SECTION C

Individual susceptibility to tobacco smoke — studies on the relationship between the immediate response to smoking and individual susceptibility.
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INTRODUCTION

An important aspect of the study of early peripheral airway changes in smokers is the assessment of the variations in individual response to smoking. While the findings presented in Section A show conclusively the adverse effects of cigarette smoking on airways, it can be seen that not all heavy smokers have altered pulmonary function. Many published observations also show that some individuals may continue to smoke with apparently little deterioration of lung function.\(^{30,86,121}\) This is because constitutional and environmental factors probably determine the susceptibility of an individual to the effects of smoking.\(^{30,76,130}\) Thus, the rapidity with which peripheral airway disease develops and progresses will vary from individual to individual. The identification of those smokers who are at a high risk of developing ill effects is essential, so that antismoking measures may be concentrated on these subjects in particular.

Sporadic attempts have been made to identify individuals at high risk of developing ill effects to tobacco smoke and other air pollutants, by various means. Thomas and Simmons (1969)\(^{217}\) used sputum histamine levels to identify those individuals who were more sensitive to air contaminants. Barter and Campbell (1976)\(^{30}\) studied the decline of FEV\(_1\).
in smokers over a period of 5 years and found that serious ventilatory deterioration occurred when the methacholine reactivity of the airways was high and when sputum eosinophilia was present. Guyatt et al. (1970) used the immediate response of the airways to tobacco smoke itself to identify the more susceptible individuals among smokers.

The immediate airway response to tobacco smoke appears to be different in the large and small airways. It has been known for many years that the immediate response of the large airways to tobacco smoke is constriction. However, such studies on the small airways have been scanty and the results have been controversial. For instance, DaSilva and Hamosh (1973) found a decrease in the maximal expiratory flow at 50% VC but not at 25% VC, and concluded that "evidence of increase in upstream resistance was found, but whether the small airways contribute to the increased resistance was not proven". These same authors later repeated their studies on the effects of smoking on the airways and reported a constriction of the large airways, but a dilatation of the small airways. McCarthy et al. (1976) found significant reductions in the flow rates at higher lung volumes but none in the flow rates at lower lung volumes. Therefore, more studies to determine the nature of the small airway
response are needed.

Since the severity of the immediate bronchomotor response to tobacco smoke differs among smokers, this difference might be utilized to detect those who are more susceptible to the chronic effects of tobacco smoking, because those who show a marked immediate response may be the ones who suffer rapid deterioration with prolonged smoking. 86

There is evidence to indicate that some of the immediate bronchomotor effects of tobacco smoking may be due to the release of histamine 193 in the lung. Cigarette smokers are known to have higher levels of histamine in their blood than nonsmokers. 193 A similar release of histamine has been found in autopsy lungs exposed to textile dusts. 68 Therefore it is possible that the severity of the immediate response to smoking may be gauged not only by the extent of bronchoconstriction but also by the extent of histamine release in the individual.

The extent of bronchoconstriction may be studied quite simply by measuring peak expiratory flows. This parameter depends on two factors, namely the state of the large airways and the effort put out by the subject. 2, 38, 160 However, in forced expiratory manoeuvres obtained from cooperative subjects who perform maximally in successive efforts, the variability
caused by the second factor is insignificant, as pointed out in Section A (page 43). Thus, a reduction of PEF may be interpreted as a narrowing of the large airways, and the magnitude of the decrease in PEF would provide an indication of the extent of bronchoconstriction.

A sensitive indicator of histamine release in the body is the absolute blood basophil count.\textsuperscript{178,180,204} The blood basophils contain at least half of the histamine in normal human blood.\textsuperscript{53,82} Graham et al. (1955)\textsuperscript{82} found that the basophils contain histamine in a concentration twenty thousand times that of the platelets and a million times that of the plasma. It has been suggested that the human basophils are probably the circulating members of the mast cell system, representing a mobile source of histamine and that they appear in some way to supplement the functions of tissue mast cells by being immediately available whenever a condition requiring histamine release arises.\textsuperscript{184} Basophil degranulation and concomitant histamine release is associated with a fall in total circulating basophils and a decrease in the absolute basophil counts.\textsuperscript{178,180,204}

The eosinophils had been implicated in the release of histamine in the blood, until Riley and West (1953)\textsuperscript{181} and Graham et al. (1955)\textsuperscript{82} provided evidence that the
blood basophils and tissue mast cells were rich in histamine, whereas the histamine content of eosinophils was very variable and at times nil. In fact, the granules of the eosinophils have been found to contain anti-histaminic properties. Eosinophils have been found to migrate to areas of histamine release. \(^{226}\) \(^{69,189}\) Riley (1955)\(^{189}\) has therefore suggested that the eosinophils may be normally concerned with the detoxication and disposal of histamine. The high sputum eosinophilia in individuals with greater sensitivity to tobacco smoke\(^{30}\) is probably caused by the mobilisation and migration of circulating eosinophils to the mucosa of the respiratory tract during histamine release following exposure to tobacco smoke. This migration of the circulating eosinophils to the respiratory tract may be expected to cause a decrease in the total circulating eosinophils.

Thus, it may be possible to detect individuals who are more susceptible to cigarette smoke, by studying the immediate response of their airways and blood basophil and eosinophil counts to smoking. The magnitude of the immediate airway response, and of the fall in basophil and eosinophil counts may be related to the deterioration of lung function over long continued periods of smoking.

This study was therefore undertaken with the
following objectives:—

1. to study the immediate effects of tobacco smoking on the large and small airways,

2. to detect the changes if any, in the absolute blood basophil and eosinophil counts soon after smoking, and

3. to assess the relationship between the above responses to smoking and the decline in flow rates observed in the longitudinal study in the same subjects, described in Section A.
METHODS

The immediate effects on the airways were tested on both human subjects and experimental animals. The animal experiments were performed to confirm and extend some of the observations made in the human subjects. The basophil and eosinophil responses were studied only on the human subjects.

Humans

The subjects were 24 healthy young male smokers. 13 of these had also participated in the longitudinal study. Nonsmokers were not included, in order to avoid initiating them into the smoking habit. None of these subjects had any acute illness at the time of the study. They were all free from chronic cardiovascular complaints. All the subjects had abstained from smoking for at least 12 hours before the test. The tests were performed at 3.00 a.m. to enable the subjects to abstain from smoking for 12 hours without much difficulty.

The following tests were performed on each subject:

- FVC
- FEV<sub>1</sub>/FVC%
- PEF
- PEF 80-70%
- PEF 55-45%
- PEF 30-20%
FEF 15-5%
FEF last 0.5 L

Total blood basophil and eosinophil counts. The methods employed for obtaining the first eight measurements were as described in Section A (page 28).

Total basophil and eosinophil counts were done by the method of Moore and James (1953)\textsuperscript{166} using the metachromatic staining principle described by Ehrlich. The diluent contains saponin to haemolyse the red cells and toluidine blue as the metachromatic stain. The basophil granules appear reddish and can be easily distinguished from the other white cells. The eosinophils appear greenish yellow. Hence, both basophil and eosinophil counts could be performed with ease at the same time. Particular care was taken to complete the counting within half an hour after collecting the blood sample, to avoid errors in the count due to basophil degranulation.\textsuperscript{166,203}

The subjects then smoked 2 cigarettes in succession, under supervision. The smoking was done in a separate room, so that the atmosphere of the laboratory was kept smoke free.

All the above mentioned tests were then repeated within fifteen minutes after the subject had finished smoking. The pulmonary function tests were done first, followed by the basophil and eosinophil counts.
Animals

4 male and 4 female mongrel dogs weighing between 2.5 kg and 15.5 kg, and 2 male and 5 female monkeys (Macaca Radiata Radiata) weighing between 2 kg and 5 kg were studied. The following measurements were made:

- Static compliance of the lung (Cstat(1))
- Dynamic compliance of the lung (Cdyn(1)) at increasing breathing frequencies.
- Vital capacity (VC)
- Static pressure volume (Static P-V) relations and Nonelastic resistance.

The animals were anaesthetized with sodium pentobarbitone, using an intravenous dose of 30-40 mg per kg for dogs, and an intraperitoneal or intramuscular dose of 30 mg per kg for monkeys. Generalised skeletal muscle paralysis was produced in the dogs by intravenous succinyl choline (initially 3 mg per kg, and maintained by 0.02% solution in saline as an intravenous drip). In the monkeys, succinyl choline 3 mg per kg was repeated intravenously every 20 minutes during the entire experiment.

A tracheostomy was done and a tracheal cannula was introduced. The animal was then placed in the prone position on a suitable stand and the tracheal cannula was connected through a Y tube (A in Fig.16b) to one side of a Silverman pneumotachograph. The
Fig. 10a

Experimental set up for the animal studies.

1. Polygraph
2. Water manometer (for calibration)
3. Spirometer with transducer
4. Animal respirator
5 and 6. Differential pressure manometers
7. Pneumotachograph
8. Intravenous drip
Diagram of the experimental setup used for the animal studies.

1. Spirometer
2. Rotational Transducer
3. Respirator
4. Polygraph
5. Y tube 3
6. Pneumotachograph
7. Y tube 2
8. Differential pressure manometer I
9. Differential pressure manometer II
10. To oesophageal catheter
11. To trachea
other limb of the Y tube was used to monitor airway pressures. To the other side of the pneumotachograph was attached a second Y tube (§ in Fig. 18b) which in turn was connected to the inlet and outlet tubes of a Starling animal respirator. Artificial ventilation was maintained with tidal volumes of approximately 25 ml per kg body weight. Figures 18a and 18b show the experimental set up.

Pleural pressures were estimated from oesophageal pressures determined by the technique of Milic Emili et al. (1964)\textsuperscript{163} using an oesophageal balloon. This is a rubber balloon 12 cm in length and 2.6 cm in perimeter. The balloon was sealed over the end of a polythene catheter of 1.5 mm internal diameter, 2 mm external diameter and 80 cm length, with a number of holes in the part enclosed by the balloon. The balloon was introduced through the mouth into the stomach. To facilitate introduction, a stiff wire was placed in the catheter so that its tip did not reach beyond the end of the catheter, and taking care not to damage the balloon. When the balloon was in the desired position, the wire was gently withdrawn and removed. The balloon now registered positive pressure with each diaphragmatic descent during inspiration. The catheter was then slowly withdrawn. As it reentered the oesophagus, the
pressure recorded became subatmospheric and more negative with each inspiration. The catheter was withdrawn a further 5-6 cm, to correspond to a distance of about 35-40 cm from the lower incisors to the lower end of the balloon. A syringe was then connected to the outer end of the catheter and 5 ml of air was introduced. About 4.5 to 4.8 ml was then withdrawn, thus leaving 0.2 to 0.5 ml of air in the balloon. The animal was kept prone throughout the experiment to avoid possible compression of the oesophagus by other mediastinal organs.\textsuperscript{220,233}

The catheter was then connected to one vent of a differential pressure manometer. The other vent was connected to the tube monitoring airway pressure and the manometer was connected to one channel of a Grass model 7 polygraph. Thus, transpulmonary pressure (Ptp, i.e. the difference between intrapleural and airway pressure) was recorded.

During the measurements of Cdyn (l), the inspired air was obtained from a spirometer, by connecting it to the intake tube of the Starling respirator. By means of a rotational transducer attached to the spirometer, volume changes were converted to electrical signals and recorded on the polygraph.

Respiratory airflows were measured with the pneumotachograph by connecting it to another differential
pressure manometer, which in turn was connected to the polygraph.

Volumetric calibration was done with the aid of a one litre gas syringe. The manometer recording pressure was calibrated against a water manometer. Flows were calibrated using a small vacuum cleaner and a dry gas meter. Calibrations were done before each experiment.

The set up was tested for leaks before each experiment. The response of the equipment at the various frequencies needed in the procedure was tested by using (a) a bottle and (b) a balloon in place of the animal.

The following procedure was used on each animal.

The lungs were fully inflated by manually closing off the outlet tube of the respirator, until Ptp rose to about 30 cm H₂O. To measure vital capacity, the pneumotachograph was disconnected from Y tube A. A 100 ml. syringe with an attached T-tap was then connected to Y tube A in place of the pneumotachograph. Air was gently withdrawn until transpulmonary pressure fell to 0 cm H₂O. Next, air was introduced in steps of 50 ml for the dogs and 25 ml for the monkeys, until the Ptp reached 30 cm H₂O. Air was then withdrawn in similar steps until Ptp reached 0 cm H₂O, the whole inflation and deflation taking 1 to 2 minutes. Static P-V curves were constructed from these values. VC was
Tracing of static pressure volume relations in a dog. Each step wise increase or decrease in the pressure tracing was caused by the introduction or withdrawal of 50 ml of air respectively.
defined arbitrarily as the volume of air that could be withdrawn from the lung when Ptp fell from 30 to 0 cm H₂O. Static P-V hysteresis was obtained from static P-V curves by plotting the P-V curves on cm graph paper using the same scale for the values obtained before and after smoking and then counting the total number of mm squares enclosed. The area enclosed was expressed as mm squares, and was used as a measure of the hysteresis. Cstat(1) was measured as the slope of the inflation static P-V curve over the tidal volume range used for the dynamic compliance measurements. Figure 19 shows the pressure changes obtained during stepwise inflation and deflation of the lungs in a dog.

The lungs were again fully inflated and allowed to deflate to functional residual capacity (FRC). This was done in all the animals to ensure uniform volume histories, as variations in volume history can affect Cdyn (1). The pneumotachograph was now reconnected to Y tube A. The spirometer was connected to the intake tube of the Starling respirator and inspired volume, airflow and Ptp were recorded simultaneously at respiratory frequencies of 15, 25, 35 and 45 per minute. A chart speed of 25 mm per second was used for a frequency of 15 per minute and a speed of 50 mm per second was used for the higher respiratory frequencies.
Fig. 20

Calculation of \( C_{\text{dyn}(1)} \) from simultaneous recordings of respiratory airflow, transpulmonary pressure changes and lung volume changes.
Inspiratory Cdyn (l) was calculated as the ratio of the inspiratory volume change to pressure change taken at points of zero flow. Cdyn (l) was measured at respiratory frequencies of 15, 25, 35 and 45. At each frequency, the average value from 5 respirations was taken. Figure 20 illustrates the calculation of Cdyn (l) from the tracings.

Nonelastic resistance was calculated during tidal breathing at a respiratory frequency of 15 per minute from the pressure and flow tracings. Nonelastic resistance equals \( \frac{\text{nonelastic pressure}}{\text{flow}} \). Nonelastic pressure was obtained by subtracting elastic pressure from total pressure change. Elastic pressure was calculated from the dynamic compliance and the lung volume change. Volume was obtained from the area under the flow curve which was determined using the trapezoidal rule, \(^85,212\) (Fig. 21). Nonelastic resistance was measured at a lung volume equal to about 10% of the VC above FRC. This is approximately 35% of the VC above residual volume, since the normal tidal breathing range is between 25% and 50% of the VC. \(^138\)

Dynamic pressure volume loops were constructed using pressure and volume changes obtained from the pressure and flow tracings, at a respiratory frequency of 15 per minute.

The pneumotachograph was now disconnected and
replaced by a polythene tube about 25 cm long and 2 cm wide, connecting Y tubes A and B. The limb of Y tube A, that was used to monitor airway pressure was disconnected from the differential pressure manometer and closed off, to avoid smoke reaching the manometer. The spirometer was then disconnected and a cigarette was fixed to the intake tube of the respirator and lighted. The animal was then made to smoke one cigarette. No recordings were made during smoking. Soon after the smoking, all the above measurements were repeated within 10 minutes, using the same procedures and taking the same precautions as before.

Since the mechanical characteristics of the lungs depend on the presence and extent of collateral ventilation between the lobules,\textsuperscript{140,235} it was decided to study this in the animals. Therefore, the lungs of all the experimental animals and in addition, unsmoked lungs from 5 normal dogs and 5 normal monkeys were tested, using the method of Van Allen and Lindskog (1931)\textsuperscript{225} The chest was opened and the lungs were excised. After the lungs were weighed, one lobe of each lung was carefully separated from the rest of the lung. The lobar bronchus was gently dissected free down to its division and then cut. Generally at this level, 3 daughter bronchial openings appeared. Into each, a polythene tube was introduced and tied securely.
Fig. 22

Demonstration of interlobular collateral ventilation.

a. Lung lobe
d. Polythene catheter
b. Syringe
e. Three-way attachment
c. Container of water → Direction of airflow
One tube was connected to a glass syringe with a 3 way Luer lock attachment. The other two tubes were extended into a container of water (Fig. 22). Air was drawn from the atmosphere into the syringe and then very gently introduced into the lobule through the tube. As the lobule became almost fully inflated air began to escape freely from the other lobules even before the rest of the lobe was fully distended. The syringe was now connected in turn to the other two tubes, and the procedure repeated. The same findings were observed. At no time during the procedure was there any overdistension of any part of the lobe. It was possible to fully inflate the whole lobe through one tube by preventing the escape of air from the other two tubes.
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MEAN DIFFERENCE AFTER-BEFORE</th>
<th>S.E. OF THE MEAN OF DIFFERENCES</th>
<th>t value</th>
<th>P</th>
</tr>
</thead>
</table>
| FVC L             | -0.03                        | 0.095                           | 1.51    | n.s.
| FEV1.0/FVC%       | 0.03                         | 2.55                            | 0.15    | n.s.
| PEF L/min         | -25.30                       | 17.98                           | 7.14    | P < .001 |
| FEF 80-70% L/sec  | -0.51                        | 0.91                            | 2.69    | P < .05 |
| FEF 55-45% L/sec  | -0.13                        | 0.71                            | 0.88    | n.s. |
| FEF 30-20% L/sec  | -0.01                        | 0.27                            | 0.19    | n.s. |
| FEF 15-5% L/sec   | -0.04                        | 0.36                            | 0.53    | n.s. |
| FET Last 0.5L/sec | -0.05                        | 0.42                            | 0.57    | n.s. |
| Total Basophil Count* | -6.42                      | 11.5                            | 2.63    | P < .05 |
| Total Eosinophil Count | -47.50                    | 100.33                          | 2.26    | P < .05 |

n.s. = not significant

* Total basophil counts were obtained only on 23 subjects, as these counts could not be completed within half an hour in one subject.
Immediate effects of smoking on PEF and FEF 30-70%. The abscissa represents the values obtained before smoking and the ordinate, the values obtained after smoking. The graphs also show the lines of identity.

**Fig. 23a**

**Fig. 23b**
Immediate effects of smoking on blood basophil and eosinophil counts. The abscissa represents the counts obtained before smoking and the ordinate the counts obtained after smoking. The graphs also show the lines of identity.

Total basophil counts were obtained on only 23 subjects.
Fig. 24

The relationship between the changes in blood eosinophil and basophil counts after smoking. Only 23 values are shown, as basophil counts were obtained on only 23 subjects.
RESULTS

Humans

Table 13 presents the changes in pulmonary function values and total basophil and eosinophil counts caused by smoking in the 24 subjects. Figures 23a - f represent the changes in PEF, PEF 80-70%, PEF 55-45%, PEF 30-20%, blood basophil counts and blood eosinophil counts respectively.

The flow rates at high lung volumes, namely PEF and PEF 80-70%, decreased significantly (P < 0.001 and P < 0.05 respectively). However, none of the other flow rates showed significant change.

The mean presmoking eosinophil and basophil counts were 333 and 45.3 cells per cu. mm respectively. The total blood eosinophil and basophil counts decreased to 286 and 39.3 per cu.mm respectively after smoking (P < 0.05).

Figure 24 shows the relationship between the percentage fall in basophils and eosinophils after smoking. The mean percentage changes in the eosinophil and basophil counts were 14% and 13% respectively, and the correlation coefficient between these changes was 0.76.

The percentage decrease in PEF, PEF 80-70% and the cell counts were correlated with the percentage
**TABLE 14**

CORRELATION COEFFICIENTS ($r$) BETWEEN THE IMMEDIATE RESPONSE TO SMOKING AND THE DECLINE IN PULMONARY FUNCTION IN THE LONGITUDINAL STUDY.

<table>
<thead>
<tr>
<th>IMMEDIATE RESPONSE % DECREASE</th>
<th>LONGITUDINAL STUDY % CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DECLINE IN FEV₁,₀/FVC%</td>
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<tr>
<td>PEF L/min</td>
<td>0.273</td>
</tr>
<tr>
<td>PEF 80–70% L/sec</td>
<td>0.026</td>
</tr>
<tr>
<td>Blood Basophil Count</td>
<td>0.335</td>
</tr>
<tr>
<td>Blood Eosinophil Count</td>
<td>0.383</td>
</tr>
</tbody>
</table>

These $r$ values were not significant ($P > 0.05$).
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Body Weight kg</th>
<th>Lung Weight gm</th>
<th>Procedure</th>
<th>Compliance ml/cm H₂O</th>
<th>VC ml</th>
<th>Expiratory Nonelastic Resistance cm H₂O/Lps</th>
<th>Static P-V Hysteresis mm</th>
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</thead>
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<tr>
<td>1</td>
<td>F</td>
<td>5.0</td>
<td>55.5</td>
<td>BEFORE</td>
<td>25.43 24.64 24.97 23.99 28.33</td>
<td>583</td>
<td>2.14</td>
<td>1937</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>5.0</td>
<td>57.0</td>
<td>BEFORE</td>
<td>39.19 37.05 39.44 41.76 46.31</td>
<td>453</td>
<td>1.23</td>
<td>1219</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AFTER</td>
<td>39.19 33.60 42.46 44.47 44.70</td>
<td>443</td>
<td>0.61</td>
<td>543</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>11.5</td>
<td>101.0</td>
<td>BEFORE</td>
<td>31.30 39.62 54.41 60.47 60.47</td>
<td>693</td>
<td>6.30</td>
<td>2703</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AFTER</td>
<td>32.50 41.22 59.17 65.52 63.79</td>
<td>703</td>
<td>5.56</td>
<td>2313</td>
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<tr>
<td>4</td>
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<td>131.0</td>
<td>BEFORE</td>
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<td>2.33</td>
<td>4441</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AFTER</td>
<td>69.27 84.47 32.14 34.44 90.90</td>
<td>1223</td>
<td>0.42</td>
<td>3123</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>10.0</td>
<td>73.5</td>
<td>BEFORE</td>
<td>76.43 73.66 71.93 77.24 70.92</td>
<td>366</td>
<td>2.00</td>
<td>1457</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>AFTER</td>
<td>69.30 64.71 60.63 60.34 59.32</td>
<td>723</td>
<td>1.42</td>
<td>1263</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>10.0</td>
<td></td>
<td>BEFORE</td>
<td>.. 23.03 23.95 23.73 23.50</td>
<td>..</td>
<td>..</td>
<td>..</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>AFTER</td>
<td>.. 22.93 23.44 23.47 23.44</td>
<td>..</td>
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<tr>
<td>7</td>
<td>F</td>
<td>2.5</td>
<td>27.0</td>
<td>BEFORE</td>
<td>15.90 15.30 15.00 15.00 15.34</td>
<td>471</td>
<td>15.50</td>
<td>3360</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AFTER</td>
<td>13.06 13.04 11.72 9.20 3.34</td>
<td>305</td>
<td>20.70</td>
<td>770</td>
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<tr>
<td>8</td>
<td>M</td>
<td>5.5</td>
<td>55.0</td>
<td>BEFORE</td>
<td>76.40 .. .. .. ..</td>
<td>636</td>
<td>1.00</td>
<td>..</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>AFTER</td>
<td>40.30 .. .. .. ..</td>
<td>510</td>
<td>0.23</td>
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Immediate effects of smoking on the dynamic pressure volume relations at a breathing frequency of 15 per minute, in Dog 1. The abscissa represents the pressure change in relation to the pressure (pleural - airway) at functional residual capacity, and the ordinate represents the lung volume change expressed as a percentage of the tidal volume.
Immediate effects of smoking on the static pressure volume curve in dog 1. The abscissa represents transpulmonary pressures, and the ordinate the lung volume changes expressed as a percentage of vital capacity.
Fig. 25c.

Immediate effects of smoking on the dynamic compliance of the lung expressed as a percentage of the static compliance at different breathing frequencies, in Dog 1.
Immediate effects of smoking on the dynamic pressure volume relations at a breathing frequency of 15 per minute in Dog 5. The abscissa represents the pressure changes in relation to the pressure (pleural ~ airway) at functional residual capacity, and the ordinate represents the lung volume change expressed as a percentage of the tidal volume.
Immediate effects of smoking on the static pressure volume curve in Dog 5. The abscissa represents transpulmonary pressures, and the ordinate the lung volume changes expressed as a percentage of vital capacity.
Immediate effects of smoking on the dynamic compliance of the lung expressed as a percentage of the static compliance at different breathing frequencies in Dog 5.
decline in FEV$_{1.0}$% and PEF 30-20% in the longitudinal study in order to evaluate the relationship if any, between the immediate response and the deterioration in lung function over periods of long continued smoking. These results are shown in Table 14 which gives the r values and their significance. As can be seen, no significant correlation exists.

**Animals**

*Dogs.* Table 15 presents the data obtained in the dogs. The nonelastic resistance at low lung volumes which was measured in 7 dogs, decreased in 5 animals. One showed an increase and the remaining animal showed no change. Vital capacity showed a decrease in 5 animals and only minimal change in the rest. Of the 7 dogs in which static compliance was measured, 4 showed a fall in Cstat(4). The rest showed no change. Of the 7 dogs in which Cdyn (1) was measured, 3 showed a fall, but none of the animals except No. 7 showed any frequency dependence of Cdyn (1). Static P-V hysteresis was measured in 6 dogs. In all the animals it decreased after smoking.

The dynamic P-V loops, static P-V curves and the Cdyn (1) at different respiratory frequencies in dogs No. 1, 5 and 7 are depicted in Figures 25 (a, b and c), 26 (a, b and c) and 27 (a, b and c) respectively. The findings of dogs No. 1 and 5 are representative of
Immediate effect of smoking on the dynamic pressure volume relations at a breathing frequency of 15 per minute in Dog 7. The abscissa represents the pressure changes in relation to the pressure (pleural ≈ airway) at functional residual capacity, and the ordinate represents the lung volume change expressed as a percentage of the tidal volume.
Immediate effects of smoking on the static pressure volume curve in Dog 7. The abscissa represents transpulmonary pressures, and the ordinate the lung volume changes expressed as a percentage of vital capacity.
Dog No. 7

DYNAMIC COMPLIANCE EXPRESSED AS A PERCENTAGE OF STATIC COMPLIANCE AT DIFFERENT FREQUENCIES

Before
After

Fig. 27c

Immediate effects of smoking on the dynamic compliance of the lung expressed as a percentage of the static compliance at different breathing frequencies in Dog 7.
<table>
<thead>
<tr>
<th>NO.</th>
<th>SEX</th>
<th>BODY WEIGHT kg</th>
<th>LUNG WEIGHT gm</th>
<th>PROCEDURE</th>
<th>COMPLIANCE ml/cm H₂O</th>
<th>VC ml</th>
<th>EXPIRATORY NONELASTIC RESISTANCE cm H₂O/Lps</th>
<th>STATIC P-V HYSSTERESIS mm²</th>
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<tr>
<td>1</td>
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<td></td>
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<tr>
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the group. It can be seen that the width of the dynamic P-V loop decreased after smoking in these animals denoting a fall in the nonelastic resistance (Figs. 25a and 26a). The static P-V curve showed a decrease in hysteresis, a decrease in vital capacity and an increase in elastic recoil of the lung (Figs. and 26b). Cdyn (1) did not become frequency dependent after smoking in either animal (Figs. 25c and 26c).

Figures 27a, 27b and 27c show these same parameters in dog No. 7. In this animal the nonelastic resistance as seen from the dynamic P-V loop (Fig. 27a) increased markedly after smoking. Vital capacity and static P-V hysteresis decreased, lung elastic recoil increased (Fig. 27b), and Cdyn (1) became frequency dependent after smoking (Fig. 27c).

Monkeys. Table 16 presents the data obtained in the monkeys. The nonelastic resistance was measured in 3 animals; 2 of these showed an increase, and 1 animal showed a fall. Vital capacity was measured in 5 animals; in 2 it showed a fall and in 3 animals there was no change. The static compliance was measured in 5 animals; 2 showed a fall and the others showed either a small rise or no change. The Cdyn (1) showed a variable fall in 6 out of the 7 animals. However, none of the animals showed frequency dependence of Cdyn (1) except No. 5. In this animal, Cdyn (1) was frequency
Fig. 2a

Immediate effects of smoking on the dynamic pressure volume relations at a breathing frequency of 15 per minute in Monkey 4. The abscissa represents the pressure changes in relation to the pressure (pleural airway) at functional residual capacity, and the ordinate represents the lung volume change expressed as a percentage of the tidal volume.
**Fig. 23b**

Immediate effects of smoking on the static pressure-volume curve in Monkey 4. The abscissa represents transpulmonary pressures, and the ordinate the lung volume changes expressed as a percentage of vital capacity.
Monkey No.4

DYNAMIC COMPLIANCE EXPRESSED AS A PERCENTAGE OF STATIC COMPLIANCE AT DIFFERENT FREQUENCIES

Fig.23c

Immediate effects of smoking on the dynamic compliance of the lung expressed as a percentage of the static compliance at different breathing frequencies in Monkey 4.
Dynamic compliance expressed as a function of frequency in a) a bottle and b) a balloon. This was done in order to test the response of the equipment to changes in frequency.
dependent both before and after smoking. Static P-V hysteresis was measured in 5 monkeys. It showed a fall in 4 and an increase in 1 animal.

Figures 28a, 28b and 28c depict the dynamic P-V loops, static P-V curves and Cdyn (l) at different respiratory frequencies in monkey No. 4 which was representative of the group. The nonelastic resistance showed a decrease (Fig. 28a), the vital capacity and static P-V hysteresis decreased, and lung elastic recoil increased (Fig. 28b) after smoking. Cdyn (l) showed no frequency dependence (Fig. 28c).

Figure 29 shows the response of the equipment to different frequencies, when a balloon or a bottle was substituted for the animal. There was no change in the response of the equipment at different frequencies.

The lungs of all the dogs and monkeys subjected to cigarette smoke and those of five normal dogs and five normal monkeys not subjected to cigarette smoke were tested for collateral ventilation. Free interlobular communications were demonstrated in each of these animals.

The results from the animal experiments show that

1. the immediate effects of cigarette smoking on the small airways as measured by changes in the resistance at low lung volumes were variable; most
animals showed a dilatation, whereas the others showed a constriction.

2. in spite of these changes in the small airways, frequency dependence of $C_{dyn}$ (1) did not develop in these animals.

3. the static P-V hysteresis decreased in almost all the animals after smoking.

4. in some animals there was an increase in the elastance of the lungs after smoking and

5. the lungs of both these species of animals exhibited extensive interlobular collateral ventilation.
DISCUSSION

**Humans**

It is clear from the results presented that there is a significant fall in PEF and PEF 80-70% ($P < 0.001$ and $P < 0.05$ respectively) after smoking (Table 13). The chief determinants of peak expiratory flow are large airway resistance and muscle power.\textsuperscript{38,160} Hence, a decrease in PEF may either be due to a decrease in effort or an increase in the large airway resistance. Since the subjects performed maximally in all the presmoking and postsmoking manoeuvres, a decrease in effort could not have been the reason for the fall in PEF. Hence, it must be assumed that the decrease in PEF after smoking was due to an increase in large airway resistance. This is consistent with the generally accepted view on the immediate response to tobacco smoking.\textsuperscript{153,171,211} The mean fall in PEF and PEF 80-70% was 5.01% and 7.20% respectively. This may be compared with the findings of McCarthy et al. (1976)\textsuperscript{153} who in their studies observed a mean fall of 14.9% in PEF. However, their subjects smoked from 1 to 20 cigarettes each during the acute session, deeply inhaling the smoke, whereas in the present study the subjects smoked only 2 cigarettes each. This probably accounts for the difference in the magnitude of the fall between the two studies.
Though the PEF fell in all the subjects studied, there was a wide range in the magnitude of the fall, from 0.2% to 13%. This is consistent with the view that a wide variation exists in the magnitude of the response of the large airways to tobacco smoke. 86

There was no significant change in the flow rates at low lung volumes. Four possibilities must be considered here. It could mean that (1) a sufficient number of smoke particles failed to reach the small airways, or having reached the small airways, failed to elicit a significant response, (2) significant changes in the small airways had occurred, but that the tests employed were not sensitive enough to detect them, (3) antagonistic chemical and/or nervous influences acting on the small airways, had nullified the effects of each other, or (4) in spite of changes having occurred in the small airways their effect on the flow rates had been offset by a simultaneous change in the elastic recoil pressure of the lung, because flow at low lung volumes during a forced expiratory effort is directly related to the elastic recoil pressure of the lung and indirectly related to the resistance of the upstream segment (small airways). Thus, $V_{\text{max}}$ at low lung volumes $= \frac{\text{Pst} (1)}{\text{Rus}^{10}}$ where $V_{\text{max}}$ is maximal flow, Pst (1) is static recoil pressure of the lung and Rus is the resistance of the upstream segment.
With regard to the first possibility, although DaSilva and Hamosh (1973) have suggested that a concentration gradient of smoke particles might exist along the bronchial tree and consequently sufficient particles may not reach the small airways, this is extremely unlikely, as it is known that most of the particles in cigarette smoke being less than 2 microns in size, are deposited in the small airways and alveoli. Furthermore, as will be seen later in this discussion, one of the mechanisms by which cigarette smoke induces airway changes is the release of histamine. It is highly improbable that histamine would exert a constrictor effect on the smooth muscle of the large airways without a similar effect on the smooth muscle of the small airways. Therefore, it must be inferred that not only do smoke particles reach the small airways but that they also exert an effect there.

The second possibility that the tests used here were not sensitive enough to detect the small airway changes cannot be valid, because the results in Section A clearly show that the flow rates at low lung volumes (especially FEF 30–20%) are sensitive tests of small airway changes.

The third possibility that the effect of histamine on the small airways was masked by some other opposing mechanism must be conceded, since the observed effect
was not one of constriction as would be expected if histamine were acting unopposed.

Lastly, it is also possible that the static recoil pressure of the lung increases following smoking, thus nullifying the effect of the increased small airway resistance on the flow rates at low lung volumes, in accordance with the relationship between Vmax, Pst (l) and Rus expressed above (page 113). One or both of the last two possibilities probably operate to varying degrees, accounting for the lack of significant changes in the flow rates at low lung volumes.

The results from the animal studies discussed later (page 118) help further substantiation of these two possibilities.

The mean presmoking eosinophil and basophil counts of 333 and 45.3 cells per cu.mm were within the normal range. Moore and James (1953) obtained mean basophil counts of 46.7 per cu.mm in normal young men. The mean percentage decreases in the eosinophil (14%) and basophil (13%) counts soon after smoking were statistically significant (P < 0.05) (Table 13). There was a high correlation (r = 0.76) between the fall in basophils and the fall in eosinophils (Fig. 24). These findings suggest that there was a basophil degranulation and histamine release following the cigarette smoking. Douglas et al. (1969) studied the histamine release from human
autopsy lungs after exposure to cigarette smoke and found only minimal histamine release. However, they used minced lung tissue which had been washed before exposure to smoke. These procedures would have caused mast cell degranulation and histamine release, as mast cells and basophils are known to be very sensitive to various experimental procedures.\textsuperscript{190,195} This probably explains their failure to observe significant histamine release in minced lung following exposure to smoke.

The fall in eosinophil count in the present study is most likely to be due to a mobilisation of the cells towards the area of histamine release.\textsuperscript{69,189} In this context it may be noted that Kilburn and Mckenzie (1975)\textsuperscript{113} have demonstrated a leucocyte recruitment to airways in response to cigarette smoke.

It can reasonably be assumed that this histamine release is a part of the mechanism of large airway constriction following smoking, which was discussed earlier (page 112). Samanek and Aviado (1965)\textsuperscript{193} have provided evidence in animals that some of the bronchomotor effects of nicotine are mediated by histamine. Palacek et al. (1967)\textsuperscript{177} have shown in dogs, that the bronchoconstrictor effect of cigarette smoke is abolished after alpha hydrazine histidine, an inhibitor of histidine decarboxylase. Cigarette smoke has been shown to contain water soluble histamine releasing substances
which cause airway constriction in guinea pigs. The exact mechanism by which histamine once released, acts on the smooth muscle of the airways is not definitely known although it has been suggested that it could be a direct action on the smooth muscle, or a reflex action through the vagus. Another possibility is that histamine causes bronchoconstriction through a local axon reflex. Since atropine blocks the bronchoconstrictor response to cigarette smoke in dogs, and in man, a parasympathetic mechanism seems to be involved. Parasympathetic nerve fibres are chiefly distributed to the larger airways. Therefore, the constrictor effect of tobacco smoke could be expected to be predominantly in the larger airways. This view is supported by the findings presented here of a significant fall in PEF and PEF 80–70%, but not in PEF 30–20%.

In addition to its bronchoconstrictor effect through the release of histamine, there is evidence that tobacco smoke may directly stimulate the mechanoreceptors of the airways. Once stimulated, these could bring about reflex vagal bronchoconstrictor effects.

Though there were significant decreases in PEF, PEF 80–70%, eosinophil counts and basophil counts soon after smoking, these changes did not correlate
significantly with the decline in FEV$_{1.0}$% and FEF 30-20% observed in the longitudinal study. The r values obtained (Table 14) are suggestive of a possible relationship between the immediate response and the susceptibility of an individual. However, these values were not statistically significant. This suggests that the immediate response to smoking is not a measure of the long term susceptibility of an individual to cigarette smoke. Although this appears surprising, it must be recognised that the mechanisms by which the immediate response is brought about may be entirely different from those by which the long term effects are caused. The immediate response as described above is probably caused by the release of histamine and through reflexes initiated in the airways, whereas the long term effects are probably caused by inflammatory changes and hypersecretion of mucus.\textsuperscript{71,150,175}

**Animals**

The nonelastic resistance measured at low lung volumes had decreased in most animals following smoking (Tables 15 and 16). The total nonelastic flow resistance is the sum of the resistance in the large and small airways. A greater proportion of this resistance is contributed by the small airways. at low lung volumes, particularly in conditions of passive recoil.\textsuperscript{137,205} Hence, a fall in this parameter may be due either to a dilatation of
both the large and small airways or a dilatation of one and constriction of the other, the net result being a fall in resistance. However, published data\textsuperscript{47,48,171} and the results obtained here on the human subjects have shown that the immediate response of the large airways to tobacco smoke is constriction which lasts for more than one hour.\textsuperscript{171} Since the resistance in the animals was measured within 10 minutes of smoking it may reasonably be assumed that during this period, constriction of the large airways was present. Therefore the observed decrease in nonelastic resistance, at a time when the large airways were constricting must be attributed to a dilatation of the small airways. It must be pointed out that the bronchoconstrictor effect of cigarette smoke may possibly have been decreased by the deep inspirations preceding the measurements which were necessary to ensure uniform volume histories.\textsuperscript{158} However, Nadal and Tierney (1961)\textsuperscript{172} have shown that this effect is transitory, lasting only a minute or two. Therefore, this factor could not have affected the measurement of resistance in this study as these were made at least three minutes after the deep inspirations.

That the constrictor effect in the large airways is not always exceeded by a dilator effect in the small airways is brought out by the fact that in a few animals there was an increase in nonelastic resistance.
The results of the human studies show that histamine release is probably part of the mechanisms by which the large airway constriction is brought about. As discussed earlier (page 114) it is very unlikely that histamine would have different effects on the smooth muscle of the large and small airways. Histamine release therefore, would be expected to produce bronchoconstriction in both large and small airways. In such a situation, the difference in the response of large and small airways to tobacco smoke is most likely to be due to other mechanisms. It is known that the small airways in dogs are rich in beta receptors in contrast to the large airways where they are sparse. 236 It is also known that significant quantities of nicotine are absorbed into the circulation during smoking. This may be of the order of up to 1 mg of nicotine per cigarette or up to 150 microgram per puff. 15, 118 Thus, smoking a single cigarette raises the plasma nicotine in smokers from a pre-smoking level of about 1-5 ng per ml to about 15-50 ng per ml within 5 to 10 minutes. 105 Nicotine stimulates the adrenal medulla with the release of significant amounts of epinephrine 55, 230, 231 which must exert its maximum effect on those areas where the beta receptors are most numerous, namely the small airways. Evidence to support this view comes from two reports. Zuskin et al. (1974) 243 showed that blockade of beta receptors by propranolol
augmented the bronchoconstrictor effects of tobacco smoke. Also, Woolcock et al. (1969)\textsuperscript{236} using propranolol have shown in dogs that vagal bronchoconstriction can occur in all the airways, but that its effect on peripheral airways is masked by adrenergic mechanisms. Therefore, it follows that in the small airways the dilator action of epinephrine brought about through the beta receptors may mask the constrictor effect of tobacco smoke brought about by histamine release. This masking action would be marginal or absent in the large airways where beta receptors are scarce. Consequently, the predominant residual effect of tobacco smoke on the large airways is constriction.

A somewhat parallel mechanism for the differing response of the large and small airways to tobacco smoke may be based on the fact that there is a rich sympathetic innervation of the small airways in contrast to the predominant parasympathetic innervation of the large airways.\textsuperscript{138} Cabezas et al. (1971)\textsuperscript{43} found that sympathetic stimulation could mask a parasympathetic bronchoconstriction, particularly in the smaller airways. Stimulation of sympathetic and parasympathetic ganglia by absorbed nicotine could then cause a constriction of the large airways, but a dilatation of the small airways.

Thus, the particulate phase of tobacco smoke
would cause a bronchoconstrictor effect through histamine release and parasympathetic stimulation chiefly on the large airways, whereas the absorbed nicotine would cause a bronchodilator effect through catecholamine release and sympathetic stimulation chiefly on the small airways. Zuskin et al. (1974)\textsuperscript{243} have postulated an interaction between histamine and autonomic mediators as a possible mechanism in controlling the balance between sympathetic and parasympathetic stimuli acting on the airways. Woolcock et al. (1969)\textsuperscript{236} consider that the rich sympathetic innervation of the small airways has a protective effect against undue narrowing.

The dilatation which characterizes the immediate response of the small airways to tobacco smoke has probably no cumulative effect as by its very nature it is short lived. The narrowing of small airways described in smokers in Section A is a more chronic response to tobacco smoke, brought about through inflammatory changes and increased secretion of mucus.\textsuperscript{71,175} Alterations in smooth muscle tone are probably not involved in these chronic effects.

**Static compliance**

Of the 7 dogs and 5 monkeys in which C\textsubscript{stat} (l) was measured 4 dogs and 2 monkeys showed a fall in this parameter. The other animals showed no change or only slight changes in C\textsubscript{stat} (l). A fall in static compliance
could be caused either by an increase in the elastic recoil of the lung or by a narrowing of the peripheral airways. Woolcock et al. (1969) have provided evidence to show that narrowing of the small airways could lead to a decrease in compliance. However, since most of the animals in this study did not show small airway narrowing but rather a dilatation, it must be presumed that the fall in compliance was due to an increase in the elastic recoil pressure of the lung. This increase is probably not due to haemodynamic changes in the pulmonary circulation, which are known to follow the smoking of a cigarette, as the nature and magnitude of such changes are unlikely to alter the mechanical properties of the lung.

The probable reasons for the increase in elastic recoil pressure are discussed more fully later in this section (page 125).

**Dynamic compliance**

None of the animals except dog No. 7 and monkey No. 5 showed a fall in Cdyn(l) with increasing breathing frequency. However, monkey No. 5 showed frequency dependence prior to smoking as well. The frequency dependence of Cdyn (l) in dog No. 7 may have been due to the large increase in resistance and/or the large decrease in static compliance which this animal showed after smoking. A marked constriction of the large bronchi or a marked
increase in lung elastic recoil are known to cause frequency dependent behaviour.\textsuperscript{234}

Three dogs had an increase in $C_{dyn}$ (l) with increasing breathing frequency before smoking which did not change after smoking. A rise in $C_{dyn}$ (l) with increasing breathing frequency has been observed by other workers,\textsuperscript{65,234} in spite of careful attention to the phase shifts of their measuring instruments. Dosman et al.\textsuperscript{(1975)}\textsuperscript{65} attribute this to a rise in pulmonary inerance in some subjects at high respiratory frequencies.

It is surprising that most of the animals did not show a fall in $C_{dyn}$ (l) with increasing frequency. Theoretically $C_{dyn}$ (l) will not fall with increasing frequency if all the airways constrict or dilate to the same degree. However, it is hardly likely that all airways would show identical changes in lumen. Woolcock et al.\textsuperscript{(1969)}\textsuperscript{235} did not observe frequency dependence during vagal stimulation in dogs though there was peripheral airway constriction. Brown et al.\textsuperscript{(1969)}\textsuperscript{40} caused experimental obstruction of the small airways of dogs with beads, but did not find frequency dependence of $C_{dyn}$ (l). In contrast, small airway obstruction in pigs caused frequency dependence. This difference in the mechanical characteristics of dog and pig lungs is probably due to differences in their structure. Van Allen and Lindskog \textsuperscript{(1931)}\textsuperscript{225} have demonstrated free collateral
ventilation between lobules in dogs, but not in pigs. The animals used in the present study, both dogs and monkeys, showed the presence of free collateral ventilation. Thus, in spite of changes in the calibre of the small airways, no asynchrony would have developed and therefore no frequency dependence. 140

Vital capacity

In almost all the animals in which static compliance fell, there was also a fall in vital capacity. This may have been either due to a decrease in compliance (i.e. increase in the static recoil) or due to constriction of small bronchioles and alveolar ducts, which normally account for 20% of the VC. 235 However, since the small airways did not show an increase in resistance in the majority of the animals studied here, it must be inferred that the fall in VC was due to a decrease in compliance.

Pressure volume characteristics

As seen from figures 25b, 26b, 27b and 28b, the striking change after smoking was a decrease in P-V hysteresis. Hysteresis is "the failure of a system to follow identical paths of response upon application and withdrawal of a forcing agent". 5 The area of the P-V hysteresis loop decreased in all but 1 of the 11 animals in which it was measured.

In normal lungs, three factors are responsible for
static P-V hysteresis. One is tissue hysteresis, another is surface hysteresis and the third factor is based on the difference in the number of open air spaces during inflation and deflation at identical transpulmonary pressures. 5 Most of the hysteresis in gas filled lungs is normally due to surface forces, 159 and can be accounted for by the properties of the alveolar surface film.

A decrease in static P-V hysteresis has been observed in many conditions. Lempert and Macklem (1971) 131 observed that a decrease occurred with a rise in the temperature of the lung. The width of the P-V curves at 40% maximum, fell from 12 cm H2O at 27°C to 4 cm H2O at 47°C. Lowering the temperature reversed these effects. They also observed that heating increased the minimum surface tension and decreased the maximum surface tension of lung extracts and tracheal washings. Menkes et al. (1971) 162 have shown a decrease in static P-V hysteresis in isolated dog lung lobes after insufflation of kerosene and have suggested that this was due to inactivation of surfactant. Kahana and Thurlbeck (1972) 110 observed decreased hysteresis in emphysematous subjects as compared to normal subjects. A decrease in static P-V hysteresis has also been observed in rat lungs exposed to 70% oxygen for a week. 187 The common factor in most of these studies causing the decrease in hysteresis, was thought to be a change in the pulmonary surfactant
activity.

Changes in pulmonary surfactant by inhaled pollutants have been reported in the literature.\textsuperscript{30,90,164,229} Miller and Bondurant (1962)\textsuperscript{164} found that exposure to cigarette smoke caused a marked decrease in the surface tension at large surface areas, in extracts prepared from rat lungs. Giammona (1967)\textsuperscript{80} noted that cigarette smoke consistently lowered the maximal surface tension of lung extracts. Webb et al (1967)\textsuperscript{229} observed a decrease in maximal and an increase in minimal surface tension of bronchial washings of dogs when exposed to cigarette smoke. These findings are all suggestive of an inactivation of pulmonary surfactant by cigarette smoke. Since nonspecific dust also produces a similar effect the change is thought to be only a mechanical one on molecular cohesive forces.\textsuperscript{229} The temperature of the cigarette smoke inhaled is unlikely to exert a significant effect on surfactant as it is known that the inhaled smoke comes down to body temperature by the time it reaches the lung.\textsuperscript{129} The findings of the present study strongly suggest a similar inactivation of surfactant by cigarette smoke. Inactivation of surfactant would explain the increase in lung elastic recoil and the decrease in static P-V hysteresis.

If such a mechanism occurs in humans immediately following cigarette smoking, it would tend to increase the forced expiratory flows at low lung volumes
according to the relationship $V_{\text{max}} = \frac{P_{\text{st}} (1)}{R_{\text{us}}}^{160}$ as described earlier (page 113). Thus, even if $R_{\text{us}}$ increased, the flow rates would still increase provided the increase in $P_{\text{st}} (1)$ was greater.\textsuperscript{215} It has been shown in this study that the recoil pressure of the lung increased in the animals after smoking. It is reasonable to infer that this could also occur in human beings after smoking although this parameter was not measured in the human subjects in this study. Other studies have shown that such a change does occur in humans, as an immediate response to smoking.\textsuperscript{169}
SUMMARY

The immediate response of the airways and the blood basophil and eosinophil counts to tobacco smoking were determined on 24 human subjects. Airway response was studied using forced expiratory spirograms. A correlation between the immediate response and the deterioration in forced expiratory flow rates observed over long continued periods of smoking was attempted.

In addition, the immediate effects of cigarette smoking on the static compliance of the lung, dynamic compliance of the lung at different respiratory frequencies, vital capacity, static P-V relations and nonelastic resistance were studied in 15 animals. The immediate response of the large airways was found to be constriction. Small airway changes were variable.

A significant fall in blood basophil and eosinophil counts was observed in the human subjects, indicating histamine release as a probable mechanism of broncho-constriction.

No significant correlation was observed between the magnitude of the immediate response and the susceptibility to long term smoking in the human subjects.

There was evidence from the animal studies that tobacco smoke caused alterations in the surface properties of the lung, probably as a result of
inactivation of surfactant leading to an increase in the elastic recoil of the lung.

The significance of these findings and the probable causes of the variable response of the small airways are discussed.