PAPERS AND ORIGINALS

Spectrum of Asthma in Children—I, Clinical and Physiological Components

K. N. McNICOL, H. B. WILLIAMS

British Medical Journal, 1973, 4, 7–11

Summary

A sample of 315 asthmatic children, representative of the whole range of asthma in childhood, and a control group of 82 children were studied clinically and physiologically from 7 to 14 years of age. The asthmatic children were arbitrarily classified into four grades according to the relative frequency and persistence of their asthma to 14 years of age. Each of these grades could be more clearly defined on analysis of other clinical and physiological characteristics.

The characteristics of severe persistent asthma were: onset usually in the first three years of life, a high frequency of attacks in the initial year, clinical and physiological evidence of persisting airways obstruction and pulmonary hyperinflation, chest deformity, and impairment of growth. By contrast, mild asthma usually began later in childhood, was episodic, and there was little or no evidence of airways obstruction between attacks. The attacks generally stopped before 10 years of age. In between these two extremes were two intermediate grades.

The clinical and physiological characteristics of each grade of asthma at 14 years of age were usually evident by 10 years, and in the most severe grade by 7 years of age. These characteristics provide a sound basis for assessment, management, and prognosis.

Introduction

Opinions on the prevalence, natural history, and clinical patterns of asthma in childhood have differed widely (Williams and McNicol, 1969). Some think that asthma and wheezy bronchitis ("pseudoasthma") are unrelated disorders (Aas, 1969), others that wheezy bronchitis is a variant of asthma. Also the many names used to describe so-called different clinical entities, such as extrinsic and intrinsic asthma, infective asthma, psychogenic asthma, allergic asthma, pollen asthma, and a number of specifically named types (Rackemann and Edwards, 1952), confuse rather than clarify concepts of the disorder. Reported differences in prevalence and patterns of asthma and in aetiological factors are more likely to be due to variation in methods of study than population differences. There has been no uniformity in sample selection, definition of asthma, methods of examination, assessment, or follow-up, so that comparisons are difficult.

To try to resolve some of these difficulties we studied a large representative sample of 7-year-old asthmatic children. They were assessed clinically, physiologically, immunologically, socially, and psychologically and followed until adolescence. An interim report (Williams and NcMicol, 1969) on the children when they were aged 10 concluded that all of them had the same basic disorder and that there was no evidence of separate subgroups who could be designated as having specific types of asthma. The clinical manifestations ranged from mild episodic asthma which ceased early to severe continuing asthma. As there were too few severely affected children in the original sample a representative sample of severely affected patients was included at the 10-year stage and the whole group followed to 14 years of age. The findings at that age are reported in this and the two following papers (McNicol and Williams, 1973; McNicol *et al.*, 1973). Their purpose is to give a concept of the spectrum of asthma in children, to show how different aetiological factors may be involved in the same child and how a variety of features should be taken into account in assessment so as to provide a sound basis for investigation, prognosis, and management.

The aim of this paper is to define the range and natural history of clinical and physiological manifestations up to 14 years of age and to show how asthma may be simply classified on this basis.

Clinical Research Unit, Royal Children's Hospital, Melbourne, Australia
K. N. McNICOL, M.D., Research Fellow
H. E. WILLIAMS, M.D., F.R.A.C.P., Director

Subjects and Methods

The survey comprised a seven-year follow-up of a representative sample of wheezing children and of a control group from a single

age-stratum selected at 7 years of age from 3,000 children, and a parallel follow-up over three to four years of a sample of more-severely affected asthmatic children taken from 20,000 10-year-olds in 1968. The sampling methods have been described previously (Williams and McNicol, 1969; McNicol *et al.*, 1970).

At the end of the study, when the subjects were aged 14, 315 of the original sample of 378 asthmatic children and 82 of the original 106 control children were examined. All the control children and 295 of the 378 asthmatic children were originally seen at 7 years of age, while 83 additional severe asthmatic children were selected at 10 years of age. The original representative samples of wheezing children and controls were examined at 7, 10, and 14 years of age. The additional severe asthmatic group was examined at 10 and 14 years of age.

A number of features were studied at each examination and the findings coded and stored on punch cards. Computer and card-sorter analysis facilitated the development of a range of tables of comparisons and correlations among clinical, immunological, physiological, social, and behavioural findings in the whole range and in various subgroups of the asthmatic children. The definitions used and methods of assessing the clinical, radiological, and physiological data have already been reported (Williams and McNicol, 1969; McNicol *et al.*, 1970). All the assessments were "interval-phase" ones—that is, they were made between attacks of asthma if the asthma was episodic or in an optimum phase if the asthma was severe

Since knowledge of the natural history, spontaneous remission, amelioration, or persistence of asthma is important to the patient, parent, and doctor, the asthmatic population at 14 years of age was graded according to the overall frequency of attacks and their persistence to that age. The clinical and other findings in each grade at 7, 10, and 14 years of age were then compared. Since there was a continouus spectrum from mild evanescent to severe persistent asthma, the grading was arbitrary, but four grades were defined according to the frequency of episodes up to 14 years of age.

Grade A contained 64 children who had no more than five episodes of wheezing up to 14 years of age.

Grade B contained 87 children who had more than five episodes of wheezing but no asthma within 12 months of examination at 14 years.

Grade C contained 106 children with a continuing history of episodic asthma over a number of years and who had asthma within 12 months of examination at 14 years.

Grade D contained 57 children with a current history of very frequent or chronic unremitting asthma, having either periods of severe or prolonged asthma during the last year with remissions of less than one month or more than 10 attacks in the last three months.

The control group was made up of 82 children who had no episodes of wheezing up to 14 years of age.

Results

The relative distribution among the four grades of the numbers of episodes, the age at onset, the age at last episode of asthma, the time lapse since the last episode, and the changes in frequency and severity of the episodes after 10 years of age are shown in tables I to V. These show that the gradings of asthmatic children defined on simple "cut-off" indices for data-processing convenience do constitute meaningful subdivisions of the continuous spectrum of clinical manifestations of asthma.

Grade A children usually started wheezing after 3 (table II) and stopped generally before 8 years of age (table III). Most grade B children had ceased to wheeze or had substantial amelioration of their symptoms well before 13-14 years and usually before 10 years of age (tables III and V). Most had had fewer than 20 attacks with a history of three or four episodes a year over a period of five to six years. Grade C children had early onset, a long-standing history, and a relatively high frequency of episodes in the earlier years, but by 14 years their asthma was less frequent and less severe (table V).

Grade D children were really a subgroup of grade C. The difference between them was that over 60% of grade D children had been wheezing within the week of examination, and almost all within a month, whereas most grade C children had had their last episode three to six months before (table IV). Only in grade D were the majority of children having episodes as often as or more often than at 10 years (table V). Half of these children had started wheezing in the first year of life and more than a quarter in the first six months.

There was a total prevalence of 18-19% for all grades, including grade A children, whose asthma was "sub clinical" (table VI) (Williams and McNicol, 1969). While there was a slight preponderance of girls with mild asthma the proportion of boys increased as the asthma became more severe, and boys were four times as likely to develop chronic asthma by 14 years of age.

Each grade of asthma had a pattern of clinical and physiological signs which was usually discernible at 7 years of age and became more defined by 10 years (tables VII-XIV). About half of the grade D children showed barrel or pigeon chest deformity at 10-14 years of age and a quarter of them at 7 years. About one-third of the grade C children had minimal barrel chest deformity at 10 years of age but a much smaller proportion had it at 14 years. Pigeon chest deformity predominated in the grade

TABLE I—*Number of Asthmatic Episodes experienced by the Children. Results expressed as Proportion of Children*

	Grade A	Grade B	Grade C	Grade D
1-5 Episodes	100%			
6-10 „		33%	5%	
11-20 „		48%	9%	
21-50 „		18%	28%	
>50 „		1%	38%	22%
Prolonged wheezing			20%	78%

TABLE II—*Age at Onset of Asthma (Cumulative Percentages)*

	Grade A	Brade B	Grade C	Grade D
Before 6 months	3%	3%	7%	28%
Before 2 years	22%	41%	47%	60%
Before 3 years	36%	69%	71%	74%

TABLE III—*Age when Last Episode of Asthma occurred. Results expressed as Proportion of Children*

	Grade A	Grade B	Grade C	Grade D
Before 5 years	17%	5%		
5-8 years	63%	41%		
8-10 years	9%	22%		
After 10 years	11%	32%	100%	100%

TABLE IV—*Time since Last Episode of Asthma. Results expressed as Proportion of Children*

	Grade A	Grade B	Grade C	Grade D
<1 Week			12%	62%
1 Week to 1 month			24%	36%
1 to 3 Months			25%	2%
3 to 12 Months	5%		39%	
>1 Year	95%	100%		

TABLE V—*Changes in Frequency and Severity of Asthma in Children still Wheezing between 10 and 14 Years of Age. Results expressed as Percentage of Children*

	Grade A	Grade B	Grade C	Grade D
Less frequent	3%	18%	59%	18%
Similar frequency	3%	1%	28%	41%
More frequent			13%	41%
Less severe	6%	17%	83%	65%
Similar severity		3%	12%	21%
More severe			5%	14%

TABLE VI—*Community Prevalence (in Parentheses) and Sex Ratios of Each Grade of Asthma*

Prevalence	Grade A (6-7%)	Grade B (6-7%)	Grade C (4-5%)	Grade D (0·5%)
Proportion of Boys	45%	60%	68%	79%
Proportion of Girls	55%	40%	32%	21%
		(P <0·001)		

TABLE VII—*Severity of Barrel Chest. Results expressed as Proportion of Children*

	Controls	Grade A	Grade B	Grade C	Grade D
1st Stage (7 yr):					
Mild		2%	4%	5%	27%
Moderate			2%	3%	
P		N.S.	<0·05	<0·01	<0·001
2nd Stage (10 yr):					
Mild		6%	9%	24%	36%
Moderate				7%	13%
Severe					5%
P		<0·05	<0·01	<0·001	<0·001
3rd Stage (14 yr):					
Mild			%1	13%	32%
Moderate				2%	10%
Severe				1 %	6%
P		N.S.	N.S.	<0·001	<0·001

N.S. = Not significant.

D group and was present at 7 and 10 years in most of those with this deformity at 14 years of age. Moderate and severe degrees of Harrison's sulcus occurred only in grades C and D, predominantly in D. There was no significant difference in minor degrees in the asthmatic groups compared with the controls.

A significant degree of pulmonary hyperinflation at 14 years of age was found on radiological examination only in grades C and D, predominantly in grade D (table X). These findings correlated well with those of barrel and pigeon chest deformity.

There was no significant difference in the mean height and weight of the children in any of the grades at 7 years of age. Some impairment of growth in grade D children was found at 10 years of age and this became more marked by 14 years (table XI). Owing to a difficulty in timing, the mean age of the grade D children at the third stage examination was lower than the others, but even allowing for their younger age both their weight and height were significantly less than those of the controls and of the children in the other asthmatic grades.

Spirometry findings at the three stages of the study showed a close correspondence of the mean vital capacity (VC) in children in each of the grades and in the controls at 7, 10, and 14 years with the exception of grade D children at 14 years of age, in whom it was substantially reduced (table XII). The forced expiratory volume in one second (FEV_1), however, and more specifically the FEV_1/VC ratio, was a more sensitive index of airways obstruction. Grades C and D children showed a significantly lower mean FEV_1 and FEV_1/VC ratio at both 10 and 14 years of age.

Obstruction in one or both nostrils was chosen as an index of "allergic rhinitis," and nasal catarrhal symptoms and varying degrees of nasal obstruction were significantly much more common in the whole range of asthmatic children than in controls at 7, 10, and 14 years of age (table XIII). Grade D children had a much higher incidence and their symptoms and signs appeared at a much earlier age.

There was no significant difference in the incidence of rhonchi in the chest in the interval phase in children in grades A and B compared with controls at each stage of the study (table XIV). A few more grade B children than controls had rhonchi at 7 and 10 years, which was during their most active asthmatic phase. Grades C and D children showed a significantly higher incidence of rhonchi at 7 and 10 years of age; over half of the grade D children had rhonchi at 10 years and two-thirds at 14 years of age.

TABLE VIII—*Severity of Pigeon Chest. Results expressed as Proportion of Children*

	Controls	Grade A	Grade B	Grade C	Grade D
1st Stage: (7 yr):					
Mild	1%		1%		13%
Moderate					7%
P		N.S.	N.S.	N.S.	<0·001
2nd Stage: (10 yr):					
Mild		2%		5%	23%
Moderate			1%	2%	5%
P		N.S.	N.S.	<0·05	<0·001
3rd Stage (14 yr):					
Mild		1%	1%	6%	17%
Moderate				1%	8%
P		N.S.	N.S.	<0·05	<0·001

TABLE IX—*Severity of Harrison's Sulcus. Results expressed as Proportion of Children*

	Controls	Grade A	Grade B	Grade C	Grade D
1st Stage (7 yr):					
Mild	1%		4%	8%	13%
Moderate			1%	2%	7%
P		N.S.	N.S.	<0·01	<0·001
2nd Stage (10 yr):					
Mild	4%		1%	13%	25%
Moderate				3%	9%
Severe					2%
P		N.S.	N.S.	<0·05	<0·001
3rd Stage (14 yr):					
Mild	3%	4%	4%	13%	26%
Moderate				2%	5%
Severe					1%
P		N.S.	N.S.	<0·01	<0·001

TABLE X—*Radiological Evidence of Pulmonary Hyperinflation at 3rd Stage of Examination (14 Years). Results expressed as Proportion of Children*

	Controls	Grade A	Grade B	Grade C	Grade D
Present	1%		3%	9%	24%
Severe				1%	3%
P		N.S.	N.S.	<0·01	<0·001

TABLE XI—*Age, Height, and Weight of Subjects at Three Stages of Examinations*

		Controls	Grade A	Grade B	Grade C	Grade D
Mean age (yr/months) ± S.D. in months	1st Stage	7/6 ± 6·2	7/7 ± 6·6	7/5 ± 5·9	7/6 ± 6·0	7/6 ± 5·4
	2nd Stage	10/3 ± 7·0	10/4 ± 8·1	10/3 ± 6·9	10/7 ± 8·6	10/7 ± 6·2
	3rd Stage	14/1 ± 8·0	14/3 ± 8·1	14/1 ± 7·4	14/1 ± 7·8	13/7 ± 7·4
Mean height (cm) ± S.D.	1st Stage	124·7 ± 5·5	123·5 ± 4·8 (N.S.)	122·6 ± 6·0 (P 0·05)	124·1 ± 5·6 (N.S.)	124·7 ± 6·0 (N.S.)
	2nd Stage	139·2 ± 6·5	138·5 ± 7·0 (N.S.)	136·8 ± 7·7 (N.S.)	138·8 ± 7·7 (N.S.)	137·1 ± 6·8 (N.S.)
	3rd Stage	161·3 ± 7·0	159·0 ± 7·2 (N.S.)	159·5 ± 7·9 (N.S.)	159·0 ± 8·9 (N.S.)	153·7 ± 10·8 (P <0·010)
Mean weight (kg) ± S.D.	1st Stage	25·7 ± 3·8	25·4 ± 3·8 (N.S.)	24·6 ± 4·2 (N.S.)	24·9 ± 3·6 (N.S.)	24·5 ± 3·3 (N.S.)
	2nd Stage	34·0 ± 6·5	33·7 ± 7·8 (N.S.)	32·8 ± 7·1 (N.S.)	32·3 ± 5·8 (N.S.)	31·2 ± 6·6 (P <0·001)
	3rd Stage	52·9 ± 10·4	51·7 ± 10·6 (N.S.)	50·6 ± 9·9 (N.S.)	48·6 ± 10·2 (P <0·01)	43·0 ± 9·7 (P <0·001)

TABLE XII—*Spirometry Findings at Three Stages of Examinations*

		Controls	Grade A	Grade B	Grade C	Grade D
Mean FEV_1 (l.) ± S.D.	1st Stage (7 yr)	1·70 ± 0·19	1·66 ± 0·24 (N.S.)	1·59 ± 0·26 (P 0·01)	1·56 ± 0·31 (P 0·01)	1·51 ± 0·26 (P 0·01)
	2nd Stage (10 yr)	1·89 ± 0·27	1·89 ± 0·33 (N.S.)	1·86 ± 0·30 (N.S.)	1·69 ± 0·41 (P 0·01)	1·68 ± 0·44 (P 0·01)
	3rd Stage (14 yr)	3·04 ± 0·51	2·99 ± 0·55 (N.S.)	2·93 ± 0·52 (N.S.)	2·71 ± 0·61 (P <0·001)	2·12 ± 0·73 (P <0·001)
Mean VC (l.) ± S.D.	1st Stage (7 yr)	1·83 ± 0·21	1·79 ± 0·27 (N.S.)	1·75 ± 0·28 (P 0·05)	1·78 ± 0·29 (N.S.)	1·79 ± 0·33 (N.S.)
	2nd Stage (10 yr)	2·15 ± 0·35	2·14 ± 0·38 (N.S.)	2·13 ± 0·40 (N.S.)	2·18 ± 0·43 (N.S.)	2·18 ± 0·41 (N.S.)
	3rd Stage (14 yr)	3·48 ± 0·66 (N.S.)	3·38 ± 0·62 (N.S.)	3·41 ± 0·64)N.S.)	3·43 ± 0·65 (N.S.)	3·24 ± 0·98 (N.S.)
Mean FEV_1/VC − S.D.	1st Stage (7 yr)	92·8%	92·7%	90·8%	87·6%	84·4%
	2nd Stage (10 yr)	87·9%	88·3%	87·3%	77·9%	77·0%
	3rd Stage (14 yr)	87·4% − 6·9%	87·4% − 5·9% (N.S.)	85·8% − 8·0% (N.S.)	78·6% − 10·9% (P <0·001)	65·0% − 14·8% (P <0·001)
FEV_1/VC at 14 yr. Proportion of children outside normal range of 2 S.D. from control mean		4·9%	3·1%	6·9%	30·2%	75·8%

TABLE XIII—*Presence of Complete Nasal Obstruction in One or Both Nostrils. Results expressed as Proportion of Children*

	Controls	Grade A	Grade B	Grade C	Grade D
1st Stage (7 yr)		6% (P 0·05)	9% (P <0·01)	8% (P <0·01)	27% (P <0·001)
2nd Stage (10 yr)	4%	8% (N.S.)	14% (P <0·05)	22% (P <0·01)	57% (P <0·001)
3rd Stage (14 yr)	6%	13% (N.S.)	12% (N.S.)	30% (P <0·001)	43% (P <0·001)

TABLE XIV—*Presence of Rhonchi in Interval Phase. Results expressed as Proportion of Children*

	Controls	Grade A	Grade B	Grade C	Grade D
1st Stage (7 yr)	4%	2% (N.S.)	7% (N.S.)	17% (P <0·05)	40% (P <0·001)
2nd Stage (10 yr)	1%	5% (N.S.)	9% (P 0·05)	33% (P <0·001)	54% (P <0·001)
3rd Stage (14 yr)	5%	3% (N.S.)	3% (N.S.)	37% (P <0·001)	65% (P <0·001)

Discussion

NATURAL HISTORY AND PREVALENCE

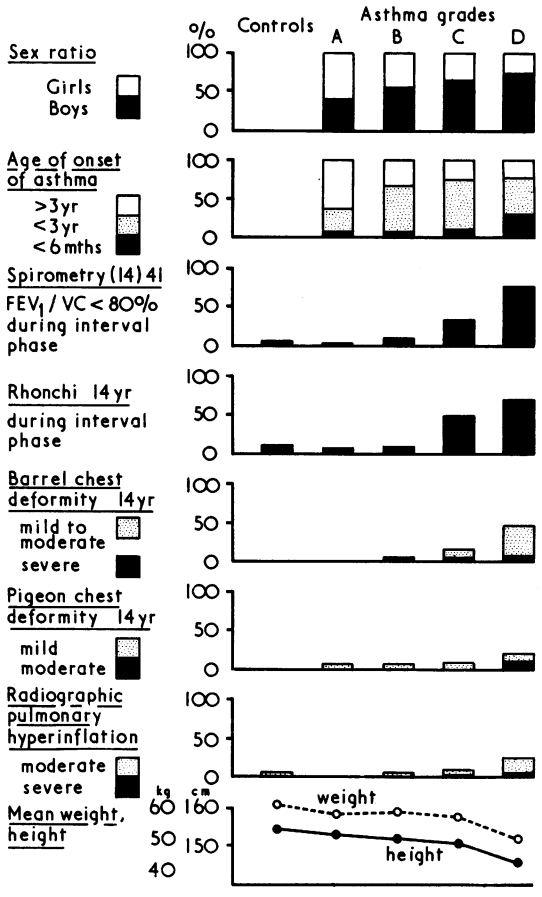
This and the two following papers (McNicol and Williams, 1973; McNicol *et al.*, 1973) aim to show how analysis of clinical, physiological, immunological, and psychological factors enables a clinician to classify asthmatic patients into grades of varying severity at a relatively early age.

The principal characteristics of the children in grades A and B, who comprise three-quarters of all asthmatic children, were the episodic nature of the asthma, its spontaneous cessation almost always before 12 years of age, and the absence of airways obstruction in between attacks. The children in grades C and D had continuing asthma to 14 years of age, the asthma usually beginning before 2 years. Their attacks were more severe and prolonged and most had evidence of airways obstruction in between episodes. These patients comprise about one-quarter of all asthmatics, one in 40 of all asthmatics being in grade D. Grade D represents the very severe end of the spectrum. Almost all the children in it had chronic airways obstruction and many had pulmonary hyperinflation (see chart).

DISTINCTIVE FEATURES OF GRADES

The distribution and clustering of the main clinical and physiological features in the controls and in the asthmatics are shown in the chart. As tables I to XIV show, the pattern of each grade was emerging by 7 years and by 10 years was more clearly defined.

One of the most important indicators of the severity of asthma is airways obstruction. The problem in using it as a yardstick is that it may change from hour to hour, day to day, or week to week, and this makes comparisons difficult. Nevertheless, in severely affected asthmatics airways narrowing persists and comparison is possible if they are examined in an interval phase. Most patients with continuing airways obstruction have varying degrees of pulmonary hyperinflation, which can be measured by gas-dilution techniques, whole-body plethysmography, and radiology (Horowitz, 1969). Persistent pulmonary hyperinflation



Summary of clinical and physiological changes.

and the consequent increased intrathoracic pressure in chronic asthmatics often produce a barrel-shaped or pigeon-shaped chest. In a series of studies of these patients at 10 years of age highly significant correlations were found between measurements of airways obstruction, pulmonary hyperinflation, and barrel and pigeon chest (Gillam *et al.*, 1970). Unequivocal degrees of barrel or pigeon chest deformity and spirometric evidence of airways obstruction were found in the present study, mainly in grade D children at 14 years of age, and in most of them the findings were evident at 7 and at 10 years of age.

At 14 years of age respiratory function was also assessed in more detail by whole-body plethysmography (Hill *et al.*, 1972) on subgroups of children from each of the grades. Maximum expiratory flow volume curves were a more sensitive index of persistent airways obstruction than FEV_1/VC measurements. Some children with normal FEV_1/VC ratios had an abnormal maximum flow at 50% total lung capacity. The amount of impairment of flow correlated well with the clinical severity of the asthma and with the degree of pulmonary hyperinflation. Significantly raised lung volumes, particularly residual volume/total lung capacity (RV/TLC) ratios, were less common and were found mostly in the severely affected asthmatics. More than half of the grade D children showed this abnormality. While these more sensitive tests are valuable for more accurate assessment they do not replace the overall reliability of the simple forced expiratory volume in routine clinical practice.

Another important sign of persistent airways obstruction was the presence of rhonchi in an interval phase in many grades C and D children. This sign correlates well with FEV_1/VC ratios and also with chest deformity, both important signs of continuing airways obstruction.

Growth was affected at 10 years of age only in the most severely asthmatic children. Weight was impaired more than height (Gillam *et al.*, 1970; McNicol, 1971), and this effect was unrelated to corticosteroid therapy (Falliers *et al.*, 1961). Growth was impaired in most children with the worst chest deformity, the highest RV/TLC ratios, and the severest airways obstruction (FEV_1/VC) ratios). Pigeon chest seemed to be the most severe form of hyperinflation chest deformity and it correlated with the highest RV/TLC ratios and the greatest impairment of growth. At 14 years of age all these abnormalities were found predominantly in grade D children.

IMPORTANCE OF GRADING

An objective grading of the severity of asthma is needed by both clinical investigators and clinicians treating cases—clinical investigators so that they can select appropriate samples for investigation, especially for therapeutic trials, and clinicians so that they can advise on prognosis and therapy.

A child with asthma rarely complains to his doctor about his symptoms. Almost invariably the mother reports the symptoms and how she considers they affect the child. Her report often correlates well with objective assessment but there may be much discrepancy. The treatment of some of the most severely affected children in the present study had been totally inadequate because the parents and doctor had not realized the severity of the illness. Parents saw the child as weak, quiet, and inactive without any severe attacks of asthma which required continued treatment. The doctor accepted the parent's assessment and did not appreciate the significance of the small stature, overinflated chest, and rhonchi, and so appropriate investigation and treatment were not carried out. By contrast some over-anxious parents reported severe attacks which they claimed handicapped the child. Objective assessment, however, provided little or no evidence of lower airways disease. Under these circumstances the child's symptoms had been unconsciously exaggerated and restrictions placed on his normal activities.

Clinical investigators are in difficulty unless they can define their asthmatic sample in objective terms. This is one reason who it is not easy to compare the results of different workers. The great variation in the natural history makes it important in therapeutic trials to define the sample selected and to randomize the treatments and controls.

This work was partly supported by a grant from the Asthma Foundation of Victoria.

References

Aas, K. (1969). *Archives of Disease in Childhood*, **44**, 1.
Dawson, B., Horobin, G., Illsley, R., and Mitchell, R. (1969). *Lancet*, **1**, 827.
Falliers, C. J., Szentivanyi, J., McBride, M., and Bukantz, S. C. (1961). *Journal of Allergy*, **32**, 420.
Gillam, G. L., McNicol, K. N., and Williams, H. E. (1970). *Archives of Disease in Childhood*, **45**, 789.
Hill, D., Landau, L. I., McNicol, K. N., and Phelan, P. D. (1972). *Archives of Disease in Childhood*, **47**, 874.
Horowitz, L. (1969). *Journal of Asthma Research*, **6**, 211.
McNicol, K. N. (1971). M.D. thesis, University of Melbourne.
McNicol, K. N., and Williams, H. E. (1973). *British Medical Journal*, **4**, 12.
McNicol, K. N., Williams, H. E., and Gillam, G. L. (1970). *Archives of Disease in Childhood*, **45**, 783.
McNicol, K. N., Williams, H. E., Allan, J., and McAndrew, I. (1973). *British Medical Journal*, **4**, 16.
Rackemann, F. M., and Edwards, M. C. (1952). *New England Journal of Medicine*, **246**, 815.
Williams, H. E., and McNicol, K. N. (1969). *British Medical Journal*, **4**, 321.