Dr. Mitchell: They had no pulmonary problems during life that we were aware of.
Dr. Macklem: Could I comment on that, Jay? In dogs, the flow rates are higher in the living dog than in the intact excised lung postmortem.
Dr. Petty: It is only fair to point out that although acetylcysteine was effective in these postmortem lungs, we have not shown that it would be more effective than, say, saline. Also with the lungs, in our hands, we could carefully suction segmental bronchi.
Dr. Simonsson: Can acetylcysteine change tone in these muscles? Is the change following acetylcysteine really due to removing mucus or could it be due to a change in muscle tone due to the acetylcysteine?
Mr. Silvers: It has been reported that acetylcysteine can cause bronchoconstriction in some patients; if there were changes in muscle tone, I would expect an increase in airway resistance in our preparation which we did not see.

Analysis of the Forced Expiratory Maneuver*

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The use of the maximum expiratory flow-volume (MEFV) curve as a test of lung function was introduced by Hyatt, Schilder and Fry in 1956.1 We have attempted to define the extent and causes of normal variability in these curves and to relate the curves to other tests of lung function, and to age and growth. Most of the data were obtained in our laboratory. Twenty-two additional subjects were studied and results kindly made available by Drs. Hyatt, Peslin and Pride. All MEFV curves were obtained in constant-pressure body plethysmographs. Static lung recoil curves were obtained from esophageal balloons by standard techniques. The subjects were all in apparently good health.

We obtained 59 adult MEFV curves and analyzed the portion below 70 percent VC. Volume was expressed as percent of each individual's vital capacity. The subjects were divided into ten-year cohorts and in each cohort the mean MEFV curves were obtained by calculating the mean flows at 10 percent VC increments. When flow was expressed in units of liters per second, there was a striking variability of MEFV curves in each age cohort and at all lung volumes (Fig 1). The mean 95 percent confidence limit intervals (that is, the 95 percent confidence limits for individuals divided by the mean and multiplied by 100) were 55 percent. It seemed logical that flow rates in adults might be size-dependent, as demonstrated in children by Zapletal et al.2 We therefore attempted size correction by expressing flow at observed vital capacities per second. To our surprise, the variability was almost unchanged (mean confidence limit intervals 52 percent). The variability was not improved by expressing flow in TLCs per second (confidence limit interval = 65 percent).

We compared the variabilities which we had obtained with the data from Bouhuys and Van de Woestijne3 who published results on 11 normal subjects aged 20 to 35 years, and with results from 90 normal males from Berlin, New Hampshire, kindly made available by Dr. B. Ferris. In both groups, the variabilities of maximum flow at 50 percent VC (V max 50) and of V max 20 were greater than ours whether flow was expressed in liters per second, VCs per second or TLCs per second.

We wondered what might cause the large variability in normal MEFV curves. It is not within-individual variability, since we found this when expressed as the confidence limit intervals, to be less than 7 percent. We know from equal pressure point descriptions that maximum flow is equal to static

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recoil pressure divided by resistance of the upstream segment. Thus, we would expect the variability in MEFV curves to relate to differences in either static recoil pressure or upstream resistance or both. We measured static recoil pressures in 37 subjects. Maximum flow and static recoil pressure at 50 percent VC were analyzed and there was no definable relationship. We conclude, therefore, that the greatest part of the variability is introduced by differences between the upstream resistances of normal subjects, and probably by anatomic variability of sizes of upstream airways.

Thus, it seems that resistance of the upstream segment and the static recoil pressure vary independently. We therefore postulate that airways and parenchyma are not morphologically and physiologically linked in a relationship which is the same for all individuals. Some individuals may have large airways and small parenchyma and vice versa. This hypothesis is attractive embryologically since parenchyma is derived from mesoderm and the airways are derived from endoderm. The concept could have pathologic consequences. An individual with airways whose size is at the lower limit of normal and with a parenchyma with low-normal static recoil pressure might develop overt lung disease after a shorter exposure to noxious agents than his colleagues. It is possible that this might prove to be a useful means of detecting high-risk sections of the population and of explaining why it is that some people are more prone to develop lung disease than others.

We compared the large variabilities that we found in maximum flows to variabilities of other lung function tests, as obtained by the three groups. The variability of VC and FEV1 are similar and considerably less than those of maximum flows. FEV1 does show a reduction in variability with size correction (FEV1/VC) indicating a correlation with vital capacity. When both FEV1 and Vmax 50 are size corrected variability of Vmax 50 (in VC/sec) is two to three times that of FEV1/VC.

This surprised us, particularly as FEV1 includes an effort-dependent part which is known to be variable. To examine this relationship we constructed various idealized MEFV curves and tested the sensitivity of lung function tests to changing the slopes of the curves. We generated five straightline MEFV curves with different slopes (see insert, Fig 2). We plotted the slope of the five curves on the horizontal axis and the computed results of various tests for each curve on the vertical axis of Figure 2. Peak expiratory flow rates and Vmax 50 are linearly related to slope as expected. Less obviously MMEF (that is, the mean flow between 75 and 25 percent VC) is also linearly related. The FEV1/VC, however, is not linear. For steeper curves, it is much less sensitive to change in slope than the other tests and hence we would predict, less vari-
able. The slope of 1.0 is about the lower limit of normal and we find for lower slopes that the FEV₁ becomes more sensitive to change in slope, and hence its sensitivity seems to increase with disease. Similar results hold for curved MEFV curves.

It might appear that the best lung function test was the one with the least variability in the normal population, and hence that maximum flows might not be very useful. On the other hand, the variability of MEFV curves we believe has to do with real mechanisms: it is a signal not noise. We therefore postulate that MEFV curves might be powerful tests in three circumstances: 1) for population studies; 2) when a subject is able to act as his own control; and 3) to test the effects of changing gas properties (as described by Macklem et al in this conference). On the other hand, we feel it is unlikely that it will be easy to use one individual's MEFV curve to characterize his normality or otherwise, in view of the large normal range.

We studied the effect of age on the shape of the MEFV curve. Figure 3 shows mean MEFV curves by age cohort from age 5 to 55. There was a small but apparent change in the shape of the curves with age. The curves become more convex to the volume axis with age in adults. Young children, however, had curves which were similar to those of old people. A single number index, D, reflecting the deviation of each curve from a straight line, was plotted against age. This confirmed that there was a statistically significant increase in convexity of the curves with age in adults, and that 15 of 24 children under 15 years had curves which were more convex than would have been predicted from extending the confidence limits of the adult data to younger ages.

We were unable to confirm the conclusions of Zapletal et al that lung growth in children was isotropic on two grounds: 1) we found changes in shape of the flow-volume curve during growth, and if anything, these were in the direction of becoming more concave with growth, and 2) we did not feel that their assumption of laminar flow conditions was justified since flow is density dependent at most lung volumes.

We were intrigued to find that the MEFV curves of children looked like those of older people. Similar statements have been made for closing volumes which have a minimum in teenagers and for static recoil pressures which are at a maximum in teenagers. The changes in closing volume and MEFV curves could both be secondary to the increase and then fall in static recoil pressure. Another possibility is that there are changes in RV and TLC, in relation to lung growth, which account for the changes in all three measurements.

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Discussion
Dr. Macklem: Is there any way of comparing the effect of the upstream resistance against the elastic recoil pressure?
Dr. Green: We have plotted flow against upstream resistance with good correlation, but this is a circular argument, as there is no independent means of measuring upstream resistance without involving a value for elastic recoil. Nevertheless, the plot of elastic recoil pressure against upstream resistance might well, as you have suggested, help identify in the general population a group at-risk for obstruc-
Physiologic Aspects of Exercise-Induced Asthma*

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It is a common observation that asthmatic patients are often provoked into an attack by exercise. The typical pattern of the response of the asthmatic to exercise is one of bronchodilation during the exercise and profound exercise-induced bronchoconstriction, (EIB) beginning toward the end of exercise and reaching its most severe about five to ten minutes after stopping. This response to six to eight minutes of running in children was clearly described by Jones et al.¹ They believe that all asthmatics display this high degree of bronchial lability on running. We have standardized the exercise test by using treadmill running at about 60-80 percent of the maximum working capacity of the subject and we have found that 75 percent of randomly selected asthmatic patients respond with EIB to a single test. If the test is repeated and if free range running is used, the proportion increases.

The type of exercise is very important for the development of EIB, some types being much more potent stimuli than others even when the work rate (ventilation, oxygen uptake and heart rate) are identical.² The percentage fall in peak expiratory flow rate below the pre-exercise level was 46.5 percent for free range running, 33.5 percent for treadmill running, 12.0 percent for treadmill walking, 23.5 percent for cycling and 14.5 percent for swimming. The severity of the exercise of any one type is also important, and for treadmill running at 3 mph (4.8 kph) a maximum degree of EIB is achieved with six to eight minutes running at 10 percent slope. A longer run or higher slope does not increase the EIB. Intermittent or progressively increasing exercise produces a more variable response. The coefficient of variation of the EIB produced by the standard running test increases with the interval between tests so that, for comparison, tests should be performed within one week when the coefficient of variation is 22 percent.

The attack of EIB exactly mimics a clinical attack of asthma and is accompanied by similar changes in lung mechanics measured plethysmographically³ and in blood gases.⁴ When comparing different types of exercise, arterial Pco₂ is lower and the blood lactate is higher for cycling than running but the EIB is less. Thus, the commonly held views that EIB is due to either hyperventilation or lactic acidosis cannot be substantiated.⁵

Exercise testing is particularly useful for assessing the potency of drugs in the treatment of asthma.⁶ By giving the drug or an identical placebo before the exercise test, the degree of protection can be judged. Moreover, by repeating the exercise at intervals after the drug, the duration of its action can be estimated. This is particularly useful for assessing the suitability of disodium cromoglycate in the individual patient.⁷

We would suggest that all investigators of exercise-induced asthma take note of the various factors which might affect their results.

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