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Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction

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Abstract

***Background*—Earlier studies of aerosol deposition in the lungs have relied on indirect labelling of Teflon spheres of a similar size distribution to the drug in question and have assumed similar aerodynamic properties. Using a modification of a new technique for directly labelling salbutamol, the deposition of salbutamol within the lungs of normal subjects and patients with asthma has been studied with the use of a metered dose inhaler (MDI) alone, an MDI with a spacer device, and a dry powder inhaler (DPI).**

***Method*—Salbutamol was directly labelled with technetium-99m and placed in an MDI or DPI. Ten normal subjects and 19 patients with asthma inhaled 200 μg of salbutamol by means of the MDI alone, the MDI with a spacer device attached, and by DPI on separate days. Deposition was assessed by a dual headed gamma camera after inhalation of the drug.**

***Results*—The total mean (SD) percentage deposition of the drug in the normal subjects was 21·6% (8·9%) with the MDI alone, 20·9% (7·8%) with the MDI with spacer, and 12·4% (3·5%) with the DPI. For the patients, the mean percentage deposition was 18·2% (7·8%) with the MDI alone, 19·0% (8·9%) with the MDI and spacer, and 11·4% (5·0%) with the DPI. Bronchodilatation achieved by the patients was similar with all three techniques. Mean peripheral lung deposition was significantly greater with a spacer device than when the MDI was used alone in both normal subjects (49·4% (6·1%) *v* 44·1% (9·9%)) and patients (38·6% (11·1%) *v* 30·4% (9·4%)).**

***Conclusions*—The deposition of directly labelled salbutamol from an MDI is greater than previously estimated by indirect labelling techniques. The deposition of labelled salbutamol from a DPI, however, is little different from that measured by indirect techniques.**

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Radiolabelling techniques have provided an important source of information on the deposition patterns of therapeutic aerosols in the lungs. Until recently most information has been obtained from indirect labelling techniques because of the inability to attach a gamma emitting radionuclide to the drug itself. An inert substance, usually Teflon or polystyrene, with size characteristics similar to the drug in question, is labelled and used either as a substitute for the drug itself[1] or mixed in with the drug in a reconstituted metered dose inhaler (MDI).[2] The latter method has the advantage of allowing bronchodilator responses to be measured at the same time as the distribution pattern of the radiolabelled particles. These techniques make the basic assumption, however, that the radiolabelled carrier and the unlabelled drug particles have similar physical properties and distribution when inhaled into the thorax.

There has been scanty information on deposition patterns of directly labelled drug within the lung. Short *et al*[3] radiolabelled ipratropium bromide with bromine-77, and a new method for directly labelling β_2 agonists has recently been described by Köhler and colleagues.[4] A similar technique to that of Köhler has been applied by Newman *et al*[5] to sodium cromoglycate with technetium-99m (^{99m}Tc) in normal subjects and also to salbutamol in asthmatic subjects using a breath actuated MDI.[6] We have recently reported a modification of Köhler's technique for the preparation of an MDI and also have developed a dry powder inhaler (DPI) containing salbutamol directly labelled with ^{99m}Tc.[7] The present study uses these techniques to assess the deposition patterns and bronchodilator responses of directly labelled salbutamol both in normal subjects and in patients with asthma using an MDI, an MDI with a spacer device, and a DPI, each with similar doses of salbutamol.

The study provided an opportunity to assess whether the commonly quoted percentage deposition of salbutamol in the lungs of normal subjects and patients with airflow obstruction (9–14%)[1-3 8 9] was the same if directly labelled salbutamol was used instead of radiolabelled substitution particles.

Methods

The detailed methods for making the MDI and DPI, together with their validation, is reported elsewhere.[7] The technique is briefly described below.

METERED DOSE INHALER

A small amount of ^{99m}Tc as sodium pertechnetate was eluted from a molybdenum-99/technetium-99m generator into butanone. Approximately 60% of the $^{99m}TcO^-_4$ was transferred to the butanone phase. After allowing the two phases to separate, the lower aqueous phase was discarded and the organic phase collected and evaporated to dryness, leaving $^{99m}TcO^-_4$ on the surface of a glass vial. A mixture of oleic acid and trichlorofluoromethane (propellant 11) was added to the micronised salbutamol and mixed in an ultrasonic bath during which the $^{99m}TcO^-_4$ was adsorbed onto the salbutamol. Further propellant 11 was then added and the mixture was carefully weighed into empty MDI canisters together with liquid dichlorodifluoromethane (propellant 12). A metering valve was crimped on to each canister. The canisters were made according to a formula, containing propellant and drug, of a typical MDI.

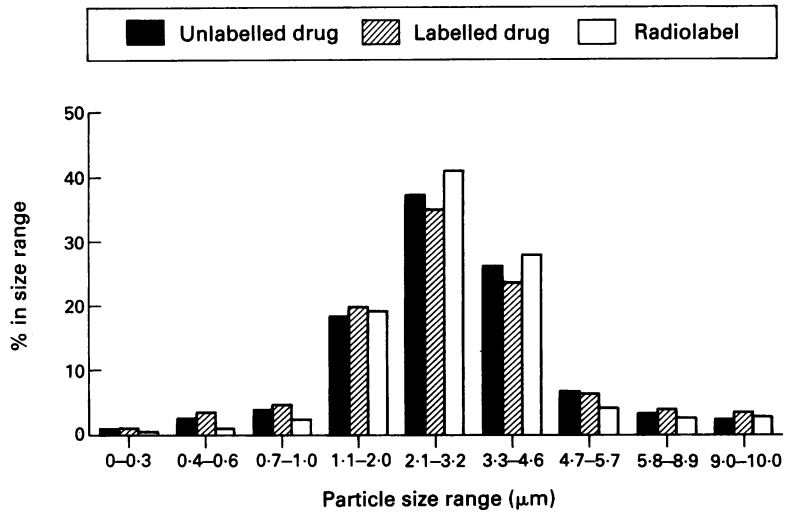

Figure 1 Mean distribution of radiolabel and salbutamol for four MDIs actuated into an Anderson Mark II cascade impactor (operated at 28·3 l/min), shown as a percentage of the total recovery for eight stages plus filter. Also shown is the mean percentage drug distribution for four MDIs containing unlabelled salbutamol.

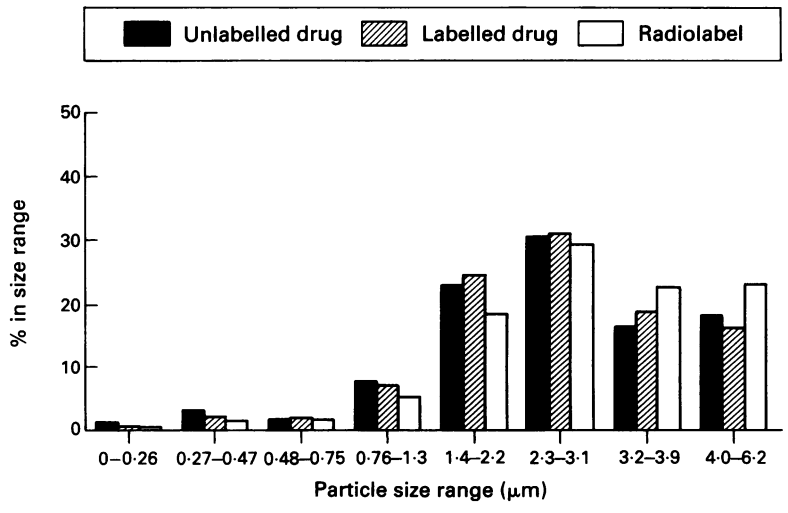

Figure 2 Mean distribution of radiolabel and salbutamol from the contents of three DPIs sampled by an Anderson Mark II cascade impactor (operated at 60 l/min), shown as a percentage of the total recovery for seven stages plus filter. Also shown is the mean percentage drug distribution for three DPIs containing unlabelled salbutamol.

DRY POWDER INHALER

For the DPI, the drug was in the form of micronised salbutamol sulphate. The salbutamol sulphate was mixed with $^{99m}TcO^-_4$ in propellant 11 in an ultrasonic bath. The propellant 11 was then evaporated off and the dried labelled salbutamol sulphate recovered and blended with lactose carrier before being dispensed into unit dose blisters, each containing 200 μg salbutamol.

VALIDATION

The distribution of the radionuclide and salbutamol particles were compared with an Anderson 8 stage cascade impactor. This device is modelled to the particle carrying characteristics of the human respiratory tract so that the potential lung penetration by both solid and liquid airborne particles can be predicted by the instrument. The percentages of the radionuclide and salbutamol measured in each stage were similar for both the MDI and DPI (figs 1 and 2). The proportion of particles of labelled and unlabelled drug and the radionuclide showed concordance throughout the range of particle sizes when each device was tested at its appropriate flow rate. With the MDI, the mass median aerodynamic diameters (MMAD) were similar for labelled (2·8 μm) and unlabelled (2·9 μm) salbutamol, and for the radionuclide (2·7 μm). The MMAD with the DPI was 2·7, 2·7, and 3·0 μm for labelled and unlabelled salbutamol, and for the radionuclide, respectively (figs 1 and 2).

Quality control of each MDI canister and DPI blister was verified on the day of each experimental study with a Twin Impinger. This device measures the proportion of small particles or droplets with an aerodynamic diameter of 6·4 μm which have a 50% probability of progressing and depositing in the second stage.

SUBJECTS

Ten normal subjects and 19 patients with asthma were studied. The normal subjects comprised seven men and three women with a mean age of 34·3 (range 23–49) years; nine were non-smokers and none had a history of any respiratory illness. The 19 patients (13 men, mean age 49·7 (range 22–71) years) all had a documented history of reversible airflow obstruction in response to bronchodilators. The patients were asked to withhold all bronchodilator therapy for at least six hours before the investigation. All subjects gave written informed consent and the study was approved by the local ethics committee.

LUNG FUNCTION TESTS

Lung function measurements were performed with a portable pneumotachograph (Flowmate, Jaeger). Each subject was tested 15 minutes before and 30 minutes after the administration of salbutamol. On each

occasion the best of three satisfactory efforts was used. Measurement of the peak expiratory flow rate (PEF, l/min), forced expired volume in one second (FEV_1), and the forced vital capacity (FVC) were made.

ADMINISTRATION OF RADIOLABELLED SALBUTAMOL

All the subjects performed the three separate parts of the study in random order on different days with at least a week between each study. The subjects were given instructions and demonstrations of how to use each type of inhaler and were allowed to practise with placebo inhalers.

With the DPI, 200 μg salbutamol was inhaled from a single unit dose containing 6–18 MBq radioactivity. With the MDI the subjects inhaled 200 μg salbutamol containing 6–18 MBq as two separate actuations of 100 μg.

The three studies were conducted as described below.

Metered dose inhaler

Subjects inhaled from the MDI after breathing out to residual volume. They then performed a steady deep inhalation actuating the MDI themselves immediately after they started to inhale. At the end of an inhalation they held their breath for 10 seconds before gently exhaling into a collecting bag. The second dose of salbutamol was then inhaled in exactly the same fashion and subjects exhaled into the collecting bag again.

Metered dose inhaler with spacer device

Before inhaling from an MDI through a spacer device (Volumatic) the subjects were first asked to breathe out. No emphasis was made to ask them to reach residual volume. They then actuated the MDI into the spacer and performed a slow gentle inhalation, effectively a large tidal breath. They held their breath for 10 seconds and then expired into a collecting bag. A second inspiration was carried out in exactly the same fashion without actuating the MDI into the spacer. After exhaling into a collecting bag the MDI was shaken vigorously and a second actuation of the MDI was performed into the spacer; this was followed by two similar inhalations.

Dry powder inhaler

With the DPI all subjects breathed out to residual volume and rapidly inhaled the contents of one unit dose prepared for use by one of the investigators. They then held their breath for 10 seconds and exhaled gently into a collecting bag. In the normal subjects two full breaths were taken from the same unit dose, but in the patients the procedure was carried out only once in accordance with the instructions of the manufacturer.

IMAGING PROCEDURES

All radiological information was acquired with a Siemens dual headed rota camera on line to a DPS-3300 nuclear medicine computer system (ADAC Laboratories). Anterior and posterior views were acquired simultaneously. Before adminstration of the radiolabelled drug all subjects underwent a krypton-81m lung scan to provide an outline image of the lung fields. The lung fields were divided into two regions of interest, a central third and peripheral two thirds.[3]

Subjects were seated between the heads of the rota camera with the mid point of their chest at the centre of the field of view. Data collection was split into five 60 second time frames so that movement of the label could be followed as well as measurement of the initial deposition. After imaging the lungs, the subject was repositioned and the throat and stomach imaged separately for 120 seconds each.

All data analysis was carried out with the ADAC computer. Regions of interest were drawn on the lung image with a light pen, the krypton image acting as a template to provide the lung outline. The anterior and posterior counts obtained for each region were multiplied together and their square root taken to give the geometric mean counts. This was corrected for background counts and radiological decay. The counts were also individually corrected for attenuation within the body because of the thickness of the chest wall. Details of this attenuation correction are given elsewhere.[7]

The total activity available from two actuations of the MDI used was calculated by actuating the MDI five times into a bag and measuring the count rates. This was done before the MDI was used by a subject or patient. The result was then divided by a factor of 2·5 to give the activity from two actuations. For the DPI, the activity of the single unit dose was measured before administration.

Dissolution of radiolabel

It was observed that the lung counts in each successive one minute time frame progressively decreased. There was a substantial decrease during the five minutes of counting—that is, 2–7 minutes after inhalation of the radio aerosol. The half life of clearance of lung radioactivity was about 10 minutes,[7] but adequate counts for analysis were obtained on each subject by five minutes after inhaling the salbutamol—that is, after three minutes of counting.

STATISTICS

Normal statistical methods of mean and standard deviation were used. Differences between the three methods of inhalation within groups were tested with the paired t test, and between patients and normals by the Student's t test. A level of $p < 0{\cdot}05$ was considered significant.

Results

Lung function for the normal subjects and the patients did not vary between the three separate days of each study (table 1). In the patients the mean bronchodilatation 30

Table 1 Mean (SD) baseline results of lung function tests in normal subjects and patients before performing the studies on each of the three separate occasions

	Normal subjects (n = 10)		*Patients (n = 19)*	
	FEV_1(l)	*FVC (l)*	*FEV_1 (l)*	*FVC(l)*
MDI alone	4·02 (0·95)	4·83 (1·04)	1·45 (0·51)	3·22 (0·95)
MDI + spacer	3·94 (0·85)	4·89 (1·05)	1·42 (0·48)	3·07 (0·89)
DPI	3·89 (0·88)	4·85 (1·03)	1·44 (0·55)	3·12 (0·98)

FEV_1—forced expiratory volume in one second; FVC, forced vital capacity; MDI—metered dose inhaler; DPI—dry powder inhaler.

Table 4 Mean (SD) percentage of total lung deposition in the peripheral portion of the lung in normal subjects and patients for the three inhalation methods.

	Normal subjects (n = 10)	*Patients (n = 19)*
MDI alone	44·1 (9·9)*	30·4 (9·4)
MDI + spacer	49·4 (6·1)*†	38·6 (11·1)†
DPI	39·4 (8·6)*	28·1 (9·6)

MDI—metered dose inhaler; DPI—dry powder inhaler. *Significantly different from patients, $p < 0·05$; †significantly different from MDI alone and DPI, $p < 0·05$.

minutes after administration of salbutamol by MDI, with or without a spacer, or by DPI were similar (table 2).

Table 3 summarises the deposition, expressed as a percentage of the total dose available of the radionuclide, in normal subjects and patients for each study in the lungs, throat, mediastinum, and stomach, and for each inhaler device. The mean (SD) percentage deposition in the lungs was least with the DPI, 12·4% (3·5%) being deposited in the normal subjects and 11·4% (5·0%) in the patients. The mean total lung deposition was significantly greater in both normal subjects and patients with the MDI than with the DPI ($p < 0·05$). The mean total lung deposition was not significantly improved by the addition of the spacer device in either group. The use of a spacer did, however, significantly improve the peripheral deposition (expressed as a percentage of total lung deposition) in both groups ($p < 0·05$, table 4). Peripheral deposition was also significantly greater in the normal subjects than in patients with all three methods (table 4). There was a wide range between individuals for each method.

With both the DPI or the MDI without the spacer, large amounts of activity were counted over the throat, mediastinum, and stomach, with small quantities remaining in the actuator of the MDI or the DPI. When the Volumatic spacer was used, significantly less of the inhaled dose was deposited in the throat, mediastinum, and stomach in both normal subjects and patients (table 3), with 44·8% and 37·9%, respectively, of the mean activity remaining within the spacer.

Because the normal subjects took two inhalations from a single unit dose with the DPI and the patients took only a single breath, there was significantly less activity remaining in the device in the normal group (11·5% (7·1%)) than in the patients (18·9% (8·9%)), $p < 0·05$. There was, however, no significant difference in mean total lung deposition between the two groups with the DPI.

By adding up the percentage activity at the different sites, the total dose accounted for was calculated. The mean values for these was similar in all the experiments in both the normal subjects and patients, but the range was wide (table 3).

Table 2 Mean (SD) percentage change from baseline lung function in patients (n = 19) after inhaling salbutamol with each of the inhalation methods. No significant difference in percentage change in FEV_1 nor FVC was seen between the three methods.

	PEF % change (SD)	*FEV_1 % change (SD)*	*FVC % change (SD)*
MDI alone	20 (16)	24 (12)	19 (12)
MDI + spacer	24 (13)	29 (15)	21 (13)
DPI	24 (19)	27 (15)	17 (11)

PEF—peak expiratory flow rate; FEV_1—forced expiratory volume in one second; FVC—forced vital capacity; MDI—metered dose inhaler; DPI—dry powder inhaler.

Discussion

This study has examined the deposition of directly radiolabelled salbutamol in patients and normal subjects with different inhaler devices. Our validation of the technique with the Anderson cascade impactor confirmed that the radiolabelled drug was deposited in a similar fashion to the unlabelled drug. For the MDI the Anderson cascade impactor was

Table 3 Mean (SD) percentage of total available activity in each of the sites studied for the three inhalation methods in normal subjects and patients.

	Lungs	*Throat/ mediastinum/ stomach*	*Actuator/ device*	*Spacer*	*Exhaled*	*Recovered*
Normal subjects (n = 10)						
MDI alone	21·6 (8·9)*	47·0 (12·6)	18·0 (4·8)	—	0·5 (0·5)	87·1 (14·8)
MDI + spacer	20·9 (7·8)*	7·7 (6·1)†	14·8 (2·9)	37·9 (14·9)	0·5 (0·5)	81·8 (18·3)
DPI	12·4 (3·5)	59·2 (7·4)	11·5 (7·1)	—	0	83·1 (5·4)
Patients (n = 19)						
MDI alone	18·2 (7·8)*	50·1 (13·9)	26·2 (15·8)	—	0·4 (0·5)	94·9 (20·4)
MDI + spacer	19·0 (8·9)*	6·3 (3·8)†	18·9 (10·4)	44·8 (16·2)	0·3 (0·3)	89·3 (14·4)
DPI	11·4 (5·0)	63·9 (9·6)	18·9 (8·9)	—	0·2 (0·5)	94·4 (6·9)

MDI—metered dose inhaler; DPI—dry powder inhaler.
*Significantly different from DPI, $p < 0·05$; †significantly different from MDI alone and DPI, $p < 0·001$.

operated at a standard configuration and a gas flow rate of 28·3 l/min. For the DPI it was operated at a flow rate of 60 l/min and the configuration included a preseparator stage for collecting the larger particles. The particle size cutoffs for each stage were therefore recalculated for the higher rate and hence the size ranges for each stage are slightly different (figs 1 and 2). Both figures illustrate the similar distribution of labelled and unlabelled salbutamol and radiolabel over a wide range of particle sizes.[7]

The percentage total deposition in the lungs of the normal subjects is higher than those previously reported from our laboratory with inhalers containing radiolabelled Teflon spheres. We have previously reported a mean deposition of 11·2% in the lung with a reconstituted MDI and a mean of 9·1% deposited with a DPI device in patients with airflow obstruction.[2] The values reported here are also higher than those obtained with either a labelled substitute,[1 8 9] or with directly labelled sodium cromoglycate.[5]

Values similar to those obtained in the present study have been reported by others who have also used directly labelled β_2 agonists. Matthys *et al*[10] reported a mean deposition of 26% directly labelled salbutamol in the lung of four normal subjects with an MDI, and 34% with the addition of a spacer device. They also obtained a lung deposition of 18·7% when inhaling from residual volume and 33% when inhaling from 50% of vital capacity.[4] Newman *et al*,[6] using a technique similar to that of Köhler to directly label salbutamol, have also found a mean total lung deposition of 22·8% in asthmatic patients when the inhaler was used properly, but only 7·2% when inhaler technique was faulty. Another study with MDIs containing propellant soluble drug has reported lung deposition of over 39%.[11] These results suggest that radiolabelled Teflon spheres probably do not have the same aerodynamic properties within the lung as the drug being tested, and that drug deposition is higher than the 10% deposition usually quoted for MDIs.[1 2 8 9 12]

The wide range of percentage deposition within the lungs in both normal subjects and patients obtained in the present study was to be expected as no attempt was made to control flow rates or the volume inhaled. It is reported that deposition may vary according to the inhalation flow rate and the lung volume at the beginning of inhalation, being optimum at an inspiratory flow rate of 30 l/min from 50% of vital capacity.[8] Our subjects were allowed to use the inhalers in their own fashion after some tuition. They inhaled according to typical instructions of the manufacturer, and these techniques were identical to those employed by us in earlier studies on patients with airflow obstruction.[2 3] It was our intention to obtain a range of deposition that would occur in clinical practice, and not to impose a rigid volume or flow governed system of inhalation. The results of this current study are therefore directly comparable to our earlier study in asthmatic patients where lung deposition from an MDI of labelled Teflon particles of similar MMAD to salbutamol was 11·2%.[2]

Our results with the addition of a spacer device showed an improvement only in peripheral lung deposition rather than in the total lung deposition as reported by others.[8] The present study does, however, confirm the dramatic reduction in the percentage deposition in the oropharynx and stomach which may be of greater relevance in reducing the ingested dosage of inhaled corticosteroids to reduce the potential for systemic side effects.

With the DPI, although total mean lung deposition was similar in normal subjects and patients, the significant improvement in peripheral lung deposition in the normal subjects, with less activity remaining in the DPI, suggests that taking two inhalations from a single blister may be more effective than one. The measurements may, however, also reflect better function of normal lungs.

The rapid dissolution of the radiolabel in the lungs was also noted by Köhler *et al*.[4] This is probably the result of the radiolabel becoming dissociated from the drug within the lungs because it is water soluble. Although we counted for five minutes after inhalation of the drug, only the first three minutes of data were used in assessing deposition because of the rapid clearance of activity from the lungs. It was not possible to count for less than three minutes as insufficient counts were accumulated. Because of this clearance the present results may well underestimate the percentage deposition in the lungs immediately after inhalation.

The current study is also the first to attempt to account for the total dosage of the radiolabel delivered in the various areas where it may have been distributed. Although the mean percentage of the estimated total dosage delivered accounted for was in the region of 82–95% for the various studies, the range within each study was wide and in some cases over 100%. A possible cause for the recovered amount falling below 100% could be the rapid clearance of the radiolabel from the lung; very little of the radioactivity was found in the expired breath.

In conclusion, we have described a relatively simple new technique for the direct labelling of salbutamol and have shown that the percentage deposition of the directly labelled drug in the lungs in both normal subjects and patients with reversible airflow obstruction is nearly double that previously reported with indirect labelling techniques when using an MDI. This technique may enable the investigation of deposition of bronchodilator drugs within the lung to be related to their clinical effect.

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Adventitia

Asthma and the psyche

John was a scruffy, doe eyed lad of 13 admitted with acute asthma. It was his 12th admission, all the previous ones being under a paediatrician. My registrar noted that he improved very quickly and he was prompted to look for precipitating factors. He found none and I also had a go at John with similar results. He was well when he went home. Two days later he was back with another attack which was again shortlived. John assured me that there were no problems at home or at school, but at a second talk he burst into tears and said: "Well, if you want to know, I hate my mum." Mum was a poor widow, big and fat, and with a terrible squint. At night she went to the pub to wash up. At school John was ashamed of his poor clothes and shoes (it was long before torn jeans became fashionable). Other boys had nice presents at Christmas and on birthdays but John had none. His sister had young children and when her lorry driver husband was away on long journeys, John babysat so that she could "carry on" elsewhere. He felt ashamed of her activities, as he was of his mother's job.

After a couple of days he said he was ready to go home and that he wouldn't get asthma again. On the way home he ran away from his mother and later he telephoned me. I picked him up and took him home with me for crumpets and tea, after which John was in hospital for the 14th time.

After a few more crises it was decided that he should be found foster parents. His new mother was also fat but had no squint. She was well dressed and exuded warmth. John lost his asthma and eczema.

Five years later he was admitted again. He was working but had quarrelled with his foster mother and gone back to his old home. A few weeks later his asthma and eczema were bad again. No, I don't think it had anything to do with the house dust mite.

Mr West, a sock manufacturer, developed asthma when he was 47 and was admitted with a bad attack which was resistant to treatment. The sister mentioned that his wife and secretary visited at different times and that he seemed to be worse after such visits. After probing he also burst into tears. His secretary was his mistress and during their liaison she had acquired half his business so he could not get rid of her, as he now wanted to. He accepted that anger, fear, and frustration were precipitants of his asthma and, after a troublesome year, peace and contentment were somehow restored and he became much better.

Some six years later I was standing at a bus stop. He drove by and stopped to pick me up. Our journey was long enough to establish that he was free of asthma but not to find out how peace had been achieved. He made very good socks and I still have a pair of them in a drawer.

I met these cases long ago, but since then I have never recognised such a clear connection between psyche and asthma. How many have I missed? As a young consultant I spent all my working hours on the wards and in outpatients. As the years went by other matters took up time and more layers of junior staff intruded between me and my patients. These days continuity of care seems even worse, with more of a consultant's time being occupied away from patients. Most asthmatics attending hospitals are likely to be seen by different doctors on most occasions. The accent seems to be increasingly on medication with scant regard for causation.

D DAVIES