Bronchiolar mucus is a common autopsy finding in patients who die with chronic airway obstruction. Hogg et al¹ have shown that bronchiolar mucus and mucus plugging in emphysematous lungs is associated with increased small airway resistance and therefore with potential reversibility. We have attempted to determine how reversible such obstruction may be by measuring forced expiratory volume in one second (FEV₁), expiratory flow and airway resistance in excised post-mortem human lungs before and after treating them with a mucolytic agent, acetylcysteine.

The postmortem FEV₁ technique of Petty et al² was used. Following this maneuver a retrograde catheter was wedged into an airway of approximately 2 mm internal diameter by the technique of Macklem et al.³ A second catheter was inserted in the wall of the mainstem bronchus flush with the side so that pressure could be measured without interfering with flow. Isovolume pressure flow curves were obtained by performing a succession of expiratory maneuvers using gradual increases of artificial thorax pressure to increase expiratory flow. Because of the location of the retrograde catheter, an isovolume pressure flow curve was determined for both central and peripheral airways.

Seventeen cases (5 normal and 12 emphysematous lungs) were obtained from the autopsies of patients dying without gross evidence of extensive pneumonia, infiltrative disease, pneumoconiosis or pulmonary edema. Three of the emphysema cases died of chronic airways obstruction.

After measuring the FEV₁, 10 ml of a 20 percent solution of acetylcysteine was instilled into the lung. After waiting three or four minutes, the airways were suctioned to remove as much mucus and fluid as possible; from 0 to 25 ml were so removed. The ventilatory studies were then repeated.

Comparison of the FEV₁'s obtained before and after treatment on the lungs from patients without emphysema showed more increases than decreases. The lungs with emphysema all showed increases after treatment. The severity of emphysema bore no relationship to the degree of increase in airflow. In addition, the amount of fluid and mucus material washed out bore no relationship to the degree of increase in airflows.

Analysis of airway resistance data prior to and after acetylcysteine treatment may be summarized as follows: in the normal lungs only minimal changes in central and peripheral airway resistance were noted after treatment. In the emphysematous lungs, while variable changes in the central airways were found after treatment, marked decreases in peripheral airway resistance were found after treatment. Technical difficulties, such as plugging of catheters with mucus or catheters that were found not to have lodged in a 2-3 mm sized airway, prevented making resistance studies in six cases, three of which were those with chronic airways obstruction.

Our study supports the hypothesis of Hogg et al¹ and suggests that mucus removal or redistribution in emphysematous lungs will improve airflow and lower small airway resistance. To what extent the increased peripheral airway resistance in lungs from patients with severe chronic airways obstruction of various types will improve after mucus washout will have to await the study of more cases.

REFERENCES

Discussion
Dr. Macklem: Did you make any measurements during inspiration? It would be of interest to see if you could dissect out what the changes were an effect of dynamic compression or collapse.
Mr. Silvers: We have those measurements with regard to the central airways, but we have not analyzed them. Since we could not get reproducible results with the pressure volume curves during inspiration, we have not tried to analyze the data on the peripheral airways during inspiration.
Dr. Thurlbeck: Thurlbeck of the United Kingdom
(laughter). I want to give visual evidence that I'm not dead, but I wish that I were (general laughter).

One of the surprising things we have found in looking at mucus in the airways was that there was much more mucus in patients with emphysema than was predicted by either a history of cough or sputum.

**Dr. Claman:** Can you do the same thing with saline washout? In asthma, acetylcysteine is tremendously irritating.

**Mr. Silvers:** I think saline washout may work just as well.

**Dr. Nadel:** What did these patients die of and what were their physiologic abnormalities in life? Could the agonal changes in these patients have affected the results? How much of this information can we apply to patients in life?

**Dr. Silvers:** The cases without emphysema were transplant donors who were usually on a respirator in the hospital from one to seven days prior to death. Other patients had myocardial infarctions.

**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.

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**Analysis of the Forced Expiratory Maneuver**

*M. Green, Ph.D.; J. Mead, M.D.; F. Hoppin, M.D.; and M. E. Wohl, M.D.*

The use of the maximum expiratory flow-volume (MEFV) curve as a test of lung function was introduced by Hyatt, Schilder and Fry in 1958. 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. 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 Woestijne 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