

distemonanthin. Unfortunately, there is no quick method for distinguishing between the two types of wood, nor is it known how the two types are distributed in commercial supplies, but a variation in extractive content such as this may account for the sporadic occurrence of ayan dermatitis.

The above results do not exclude that there may be other unidentified sensitizing constituents in the crude methanol extract which are not so readily isolated.

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## Pulmonary Hypersensitivity to the Grain Weevil

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A case of inhalant allergy to the grain weevil is described. Provocation inhalations of the weevil protein produced immediate responses shown by falls of as much as 25% in the F.E.V.<sub>1-0</sub>. These changes were reversed by a bronchodilator. Arthus-type reactions also occurred approximately three hours after the inhalation of protein. In these the transfer factor was reduced by 25% and was not affected by a bronchodilator. Antihistamines were found to inhibit the immediate response but to have no effect on the Arthus reaction.

Coincident with the fall in transfer factor there were rises in the temperature and pulse rate. An Arthus-type as well as an immediate skin response was demonstrated. Precipitating antibodies were detected in the serum.

The similarity of these reactions to those seen in farmer's lung and to reactions to avian protein is discussed, together with the possibility of the wider implications of sensitivity to the grain weevil.

Pulmonary reactions to inhaled allergens are well recognized and seem to fall into two groups. The first is associated with an immediate reaction with wheezing and a change in the forced expiratory volume; and a second variety is associated with a more delayed response or Arthus-type hypersensitivity with systemic upset and a change in the transfer factor. The report of hypersensitivity to pigeon and budgerigar excreta (Hargreave, Pepys, Longbottom, and Wraith, 1966) has recently drawn attention to this latter type of reaction. This report showed that pigeon and budgerigar fanciers suffered from pulmonary disease associated with impaired

lung function. In particular there were changes in lung function associated with systemic upsets occurring some hours after the inhalation of the allergen and with a pattern rather similar to that of farmer's lung.

Asthma caused by the grain weevil (*Sitophilus granarius*) has been described (Frankland and Lunn, 1965; Lunn, 1966). Further pulmonary function studies, skin reactions, and antibody tests have been made on one of the subjects described. In particular the immediate and later effects of the inhalation of weevil extract and the effect of antihistamines in preventing reactions has been studied, together with changes in temperature, pulse, and skin reaction.

## Materials and Methods

**Pulmonary Function Studies** Routine simple tests were carried out using the standard methods employed in the Pulmonary Function Laboratory of the London Hospital (Hughes and Lee, 1963) and 1% extracts of weevil were used in inhalation provocation tests. The solvent and weevil extract were inhaled through a mask after nebulization in a Wright's nebulizer through which oxygen was passed at a flow rate of 4 litres per minute.

**Skin Testing** Intradermal skin testing was performed using 1% weevil extract, and the reactions were observed over a period of several hours.

**The Subject** R.K. was a healthy girl of 19 years who had had no history of chest trouble or allergic responses until she began working in a laboratory where she was exposed frequently to the grain weevil. After six months she developed sneezing, conjunctivitis, and urticaria when exposed to the dust from the insect. Within a further month she developed asthma. Skin testing to the grain weevil was positive with a positive Prausnitz-Kustner transfer test. Since removal from contact with the grain weevil she has been free from any asthmatic or allergic manifestations for 18 months. Clinical examination revealed no abnormality and her blood count, E.S.R., and chest radiograph were normal.

## Results

Simple tests of pulmonary function were all normal as shown in Table I. She gave remarkably consistent results; for example, her F.E.V.<sub>1.0</sub> measured over a five-hour period during the day varied only between 2,900 and 3,025 ml., or 3%, in 16 measurements. Similarly, her transfer factor varied only between 20 and 21 ml./mm. Hg/min. in the course of four duplicate estimations by the single-breath method carried out over a two-and-a-half-hour period.

**Provocation Tests** In the first study she was given an inhalation of solvent as a control and there was no change in her F.E.V.<sub>1.0</sub>. She then received an eight-minute inhalation of 1% weevil extract. This produced a fall in F.E.V.<sub>1.0</sub> which was maximal in 30 minutes, by which time it had fallen from 2,800 to 2,100 ml., a change of 25%. This was associated with a feeling of tightness in the throat and chest. There was an 18.5% change in vital capacity from 3,300 ml. to 2,800 ml. A bronchodilator aerosol reversed this change, the vital capacity reverting to 3,250 ml., and the F.E.V.<sub>1.0</sub> to 2,725 ml., within 3.0% of the original value. The subject then returned home, but that evening, four hours later, she developed cough, breathlessness,

TABLE  
LUNG FUNCTION TESTS

Lung Volumes (ml.)	Observed	Percentage of Predicted <sup>2</sup> Value
Vital capacity	3,300	100
Inspiratory capacity	2,200	100
Expiratory reserve volume	1,100	100
Functional residual capacity	2,150	96
Residual volume (R.V.)	1,050	92
Total lung capacity (T.L.C.)	4,350	98
R.V./T.L.C.	24%	
<i>Ventilation</i>		
Vital capacity (ml.) <sup>1</sup>	3,300	
F.E.V. <sub>1.0</sub> (ml.) <sup>1</sup>	2,800	
F.E.V. %	85	
P.E.F. (l./min.) <sup>1</sup>	400	
Maximum voluntary ventilation (l./min.) <sup>1</sup>	90	
Respiratory rate/min.	15	
Tidal volume (ml.)	500	
Minute volume (l./min.)	7.5	
Transfer factor (single-breath D <sub>LCO</sub> ) <sup>1</sup>	22 ml./mm. Hg/min. (100% predicted)	

<sup>1</sup>A bronchodilator aerosol did not alter these values.

<sup>2</sup>Predicted values taken from Goldman and Becklake (1959), *Amer. rev. Tuberc.*, 79, 457.

and a tight feeling in the chest which persisted until the next morning.

Because of this delayed reaction she was challenged again two weeks later with the extract by inhalation and changes followed in F.E.V.<sub>1.0</sub>, temperature, pulse rate, and skin reaction over a period of several hours. Figure 1 shows that following a five-minute inhalation of weevil extract there was an immediate and a late fall in F.E.V.<sub>1.0</sub>. The initial change, which was maximal after 50 minutes, was 12.5%. The F.E.V.<sub>1.0</sub> then increased, though not regaining its original value, but after three hours fell to 2,250 ml., a drop of 20% from the initial value. Thereafter it remained reduced for some hours further so that 400 minutes after the initial inhalation it was still only 2,300 ml. At this stage a bronchodilator aerosol did not restore the F.E.V.<sub>1.0</sub>. The pulse rate remained reasonably constant for the first two and a half hours but showed a marked change at 150 and 170 minutes, rising from 72 to 90 beats per minute. The rise in pulse rate coincided with a steep secondary fall in F.E.V.<sub>1.0</sub>. The temperature seemed to show a bi-phasic response, there being a rise of 1.4°F. (0.8°C.) occurring maximally at 40 minutes and a similar

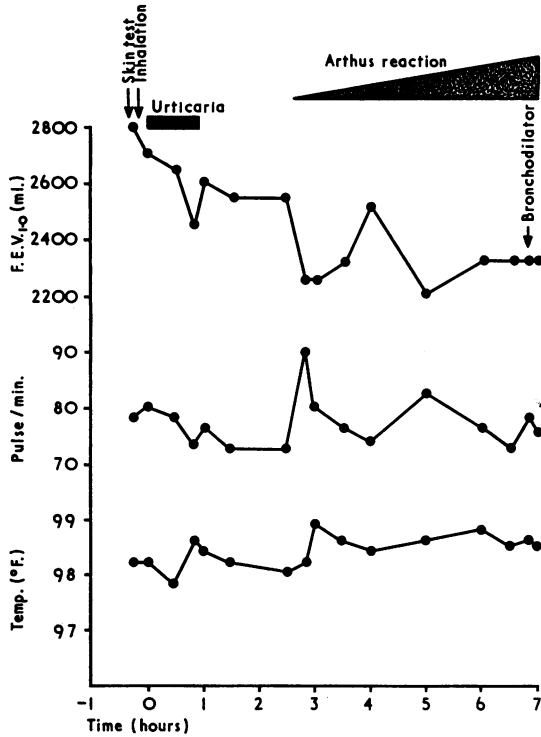


FIG. 1. The effect of a provocation inhalation on F.E.V.<sub>1.0</sub>, and the skin responses to an intradermal test.

secondary rise coinciding with the change in pulse rate and F.E.V.<sub>1.0</sub>. An intradermal test was performed immediately before inhalation. This produced an immediate urticarial weal and flare reaction with considerable itching. This was maximal at 15 minutes with a weal of 12 mm. diameter and a flare of 50 mm. diameter. It generally faded and at 40 minutes had disappeared. In just under three hours (160 minutes) a characteristic Arthus-type reaction developed, measuring 30 × 40 mm. This area of diffusely raised erythema steadily increased in size and persisted until the next morning when it was 150 × 80 mm. Although it began to fade it was still present 48 hours later.

In view of this Arthus-type reaction, it was decided to repeat the test, making measurements of the transfer factor by the single-breath carbon monoxide method. The results are shown in Figure 2. Again there were similar changes in F.E.V.<sub>1.0</sub>, temperature, and pulse, though they were less marked than in the previous study, possibly because there was no skin testing and reaction. The interesting finding was a later fall in the transfer factor which was only 75% of its original value four hours

after provocation. In absolute values it fell from 20 to 15 ml./mm. Hg/min. In addition scattered crepitations were heard at the lung bases three and four hours after the inhalation. Changes were followed for up to five hours and at the end of the experiment a bronchodilator aerosol was without effect on the F.E.V.<sub>1.0</sub> or transfer factor.

Finally the effect of an antihistamine was tested. Chlorpropheniramine, 4 mg., was taken by mouth two hours before and two hours after the provoking inhalation. The drug modified the initial but not the delayed response, as shown in Figure 3. There was virtually no change in F.E.V.<sub>1.0</sub> in the first hour (a 3.4% change, barely outside the limits of variation under control circumstances). There was a further fall of 100 ml. (3.4%) at three hours. There was a delayed fall in the transfer factor, as had occurred without the antihistamine. The maximal change was from a control value of 19.5 to one of 14.5 ml./mm. Hg/min., a change of 25.7%, almost identical to that obtained previously. The secondary rise in pulse was unaffected and again occurred at three hours. The later temperature rise still occurred but may have been modified slightly in that on this occasion it did not occur until after four hours. Because of the previous severe skin reaction an intradermal prick test was performed. There was no immediate urticarial reaction, but an area of

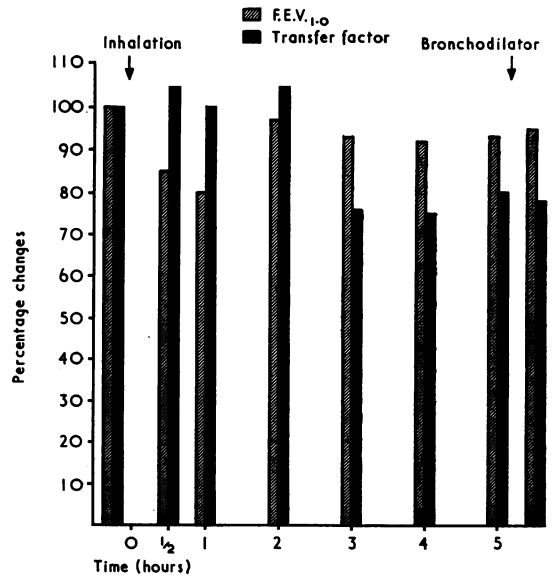


FIG. 2. Histogram of percentage change in F.E.V.<sub>1.0</sub> and percentage change in transfer factor and the effect of a bronchodilator aerosol.

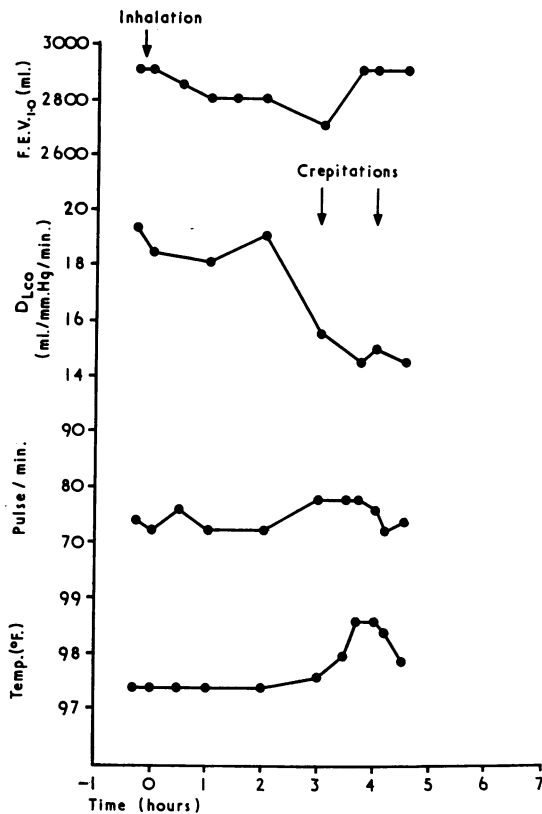


FIG. 3. The effect of chlorpheniramine on the response to inhalation.

itchy erythema appeared 20 minutes later, measuring 25 mm. in diameter at half an hour and slightly increased in size at one hour. Thereafter it faded slowly but did not completely disappear until two and a half hours after the initial test. There was no further skin reaction.

**Control Studies** Twenty-five healthy subjects were given five-minute inhalations of weevil protein without any changes occurring in their lung function.

**Serological Tests** Precipitin reactions between the patient's serum and weevil extract were demonstrated by the double diffusion method in an agar-gel plate following a two and a half times concentration of the serum.

## Discussion

Our results in this subject show certain interesting features. First there was an immediate asthmatic type response to the inhaled allergen followed some hours later by an Arthus-type response. Further, these reactions are affecting different parts of the lung structure. The former, due to a change in the airways, occurs rapidly and can be reversed by a bronchodilator aerosol and prevented by an antihistamine. The more delayed type of reaction, involving the gas exchanging part of the lungs and associated with systemic symptoms, crepitations, temperature and pulse changes, and decreased transfer factor, was unaffected by an antihistamine and by isoprenaline inhalation. Besides a biphasic response in the lungs there was a similar double response in the skin, namely an immediate urticarial reaction followed some hours later by an Arthus-type reaction. Further, precipitating antibodies were found in the serum. The delayed reaction with changes in transfer factor, Arthus skin reaction, and precipitating antibodies is very similar to those found in farmer's lung and to the recently described disease found in pigeon and budgerigar fanciers (Hargreave *et al.*, 1966). In both these conditions with repeated exposure to the provoking substances a permanent structural change can occur in the lung leading to an interstitial fibrosis with permanent alteration in lung function. When removed from exposure to the grain weevil this patient lost her symptoms. Pulmonary and systemic reactions could be produced, however, by inhalation and were associated with transient lung function changes although her chest radiograph and lung function before provocation were still completely normal. She therefore represents an early stage in the illness and fortunately has been removed from exposure before permanent damage to the lung has occurred.

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