

Problems of interpreting exercise-induced asthma

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Factors affecting exercise-induced asthma are reviewed based on studies in large numbers of children and young adults. Evidence is presented to show that running is a more potent and reproducible stimulus than cycling and that walking and swimming have a small and variable effect. The greatest amount of exercise-induced asthma is found after 6 to 8 minutes of steady-state running at a work rate equivalent to about two thirds of the working capacity of the subject. Exercise may be repeated every 2 hours throughout the day without any diminution of its effect in causing postexercise bronchoconstriction. The use of exercise in assessing drugs used to treat asthma is discussed, and the importance of the type of exercise test and the use of placebo preparations is emphasized. Serial exercise tests may be used to study the duration of protection from exercise-induced asthma afforded by drugs such as cromolyn sodium.

Although the phenomenon of exercise-induced exacerbations of asthma has been known for almost 300 years,^{1, 2} the subject has received increasing attention over the past 10 years since the studies of Jones, Buston, and Wharton.³ It has been realized that exercise causes a brief attack of asthma in the asthmatic that mimics a clinical attack in many respects, including lung mechanics,⁴ blood gases,⁵ and the response to drugs.^{6, 7} This latter application of exercise tests in asthma, namely, the assessment of drugs, has been used in several recent studies reported in this JOURNAL and elsewhere.⁸⁻¹⁰

Unfortunately, the subject of exercise-induced asthma is rather more complicated than appears at first sight, and a number of conclusions may have been drawn erroneously because of failure to take account of factors that could influence the results.

Because we believe that exercise has such potential value in the investigation of asthma, particularly in the study of the response to drugs, we have studied some of the factors that must be taken into account when conducting such tests. This paper reviews our experiences in this field and summarizes the results of a number of studies, including some published elsewhere.

SUBJECTS AND METHODS

All patients studied were children or young adults with uncomplicated bronchial asthma as defined by Scadding.¹¹ They were under the care of the Paediatric or Adult Asthma Clinics of the Brompton Hospital and had all been investigated by clinical examination, physiological and immunological tests. Normal subjects of a similar age were obtained from local schools or laboratory staff.

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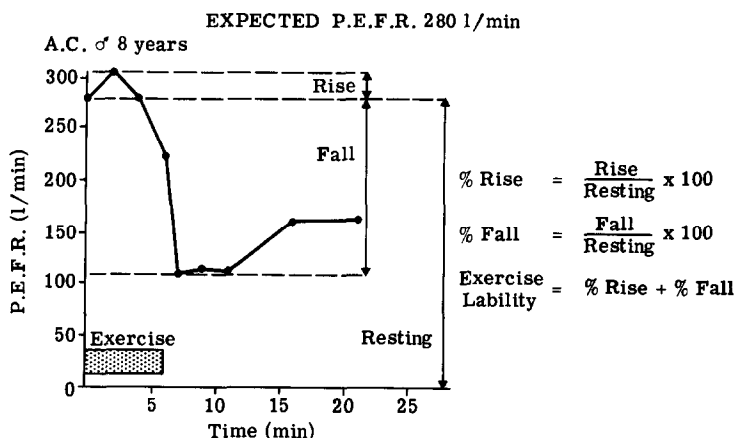


Fig. 1. Typical response to 6 minutes running of an asthmatic child showing the method of calculation of indices of bronchial liability.

All studies (except swimming) were performed in the Paediatric Physiology Laboratory using the same respiratory equipment that was regularly calibrated. Exercise studies were performed on a cycle ergometer (Lode), a treadmill (Quinton), by free range running in a corridor or around the hospital grounds, and by swimming in a heated pool. The details of these methods have been described elsewhere, and the reader is referred to our previous publications.¹²⁻¹⁴ The essential point of all exercise tests was that the subject performed one work load only, which was of sufficient severity to raise his heart rate to at least 170 beats per minute. This represents 65 to 85 per cent of his maximum working capacity. The exercise was continued for 6 minutes without pause, and the peak expiratory flow rate (PEFR) was measured with a Wright peak flowmeter (Airmed, U.K. Ltd.) before, during, and after exercise. The peak flowmeter was calibrated regularly against a pneumotachygraph. In comparative studies, ventilation and gas exchange were also measured by gas collection and analysis, and portable equipment with radiotelemetry of heart rate was used for the free range running and swimming studies. In some experiments the severity and duration of work were deliberately varied to study the importance of these factors.

Two varieties of drug investigation were carried out, the "single test" and the "all-day study." In the single test the subject performed one treadmill running test at the same time of day on each of several days within one week. He received either no drug, an active preparation, or an appropriate form of placebo shortly before the exercise test. The time interval between drug and exercise was varied in some investigations, as described later. The all-day studies consisted of treadmill running tests at identical speed and slope, repeated every 2 hours between 10 A.M. and 4 P.M. When the action of drugs was being investigated, a drug or appropriate placebo was given immediately before the first run, and no further drugs of any kind were permitted until all runs of the day had been completed. The series of all-day studies were completed within a week. In all drug studies, the order of administration of testing was randomized and the nature of the drug was known to the technician but not to the doctor or patient. All drugs, with the occasional exception of corticosteroids, were stopped for at least 6 hours before any exercise test, and if a drug was to be studied it alone was given as described above. Cromolyn sodium was never given in combination with isoproterenol.

The exercise-induced changes were quantitated from the measurements of PEFR. Various indices can be used to express the results, but the simple and most practical are as follows:

$$\% \text{ rise} = \frac{\text{Highest PEFR during exercise} - \text{Resting PEFR before exercise}}{\text{Resting PEFR before exercise}} \times 100$$

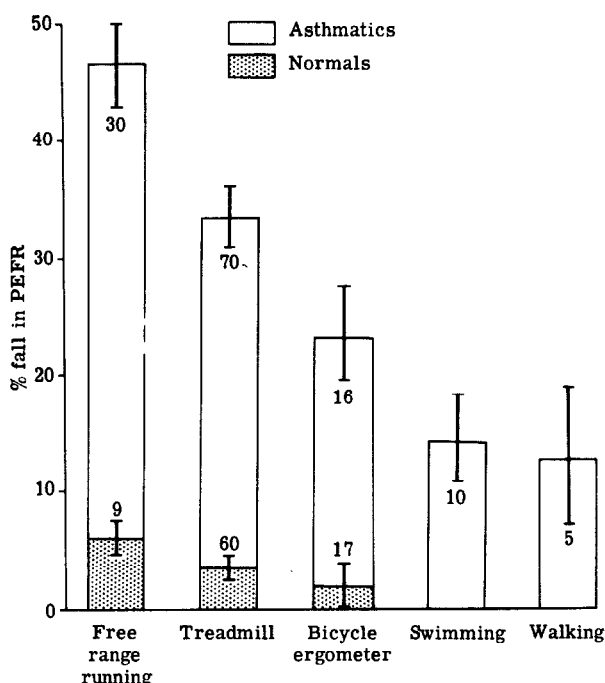


Fig. 2. Exercise-induced asthma expressed as the % fall from base line PEFR in groups of asthmatic and normal subjects. Although the individual subjects were not all the same in each group, they were all working at the same relative work load. The numbers indicate the number of subjects. The bars indicate ± 1 S.E. in this and subsequent illustrations. No normal subjects were studied for swimming or treadmill walking.

$$\% \text{ fall} = \frac{\text{Resting PEFR before exercise} - \text{Lowest PEFR after exercise}}{\text{Resting PEFR before exercise}} \times 100$$

SUMMARY OF RESULTS

General pattern of exercise-induced asthma

The typical pattern of exercise-induced asthma is shown for one subject in Fig. 1, to illustrate the changes that occur and the meaning of the various indices used. This basic pattern was seen in all asthmatic subjects, though bronchoconstriction sometimes began during the last minute or two of exercise and sometimes not until exercise had stopped. The fall in PEFR following free-range running was 47 per cent ± 3 (S.E.M.) in 30 asthmatics (Fig. 2). The lowest PEFR was reached some 2 to 10 minutes after stopping exercise, children tending to get their most severe constriction earlier than adults.¹⁵

Response of normal subjects

Normal subjects display almost no bronchial lability on exercise. The post-exercise fall in 8 normal adults was found to be 3.4 per cent ± 1.1 (S.E.M.), and in 9 normal children it was 6.4 per cent ± 1.4 (S.E.M.) in the studies of

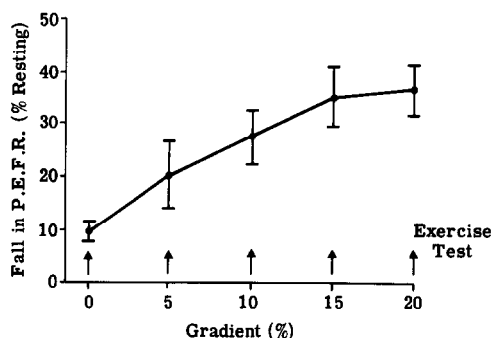


Fig. 3. Effect of gradient (work load) on asthma induced by treadmill running at constant speed for 6 minutes. Each point represents the mean of tests in 9 subjects who performed each gradient on a separate occasion. (Modified from Silverman, M., and Anderson, S. D.: *Arch. Dis. Child.* **47**: 882, 1972.)

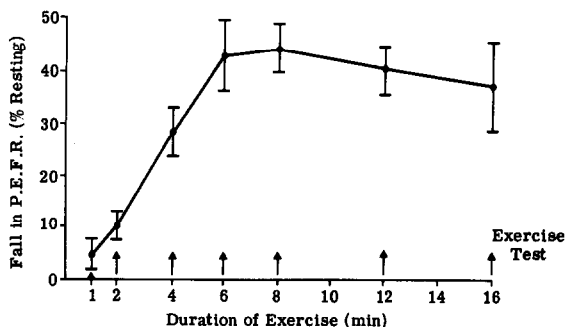


Fig. 4. Effect of duration of exercise on asthma induced by treadmill running at constant speed and slope. Each point represents the mean of tests in 10 subjects who performed each duration on a separate occasion. (Modified from Silverman, M., and Anderson, S. D.: *Arch. Dis. Child.* **47**: 882, 1972.)

Anderson.¹³ When a larger group of normal children were studied,¹⁴ the upper limit of the normal range for per cent fall was found to be 10 per cent (mean + 2 S.D.).

Different types of exercise

The results of different types of exercise in the same subjects at the same work load have been reported in detail by Anderson, Connolly, and Godfrey.¹² The work has been expanded to include swimming and walking exercise, and further studies in a larger number of subjects have been carried out. The results are illustrated in Fig. 2. Free-range running caused more postexercise bronchoconstriction than uphill treadmill running, and both these forms of exercise were significantly more potent than cycling. Swimming and walking were even less effective in causing a postexercise fall in PEFR even though the oxygen consumption, heart rate, and ventilation were similar. In only one subject was walking as potent as running in inducing bronchoconstriction.

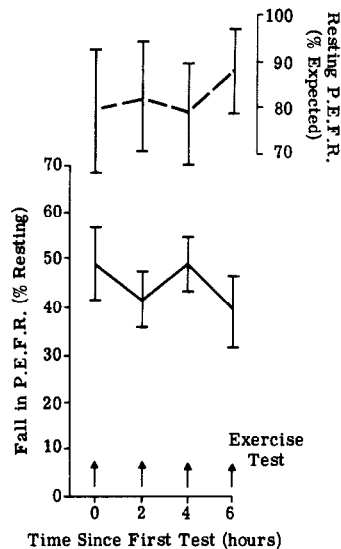


Fig. 5. Effect of treadmill running every 2 hours throughout the day on exercise-induced asthma in 8 children. There was no significant difference between the resting peak flow before each exercise test (above) or between the % fall after each exercise test. (Modified from Silverman, M., and Anderson, S. D.: *Arch. Dis. Child.* **47**: 882, 1972.)

Severity and duration of exercise

Since running was found to be the most potent stimulus for inducing post-exercise constriction, studies were carried out in a group of subjects to investigate the effect of altering the severity (by means of increase in gradient) or the duration of exercise.¹⁴ Each subject performed only a single test at a randomly selected slope or for a randomly selected time, on any one day, so that each subject performed a series of exercise tests. The gradient or duration was not altered during any one test. The results are shown in Figs. 3 and 4. It is clear that for a run of 6 minutes, the postexercise bronchoconstriction increased with gradient when the speed of the treadmill was held constant. Since the work performed on a treadmill depends on body weight, the plateau of bronchoconstriction was reached at a work load of approximately two thirds of the subject's physical working capacity, irrespective of size. Likewise at a fixed speed and gradient (i.e., fixed work load) exercise-induced asthma increased with the duration of the exercise test up to 6 to 8 minutes. For exercise tests of longer than 8 minutes, some subjects actually had less postexercise constriction, and indeed 2 subjects had none at all after running for 16 minutes, though they had developed considerable bronchoconstriction after runs lasted a shorter time.

Repeated exercise throughout the day

Serial running exercise tests were performed by 8 children at two-hour intervals without any drug premedication.¹⁴ There was no significant difference between the mean resting PEF before each test, nor in the severity of the bronchoconstriction induced by each exercise test (Fig. 5). There were some swings

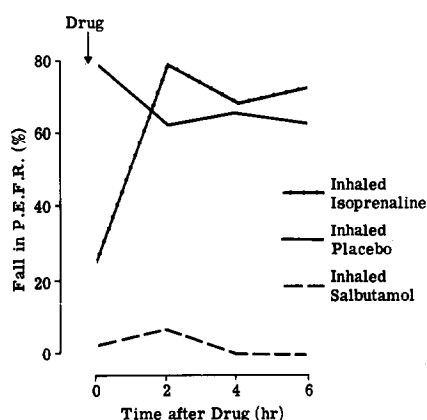


Fig. 6. Effect of inhaled isoproterenol (isoprenaline), salbutamol, or placebo on exercise-induced asthma in one subject. The test drug was given in the morning and exercise was repeated every 2 hours. The prolonged suppression of the postexercise fall in PEFR after salbutamol can be compared with the brief action of isoproterenol. There was no significant diminution of effect with placebo.

Table I. Reproducibility (within-patients) of per cent fall over various time intervals

Time interval	No. of subjects	No. of tests	Mean of individual standard deviations	Mean of individual coefficients of variation
Every 2 hours	8	30	14.6	31
Within 1 week	5	17	6.5	21
Within 1 month (± 1 week)	40	96	15.5	53
Within 1 year (± 1 month)	13	27	13.2	53

in the mean per cent fall, with the smallest values for per cent fall being recorded at about 12 noon and 4 P.M., and the greatest at 10 A.M. and 2 P.M., i.e., the greatest values occurred after meals and the lowest before meals, but the differences were not statistically significant, even when comparing the first and last tests of the day.

Reproducibility of exercise-induced asthma

Running tests were performed on 50 subjects at intervals of up to a year.¹⁴ The variability between repeated tests was explored by calculating the coefficient of variation (standard deviation/mean $\times 100$ per cent), of the per cent fall for different time intervals. The coefficient of variation was least (21 per cent) when the tests were carried out within one week. When tests were repeated at monthly or longer intervals, the coefficient of variation increased to 53 per cent (Table I). The coefficient of variation was also somewhat larger for tests performed within one day (31 per cent), which reflects the swings seen in Fig. 5.

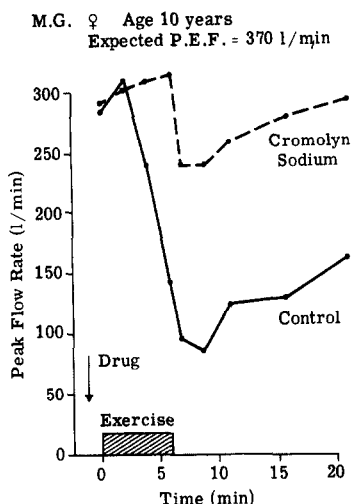


Fig. 7. Effect of inhalation of cromolyn sodium (20 mg.) or placebo (lactose) on exercise-induced asthma in one subject.

Effect of drugs in exercise-induced asthma

Many studies have been carried out to explore the effect of drugs on exercise-induced asthma, and the results given here have been chosen to illustrate points of technique. The standard six-minute running test, either singly or serially as described under "Methods," was used for all the studies.

Exercise-induced asthma was abolished by premedication with bronchodilator aerosols such as isoproterenol (0.16 mg) or salbutamol (0.20 mg). However, the duration of protection afforded by these agents was markedly different, the effect of salbutamol persisting much longer as shown by the serial exercise tests (Fig. 6).

Perhaps most controversy has arisen over the effect of cromolyn sodium. This drug was found to give a variable amount of protection, ranging from complete blocking of exercise-induced asthma (Fig. 7) to no effect at all.¹⁶ However, the duration of protection from exercise-induced asthma was also found to vary, and this could explain the variable results in published studies. In fact, we were able arbitrarily to divide subjects into three groups as shown in Fig. 8. Those with prolonged protection were termed good responders (Fig. 8, A), another group had brief protection and were termed short responders (Fig. 8, B), and the third group had no detectable protection (Fig. 8, C). There was no difference in base line PEFR between the groups, and no clinical or physiological differences were noted apart from the exercise response.

The use of exercise tests also clearly defined the considerable effect of placebo drugs in asthmatics. From our studies we were able to compare the responses to exercise of asthmatic subjects who received no premedication, a placebo given by the same route as the active drug, or an active drug (intravenous atropine, inhaled salbutamol, or inhaled cromolyn sodium), in random order.¹⁷ The results are shown in Fig. 9, and the clear-cut placebo effect is seen.

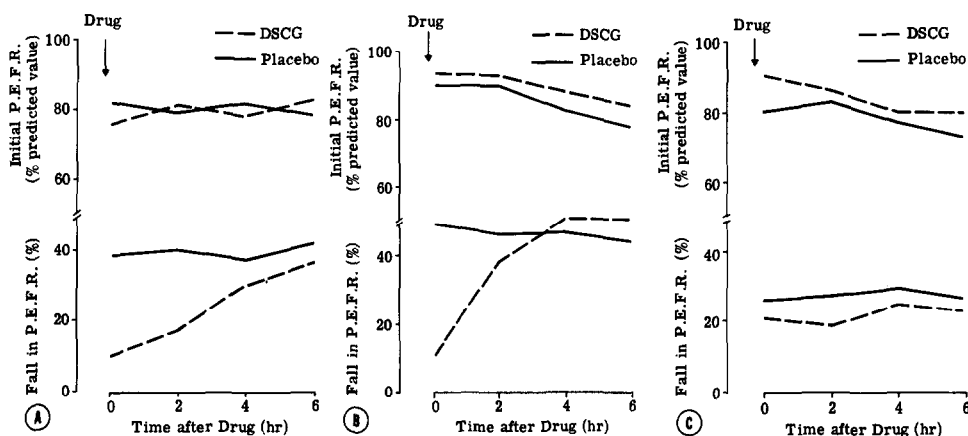


Fig. 8. Duration of effect of cromolyn sodium (DSCG) in suppressing exercise-induced asthma in three groups of patients selected by the time-course of their response. Exercise tests were performed every 2 hours. The drug appeared to exert a relatively long effect in 5 subjects, **A**, relatively short effect in 5 subjects, **B**, and no effect in 4 subjects, **C**. (From Silverman, M., Konig, P., and Godfrey, S.: In press, *Thorax*.)

Nevertheless, salbutamol and cromolyn sodium (but not atropine) caused a further statistically significant inhibition of exercise-induced asthma over and above the effect of their placebos.

The correlation between the protection from exercise-induced asthma and the clinical efficacy of drugs such as cromolyn sodium is currently being explored, and the results seem encouraging.¹⁶

DISCUSSION

This account of our experience with exercise-induced asthma has been written to offer some guidelines for the study of this interesting subject.

There is little doubt that running exercise is a more potent stimulus for inducing postexercise bronchoconstriction in asthmatic subjects than is cycling exercise, while swimming exercise has virtually no effect. This has been known for some time¹⁹ and has been confirmed in recent controlled studies.^{12, 20} Moreover, the reproducibility of the constriction is apparently higher for running than for cycling exercise, and perhaps this accounts for some differences of opinion that have been published. Thus the data of Pierson, Bierman, and Stamm²¹ yield a coefficient of variation of 54 per cent, but in a recent publication¹⁰ the same group of workers stated, "We found the cycle ergometer will consistently produce postexercise asthma." Calculations from the data of Poppius and associates²² yield a coefficient of variation of no less than 406 per cent for ergometer exercise, and yet these workers felt able to draw conclusions on the effect of cromolyn sodium from such studies.

The lesser degree of exercise-induced asthma with bicycle ergometer exercise compared with running exercise may account for the fact that Katz and associates²³ found exercise-induced asthma in only 6 out of 12 asthmatic children whom they studied. They then went on to compare arterial blood gas values in those who developed significant exercise-induced asthma with those who did not,

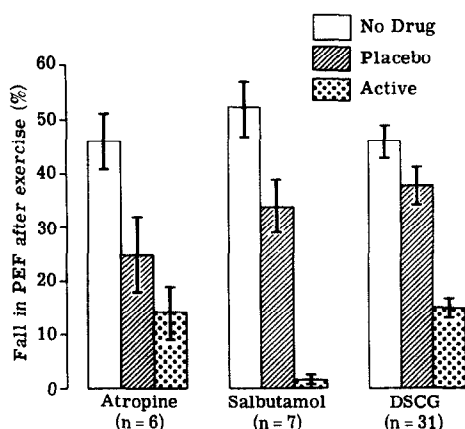


Fig. 9. Effect of drugs and placebos on exercise-induced asthma. For each drug, each subject performed three identical exercise tests, with no premedication or after receiving the drug or its placebo. The numbers of subjects are indicated for each drug. (From Godfrey, S., and Silverman, M.: *J. Psychosom. Res.*, vol. 17, no. 5, 1973.)

treating them as if they were “responders” and “controls.” We believe it is difficult to draw valid conclusions about exercise asthma from such a study, when the type of exercise and its intermittent nature were inappropriate and when no adequate control studies were performed.

Because of the considerable variation in the response to forms of exercise differing in type, severity, and duration, individual case reports such as those of Crompton²⁴ and Rebeck and Read²⁵ are only of limited value. Unfortunately, there has been a tendency to rely too heavily on these isolated and often atypical cases when deducing theories to explain exercise-induced asthma. Thus the fact that both these patients also developed bronchoconstriction after hyperventilation does not mean that this was the cause of the exercise-induced asthma, as had been previously suggested.^{26, 27} In fact, there appears to be no simple correlation between exercise-induced asthma and hyperventilation asthma in children,¹⁵ although confusing evidence claiming the contrary in adult patients has been presented.²⁸ There has also been a tendency to rely on inadequately controlled or uncontrolled data, such as those resulting in the claim that the acidosis of exercise was responsible for the exercise-induced asthma.^{29, 30} Controlled studies have now refuted this possibility.^{5, 28}

The extent of the confusion that exists in experimental design is illustrated by the conclusions of two detailed studies that appeared in successive issues of the *American Review of Respiratory Disease*.^{28, 30} The conclusions of the first paper²⁸ were that “exercise induced asthma is probably hyperventilation asthma” and that neither hypocapnia nor acidosis was an important factor. The second paper³⁰ concluded that while hyperventilation did induce a small rise in airway resistance, it was not nearly so great as that induced by exercise, and therefore hyperventilation did not cause exercise-induced asthma. Again, changes in arterial carbon dioxide tension were unrelated to exercise-induced asthma. In a detailed comparison of the responses of each of five asthmatic adults to both treadmill and bicycle ergometer exercise of similar severity,^{5, 31} we have shown

that it is unlikely that any single factor such as hyperventilation, hypocapnia, lactic acidosis, acidemia, or change in arterial oxygen tension is solely responsible for exercise-induced bronchoconstriction.

One of the most commonly quoted "facts" concerning exercise-induced asthma is the supposed reduction of the effect when exercise tests are repeated throughout a day.³² However, this result occurred in only 2 of the 4 subjects of McNeill and associates,³² who performed serial exercise. The exercise involved unquantitated stair climbing, and no evidence was given to suggest that the amount of work performed was held constant. Variation of the type described in this paper in the form, duration, and severity of exercise could easily have explained their result. In the one subject whose results were illustrated, exercise was repeated every 45 minutes. We now have evidence to suggest that such short intervals (less than 1½ hours) between tests may indeed diminish the response, but Fig. 5 illustrates quite clearly that serial exercise tests may be performed at intervals of two hours without significant loss of effect.

Perhaps it is in the field of drug tests that most difficulty has arisen owing to the use of different types of exercise test. Our studies suggest that comparative studies must be performed by running within one week, and the duration and severity of the running must be the same in each case. All drugs must be avoided for six hours before and during the test, except for corticosteroids, which do not usually seem to affect exercise-induced asthma.^{32, 33}

Those studies of cromolyn sodium that have used running exercise in young asthmatics have concluded that the drug does inhibit postexercise bronchoconstriction in most cases.^{6, 7, 18, 34} Those studies in which cycling has been used have given very much more variable results.^{9, 10, 22}

In the study by Eggleston and associates,¹⁰ standardized 5 minute ergometer exercise was used with comparisons between the active drug and the placebo, but apart from the unreliability of ergometer exercise, the drug was given an hour before the exercise. We have shown how the effect of this drug on exercise-induced asthma wears off quite rapidly even in good responders (Fig. 8, A), and it is hardly surprising that they found a small effect from a waning drug with probably an unsuitable form of exercise.

CONCLUSION

Exercise tests can be of considerable diagnostic and practical value in patients with asthma. In order to obtain the maximum response in the maximum number of subjects with the maximum reproducibility, the test should involve continuous standardized running for 6 to 8 minutes. The speed and/or slope of the treadmill should be adjusted to give a heart rate of at least 170 beats per minute in children. The tests may be repeated without loss of effect if the interval between them is 2 hours or more. Tests on different days should be completed within one week. When drug studies are performed adequate placebo tests must be undertaken, and the duration of action of the drug must be considered.

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