eczema or dermatitis (note: during the period the term seborrhoeic was not used in this unit for any child); (2) the face must have been clearly involved; (3) the patient must have been 24 months old or younger when first seen with the disease; (4) the patient must have been 12 months old or younger at the onset of the disease; and (5) there must have been no obvious acquired predisposing factor such as scabies, pediculosis, or antecedent napkin erythema.

Letters were sent to the parents requesting the attendance of these children for interview. If they did not attend and lived within 30 miles (48 km.) of Belfast, they were visited in their homes by one of us. If they lived at a greater distance the parents were provided with a form on which they could indicate the child's present state of health. This was necessary in only two of the 43 cases.

An independent observer who did not know the present state of the children reviewed the case-histories and separated the cases which he considered to indicate a diagnosis of seborrhoeic eczema from those in which a contact factor probably played a part.

Of the 43 cases of infantile eczema, three could not be traced by any means at our disposal, including visits to the last known address, contact with their family doctors, and, finally, the help of the General Health Services Board. Of the remaining 40 patients, one had died of leukaemia and one had emigrated. The cases were further subdivided as in Table I.

TABLE I

		Boys	Girls	Skin Clear in 1959
No. of cases of eczema	43	27	16	
,, traced ..	38*			13
Seborrhoeic eczema	6	3	3	5
Contact dermatitis ..	3	2	1	3
Infantile eczema ..	29	19	10	5 (2 of these had asthma)

* Two by letter only, not seen.

In attempting to assess the respiratory complications, 23 children were selected from the above group of 29 with true infantile eczema, and solely on the basis of their living within half an hour's journey of the clinic. These children were requested to attend the clinic with a parent at a time suitable to them. Three refused to come, and therefore 20 were investigated in the following manner.

The parents and children were questioned about the progress of the skin and chest conditions, family history, and other relevant points as set out in the results.

In assessing the respiratory history a four-point system was adopted to indicate the severity of the past symptomatology. Those with no such history were classed as group 0. Mild respiratory symptoms consisting of occasional wheeze or coughs which required treatment as "bronchitis" or asthma less than twice a year on average were group +. More severe symptoms requiring more frequent attention from the family doctor but having no intervening disability for periods of several weeks were group ++. The severely affected individuals with persistent symptoms of wheezing were graded group +++. At the examination of the child special attention was paid to the skin and respiratory systems. The presence and absence of an audible wheeze was noted. All relevant physical characteristics such as standing height and weight were measured.

A Gaensler spirometer with a one-second time-switch was used for the measurement of the ventilatory capacity. Each child was instructed in the technique of performing the test, being seated upright. Five readings were taken of the forced expiratory volume (1 second) and of the forced vital capacity, before and after the use of a spray containing adrenaline and atropine compound *B.P.C.* from a Wright inhaler for one minute. This was followed by a two-minute interval before repeating the tests. The mean of the last three readings was taken in

each group of tests, and this figure was corrected to B.T.P.S. The percentage ratio F.E.V.$_1$/F.V.C. of the means was calculated.

Results

Table I shows the sex ratio of the original 43 cases of infantile eczema to be 27:16 in favour of boys. Of the group of 29 cases of true infantile eczema, only 5 (17%) showed no skin lesion in 1959—that is, 8 to 11 years later—and two of these had asthma.

Of the group of 20 children who were investigated further, 13 were males and seven females, giving an almost identical sex ratio.

This small group of subjects showed no significant difference between the sexes in the severity of skin or chest manifestations of the syndrome.

The mean F.E.V.$_1$/F.V.C. for females with respiratory symptoms (5 subjects) was 75% and for affected males (11 subjects) it was 72%.

The age range of the children studied varied from 9 to 16 years (mean age, 11 years). The other physical characteristics—that is, standing height and weight—conformed closely, relative to age, to those of the normal children studied by Kennedy *et al.* (1957).

Although it is not strictly accurate to compare a forced vital capacity measurement with a normal slow vital capacity, the figures for F.V.C. before spraying agree well with those predicted from Kennedy's formula V.C. = 115.93 × height in inches − 4,348 ml. (S.D. ± 290 ml.)—as can be seen in Table II.

TABLE II.—*F.E.V.$_1$, Second and F.V.C. Before and After Spray (Litres)*

Case No.	Before Spray			After Spray			Predicted V.C.
	F.E.V.$_1$	F.V.C.	Ratio %	F.E.V.$_1$	F.V.C.	Ratio %	
1	1·3	2·0	65	1·7	2·3	74	1·8
2	2·1	2·5	84	2·2	2·5	88	2·5
3	1·6	1·8	89	1·7	1·9	89	1·6
4	1·2	2·0	60	1·3	2·1	62	2·1
5	2·6	3·1	84	2·6	3·2	81	2·9
6	2·0	3·5	57	2·4	3·6	67	3·1
7	1·7	2·2	77	1·7	2·2	77	2·0
8	1·9	2·1	91	1·9	2·1	91	2·2
9	2·9	3·4	85	2·8	3·3	85	2·7
10	3·0	4·0	75	3·2	4·0	80	3·2
11	2·3	3·3	70	2·6	3·5	74	2·9
12	1·4	1·7	82	1·5	1·9	79	2·2
13	2·1	3·1	68	2·2	3·1	71	2·2
14	2·0	2·2	91	2·2	2·3	96	2·3
15	1·6	2·0	80	1·6	1·8	89	2·1
16	1·8	2·0	90	1·8	2·0	90	1·4
17	1·9	2·6	73	2·7	3·0	90	2·2
18	2·6	2·8	93	2·7	2·9	93	2·2
19	1·3	1·7	77	1·6	2·1	76	1·9
20	0·8	2·3	35	0·8	2·4	33	2·3

The mean observed F.V.C. in this series was 2.5 l. (S.D. ± 0.66 l.), while the mean predicted V.C. was 2.3 l. (S.D. ± 0.46 l.).

For comparison, it was decided to use the range of F.E.V.$_1$/F.V.C. for normal children found by Engström *et al.* (1959)—that is, mean ratio 86.9% (S.E. ± 7.3%). This range gave a lower 95% confidence limit of 70.3%.

Six children (30%) in this investigation had a ratio below this limit before spraying (Table II).

In Table III are grouped the results of the assessment of severity of the respiratory symptoms, the presence or absence of an audible wheeze at the time of examination, the relevant family history, and any history of other diseases. Ten subjects (50%) gave a moderate (+ +) or severe (+ + +) history of respiratory symptoms, six (30%) had mild symptoms (+) only, and four (20%) were asymptomatic.

Fig. 1 shows the increasing number of children affected by respiratory symptoms with age. Below the age of 1 year only six children (30%) had respiratory symptoms. There is an increase during the second year of life to 10 children so affected (50%), and further small increases during the fourth, fifth, and seventh years, to a total of 16 children (80%).

TABLE III

Case No.	Severity of Chest Symptoms	Wheeze at Examination	Family History of Eczema or Asthma	History of Other Diseases
1	+ + +	No	0	Coeliac disease
2	+	,,	0	0
3	+ +	,,	0	0
4	+ + +	,,	Asthma: pat. grandfather	0
5	0	,,	Asthma: pat. grandmother	Hay-fever
6	+ + +	,,	Eczema and asthma: father	0
7	+	,,	Eczema: brother	0
8	0	,,	Asthma: pat. grandfather	Hay-fever
9	+ +	Yes	0	0
10	+	,,	0	0
11	+ +	No	Asthma: mat. uncle. Eczema: mat. grandmother	0
12	+	,,	Asthma: brother	0
13	+	,,	0	Alopecia areata
14	0	,,	Eczema: pat. grandfather	Hay-fever
15	+ +	Yes	Eczema: brother	0
16	0	No	Asthma: pat. uncle	0
17	+ +	Yes	0	0
18	+	No	0	0
19	+ +	Yes	0	0
20	+ + +	,,	Asthma: mat. grandfather	0

This increase in the percentage of children affected by respiratory symptoms with age is accompanied by a trend, seen in Fig. 1, for the most severe symptoms to begin at a later age.

Fig. 2 shows the comparison between the four groups of increasing severity of symptoms and the F.E.V.$_1$/F.V.C. ratios obtained before spraying. The mean ratio

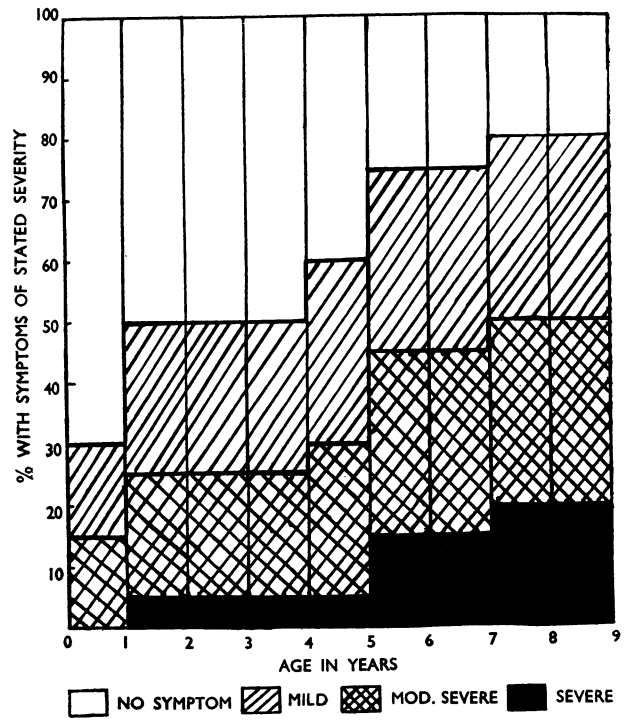

FIG. 1.—Percentage of children with respiratory symptoms and severity of these by age.

for each group is indicated as a percentage and the spread of the individual figures within the groups is represented by vertical lines about the mean. The asymptomatic group (0) has a mean ratio of 89% (normal, 86.9%; Engström *et al.*, 1959). The six children with mild symptoms (+) gave a mean ratio of 80%. The children with moderate (++) and severe (+++) symptoms had mean ratios of 79% and 54% respectively.

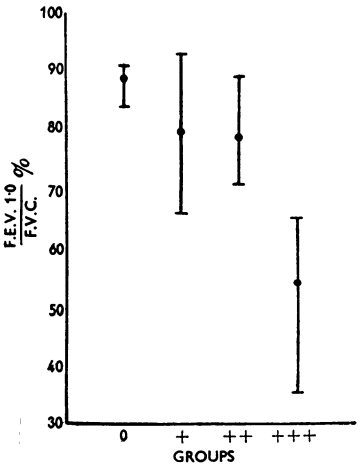

FIG. 2.—F.E.V.$_1$/F.V.C. ratios of groups by severity of symptoms.

In order to test the significance of these figures an analysis of variance was carried out on these group results. The figures for F.E.V.$_1$ showed no significant difference between the means of the four groups, but the mean of the F.E.V.$_1$ figures for group +++ is much lower than for the other three less severe groups—that is, 1.3 l. (group +++), 2.1 l. (group 0), 2.2 l. (group +), and 1.9 l. (group ++). The four groups showed no significant difference between the mean heights and mean F.V.C. figures.

Discussion

The occurrence of seborrhoeic eczema in children has been disputed on the grounds that seborrhoeic conditions cannot arise until the sebaceous glands become active at puberty (Ingram, 1955). Purdy (1953) regarded it as a negligible group and did not separate it from his series of infantile eczema, but in the present study 6 (15.8%) of the patients were thought to have had seborrhoeic eczema. Removal of this group had a marked worsening effect on the prognosis of true infantile eczema. In the group as a whole, 25 children (65.5%) still had eczema 8 to 11 years after the onset of the skin lesion, but on removal of the cases with seborrhoeic and contact factors the percentage still affected rose to 82.8%. Of the five cases who were clear of skin lesions, two had asthma, so that only 10.2% of these children could be said to enjoy normal health.

This group of children, however, is selected in that it consists of cases of infantile eczema which were admitted to hospital for one reason or another. Brereton *et al.* (1959) showed in a very large group of unselected children that only 57% of cases of infantile eczema actually reach the clinics and suggested that these are the more seriously affected children. They found 45% of children who had suffered from eczema (all types) before the age of 5 to be still affected during the school years. This is much lower than our figure of 65.5% for a similar age-group, and would suggest that initial severity of the skin lesion is directly related to the persistence in later years.

There was a high follow-up rate in this study (88%), so that a true picture of the outlook for this type of child is probably presented.

A tendency for infantile eczema to be more common in boys has been previously noted (Purdy, 1953). In the present study there was no evidence of the prognosis being different with regard to sex for either the skin or the respiratory condition.

In conjunction with the poor outlook for the progress of the skin lesions as noted above, 16 out of the 20 children submitted to tests of ventilatory function gave a history of respiratory symptoms of varying severity. Again, it should be noted that these were all children with a diagnosis which appears to have been true infantile eczema.

Six of the 16 affected children had only mild symptoms, and if one excludes these because of the difficulty of assessing the prevalence of such mild respiratory symptoms in the population as a whole, one is still left with an incidence of 50% for severe respiratory symptoms in later years.

The age at onset appears to be widely spread. Only 6 of the 20 children had developed respiratory symptoms in the first year of life, and the remaining 10 symptomatic children became affected at various ages up to 7 years (Fig. 1). There is also a trend for the more severely affected children to develop their symptoms at a later age. It is obviously necessary, therefore, in assessing the incidence of respiratory complications in such a group, to follow up these children for many years. Measurement of vital capacity appears to be of little help in assessment of the disability in these children, as it is seldom decreased below the predicted value. The F.E.V.$_1$/F.V.C. ratio does, however, have some relevance to this assessment.

Gaensler (1950) showed that patients with clinical evidence of airway obstruction had consistently reduced ratios of F.E.V.$_1$/F.V.C. In this present study a wide range of normal values was adopted (Engström *et al.* (1959) and there was less agreement between severe symptomatology and reduced ratios than Gaensler suggests. This is seen particularly in the fact that only one of the six children with an audible wheeze at examination had a lowered ratio (Tables II and III). Five children who had no audible wheeze at examination, on the other hand, had reduced ratios. This agrees with the findings of Bates (1952) and of Engström *et al.* (1959) that asymptomatic asthmatic children often have reduced F.E.V./F.V.C. ratios.

The family history in any given case appears to be of little value in prognosis, apart from the observation that there were 11 subjects (55%) in this investigation with a positive family history of asthma and/or eczema, these included three out of four severely affected individuals from the respiratory viewpoint. However, all four of the subjects who had no respiratory symptoms were also included in the group with a positive family history. Three of these were the only subjects to give a history of hay-fever. These observations differ from the views of Schnyder and Klunker (1959), who suggested a tendency for the type of manifestation of the atopic constitution to run "true to type" within a family.

Summary

The results of a review, 9 to 12 years later, of 43 children who were originally admitted to a skin unit with eczema are reported. Of these, 38 were traced and investigated. Of the 29 cases of true infantile eczema, 24 (82.8%) still had eczema. Of 20 children investigated from the respiratory viewpoint, 16 (80%) had chest symptoms. Only 10% of the 38 children were free of both skin and chest complaints.

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 phenylbutazone 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.

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

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	·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