menopause.[2] Such patients constitute 24% of all those with ovarian cancer seen at our centre. The other group to whom this applies is women with stage I disease, who have an overall five year survival of 61%[15] and a five year survival of 88% when aged 50 or under at diagnosis (figures obtained from our hospital).

In this study roughly equal numbers of women were treated with oestrogen plus progestogen as with unopposed oestrogen. Hormone replacement therapy with oestrogen alone has been associated with an increased risk of endometrial cancers but is to be preferred to combination therapy for women who have had a hysterectomy.[18] Henderson *et al* estimated that the overall benefit of unopposed oestrogen compared with oestrogen plus progestogen in such women is substantial in terms of a greater reduction in the incidence of ischaemic heart disease, with only a marginal loss of benefit in terms of hip fractures due to osteoporosis.[19] The relative effects on the breast are, however, at present unclear.[8 20]

In conclusion, there is no evidence from our study that hormone replacement therapy is detrimental to disease free survival and overall survival in patients with ovarian cancer. Whether there is a beneficial effect would have to be investigated in a large randomised controlled trial, and one is currently being proposed. Meanwhile, hormone replacement therapy in these patients will substantially improve their quality of life, particularly in those who prove to be long term survivors.

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Spontaneous pneumothorax: marker gas technique for predicting outcome of manual aspiration

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Abstract

***Objective*—To determine whether in a patient with spontaneous pneumothorax the presence or absence of a pleural leak can be shown at the time of manual aspiration by use of a marker gas. Also, to find out if the technique can predict whether manual aspiration will be successful, hence avoiding the need for intercostal tube drainage.**

***Design*—Prospective study of 25 episodes of pneumothorax during which patients breathed air from a Douglas bag that contained chlorofluorocarbon gases from a metered dose inhaler while the pneumothorax was aspirated.**

***Setting*—Medical unit of a district general hospital.**

***Patients*—22 patients who presented over nine months with acute pneumothorax.**

***Main outcome measures*—Presence or absence of chlorofluorocarbon marker gases in the aspirate. Presence or absence of sustained re-expansion of the affected lung in the chest radiograph.**

***Results*—Marker gas was detected in the aspirate from 16 out of 25 pneumothoraces. Of these, 13 required intercostal tube drainage because of failure of the the lung to re-expand. Marker gas was not detected in nine cases, and in all of these cases manual aspiration resulted in sustained re-expansion of the lung.**

***Conclusions*—The presence or absence of a pleural leak during manual aspiration of spontaneous pneumothorax can be shown by using this technique. The absence of marker gas in the aspirate implies that manual aspiration will be successful, whereas its presence predicts, in most cases, either failure of manual aspiration to expand the lung or early re-collapse of the lung.**

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Introduction

Spontaneous pneumothorax is usually treated actively with an intercostal tube and underwater seal drain on the grounds of size or if there is underlying lung disease.[1] Simple manual aspiration is an alternative procedure that spares the patient discomfort and is easier to perform.[2-5] A disadvantage of aspiration is that it has been impossible to predict which lungs will recollapse within the next 24 hours as a result of a small persisting pleural leak. Such patients require further treatment, often with an intercostal drain, resulting in a longer hospital stay, whereas those in whom the pleural leak seals off spontaneously might benefit from simple aspiration and earlier discharge.

We have previously described a flame ionisation technique for detecting the chlorofluorocarbon propellants present in pressurised metered dose inhalers.[6] We have now adapted this method to detect pleural leaks during manual aspiration of spontaneous

pneumothorax, and we describe our findings on using the technique in relation to clinical outcome.

Patients and methods

All patients presenting to our unit over a nine month period with radiographically confirmed spontaneous pneumothorax were entered into the study unless their symptoms indicated immediate intercostal tube drainage or the pneumothorax was too small to merit active treatment.[1] In all, 22 patients (17 men, five women) aged 16-88 years (mean age 48·8 years) were studied. Three patients were studied twice during separate hospital admissions, so that 25 episodes of pneumothorax were studied in total. Seventeen episodes were classified as primary spontaneous pneumothorax and eight as secondary spontaneous pneumothorax (three cases of emphysema, one of apical cavities in a patient with "healed" tuberculosis (two episodes), two of cryptogenic fibrosing alveolitis, and one of pleural mesothelioma).[1]

Each patient breathed air continuously from a Douglas bag through a mouthpiece and two way valve, five puffs of propellant gas from a placebo metered dose inhaler (Allen and Hanburys, Greenford, Middlesex), having been previously added to the bag (fig 1). A 16 gauge plastic cannula was inserted aseptically at an appropriate site in the chest wall and was connected to a 60 ml syringe by a three way tap, with an exit tube leading from the tap to a portable flame ioniser (Gas-Tec, Research Engineers, London) capable of detecting hydrocarbon gases at concentrations of less than one part per million. Each syringe full of aspirated gas was sampled by passing it into a stream of room air that was being drawn continuously through the ioniser, in which a constant voltage is applied across a hydrogen flame. The electrical current resulting from this potential is very small in the case of pure hydrogen, which has a low conductance, but when hydrocarbon gases enter the flame charged particles are produced that increase its conductivity; there is a mathematical relation between hydrocarbon gas concentration and the signal produced in the flame ioniser. Chlorofluorocarbon gases in the sample were registered on a visual logarithmic scale and by an auditory signal. Recordings were made of the volumes of gas aspirated, whether or not chlorofluorocarbon marker gases were present and, if so, the volume of the aspirate at which they were first detected. Aspiration was continued either until no more gas could be obtained or until about 5 litres of gas had been removed. If the pneumothorax was unchanged or larger on radiography immediately after aspiration an intercostal tube with underwater seal drainage was inserted. If, however, the pneumothorax was absent or shallow a repeat radiograph was taken not later than the following day. If in this second radiograph the pneumothorax was larger then a further aspiration or tube drainage was carried out according to the patient's symptoms, whereas if the pneumothorax was absent or shallow the patient was observed for a further 24-48 hours with daily radiographs being taken until discharge. (Figure 2 gives the management protocol.) Outpatient follow up with a repeat radiograph about one week later was arranged.

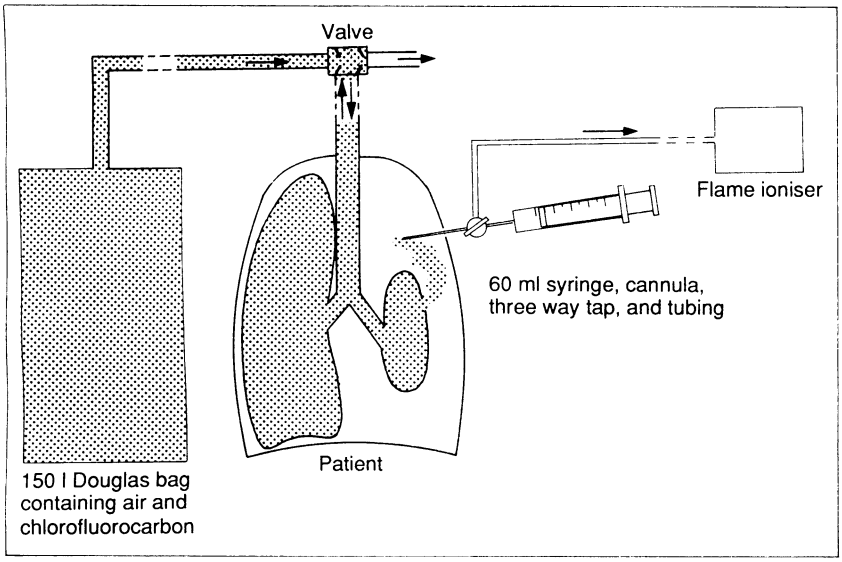

FIG 1—*Apparatus for detecting chlorofluorocarbon in pleural gas leaks during manual aspiration of pneumothorax*

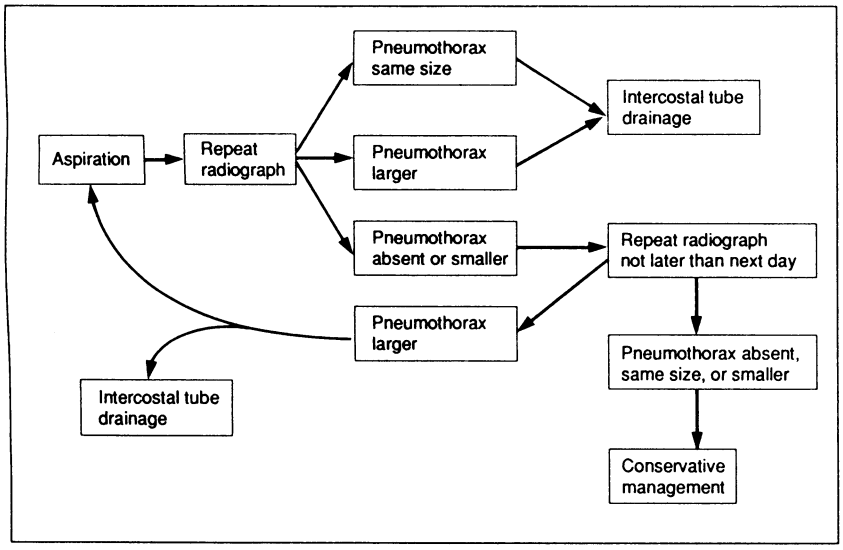

FIG 2—*Management protocol after aspiration in patients with pneumothorax*

Results

The gas sampled during 16 separate episodes of pneumothorax contained marker gas. No marker gas was found during the other nine episodes of pneumothorax.

Of the 16 episodes of pneumothorax that yielded marker gas, six (patients 1-5) showed no appreciable reduction in size on radiography immediately after aspiration, and an intercostal drain was inserted (table I). Seven pneumothoraces (44%) (patients 6-12) had expanded fully (n=5) or were much smaller (n=2) in the post-aspiration radiograph, but the lungs recollapsed within 12-48 hours with the development of symptoms; these patients were treated by insertion of an intercostal tube. One pneumothorax (patient 22) showed an appreciable reduction in size immediately after aspiration but was slightly larger on radiography the following day. After a second aspiration (which was again positive for chlorofluorocarbons) the lung was fully expanded and remained so without tube drainage. Two pneumothoraces (patients 20 and 21) were fully expanded in the post-aspiration radiograph and remained so, requiring no intercostal drainage. Chlorofluorocarbons were detected in the first 60 ml sample of gas taken after inspiration of the gas mixture in 15 cases, and in only one case they were not detected until 750 ml had been aspirated.

In all nine episodes of pneumothorax during which no marker gas was detected (patients 13-19) a substantial reduction was seen in the size of the pneumothorax in the radiograph after aspiration, with no increase in size in subsequent radiographs; no patient required intercostal tube drainage (table II). Two of these episodes occurred in patients who had been readmitted to hospital with a second episode of ipsilateral pneumothorax, indicated by

the sudden onset of symptoms at four and 17 days after discharge.

All but two of the nine episodes of secondary spontaneous pneumothorax yielded marker gas and required intercostal tube drainage. The mean volume of gas aspirated from pneumothoraces in which marker gas was detected was greater (2056 ml, range 500-5050 ml) than that aspirated from pneumothoraces in which marker gas was not found (1370 ml, range 650-1800 ml), but the difference was not significant. There were no complications of aspiration during the study.

Discussion

For a spontaneous pneumothorax to develop a leak must arise that permits gas to pass from the bronchial tree into the pleural cavity, and in order that the lung might re-expand the leak must seal off. If the leak in a partially deflated lung had already sealed off by the time of presentation to hospital a single manual aspiration of the gas contents of the pleural cavity would be expected to have a greater chance of success than if a leak was still present.

Metered dose inhalers are widely used to deliver drugs to patients with asthma and limited airflow. As well as active drugs they also contain propellants, which are volatile analogues of methane and ethane and have previously been shown to be readily detectable by flame ionisation.[6] By using the present technique we found that almost two thirds of all pneumothoraces studied contained marker gas and that these behaved differently from the remaining one third of pneumothoraces, in which no marker gas was detected. The patients with pneumothoraces in which no marker gas was found did uniformly well, and aspiration without tube drainage was required for only one of them. By contrast, 81% of pneumothoraces in which the marker gas was detected required a further drainage procedure. Six (38%) pneumothoraces in which the marker gas was detected had a large leak, for the immediate post-aspiration radiograph showed no re-expansion of lung, but in seven (44%) the radiograph alone would have been a poor guide to a continuing leak as despite complete or partial re-expansion shown in the post-aspiration radiograph further lung collapse occurred within 48 hours. The presence of marker gas at the time of aspiration in each of these cases implies a continuing leak, albeit small.

In two cases lung expansion was sustained after only one manual aspiration despite the presence of marker gas in the pneumothorax space. One explanation for this could be the presence of a very small pleural leak that closed off once the increased negative pressure of aspiration had been removed, allowing the lung to remain inflated. False positive results might be encountered, however, as a proportion of adults excrete small quantities of methane in their breath.[7] These subjects may be easily identified by holding the sampling tube of the analyser at the mouth before starting the procedure and the effect in these "methane producers" compensated for by calibrating the instrument at zero on the first syringe full of pneumothorax gas before the patient breathes from the Douglas bag containing the gas mixture. The three false positive results in this study could not be explained on the basis of methane in breath.

The procedure is easy to carry out. The apparatus is small and is kept set up and ready for use on a small trolley so that it can be moved to wherever it is required. The only appreciable financial outlay is for the flame ioniser (£2340). The results suggest that this expenditure could soon be offset by the information retrieved as the finding of no pleural leak should avoid unnecessary tube drainage and permit early discharge, whereas had these patients been treated with an intercostal tube from the outset their hospital stay would inevitably have been prolonged.

We do not suggest that manual aspiration is a better method of treating spontaneous pneumothorax than intercostal tube drainage. This area of doubt is currently the focus of a trial conducted by the British Thoracic

TABLE I—*Characteristics of patients requiring intercostal tube drainage for pneumothorax*

Patient No	Age (years)	Sex	Type of pneumothorax	Volume aspirated (ml)	Marker gas (+/−)	Radiographic size of pneumothorax after aspiration	State of pneumothorax after 12-48 h	Length of treatment with intercostal tube (days)	Outcome
1	20	F	Primary	2200	+	No reduction	No change	14	Pleurectomy (continued leak)
2	32	M	Primary	1150	+	No reduction	No change	3	Recurrence five days after discharge
			Primary (recurrent)	1400	+	No reduction	No change	4	Pleurectomy (continued leak)
3	53	M	Secondary (to emphysema)	5050	+	No reduction	No change	7	Pleurectomy (third pneumothorax)
4	84	M	Secondary (to mesothelioma)	1150	+	No reduction	No change	20	Died seven weeks later (of mesothelioma)
5	88	M	Primary	3750	+	No reduction	No change	4	Pneumothorax expanded at one month
6	32	F	Primary	2500	+	Full expansion	Recollapsed	14	Pleurodesis (continued leak)
7	68	M	Secondary (to fibrosing alveolitis)	1250	+	Full expansion	Recollapsed	7	Died of massive pulmonary embolus
8	68	M	Secondary (to emphysema)	3060	+	Full expansion	Recollapsed	3	Pneumothorax expanded at one month
9	70	M	Primary	2950	+	Full expansion	Recollapsed	24	Pneumothorax expanded at two months
10	87	M	Secondary (to fibrosing alveolitis)	2160	+	Full expansion	Recollapsed	34	Died of actinomycotic pyopneumothorax
11	26	F	Primary	1980	+	Much smaller	Recollapsed		Pneumothorax reaspirated on day 2;
				1620	+	Much smaller	Recollapsed	6	pleurodesis (continued leak)
12	66	M	Secondary (to emphysema)	1560	+	Much smaller	Recollapsed	4	Pneumothorax expanded at three months

TABLE II—*Characteristics of patients not requiring intercostal tube drainage for pneumothorax*

Patient No	Age (years)	Sex	Type of pneumothorax	Volume aspirated (ml)	Marker gas (+/−)	Radiographic size of pneumothorax after aspiration	State of pneumothorax after 12-48 h	Length of hospital stay (days)	Outcome
13	70	M	Primary	1590	−	Very shallow	No change	2	Pneumothorax expanded at one month
14	22	M	Primary	1500	−	Shallow	Very shallow	2	Pneumothorax expanded at one month
15	35	M	Primary	1500	−	Full expansion	No change	2	Pneumothorax expanded at three months
16	16	M	Primary	650	−	Very shallow	No change	1	Pneumothorax expanded at two months
17	66	M	Secondary (to apical cavities)	1800	−	Full expansion	No change	1	Further acute episode 17 days later
			(recurrent)	1700	−	Full expansion	No change	3	Elective pleurodesis as third episode
18	36	M	Primary	950	−	Very shallow	No change	2	Pneumothorax expanded at one month
19	39	F	Primary	1620	−	Full expansion	No change	1	Further acute episode four days later
			(recurrent)	1020	−	Very shallow	No change	2	Pneumothorax expanded at one month
20	40	M	Primary	1050	+	Full expansion	No change	1	Pneumothorax expanded at one month
21	20	F	Primary	500	+	Full expansion	No change	1	Pneumothorax expanded at three months
22	36	M	Primary	2600	+	Shallow	Larger		Pneumothorax respirated on day 2
				1080	+	Full expansion on second aspiration	No change	3	expanded at two months

Society. We suggest, however, that this first report of the use of a marker gas during manual aspiration of spontaneous pneumothorax has provided information about the likely short term outcome that cannot reliably be determined on the basis of the post-aspiration chest radiograph alone and that this information may guide the clinician as to whether or not tube drainage is likely to be required.

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Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs

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Abstract

***Objective*—To evaluate the efficacy and safety of immunotherapy (hyposensitisation) in patients with severe summer hay fever.**

***Design*—A randomised, double blind, placebo controlled study of a biologically standardised depot grass pollen extract.**

***Setting*—Allergy clinic, Royal Brompton and National Heart Hospital, London.**

***Patients*—40 adults (mean age 35 years) with a history of severe grass pollen allergy uncontrolled by standard antiallergic drugs. Patients with perennial asthma were specifically excluded.**

***Intervention*—Patients were randomised to receive either an active preparation (Alutard SQ, a grass pollen (*Phleum pratense*) extract) or placebo at a rate of two subcutaneous injections a week in increasing doses until a maintenance dose was reached. This maintenance dose was given once a month.**

***Main outcome measures*—Clinical efficacy was evaluated by symptom and drug diary cards, visual analogue scores during the grass pollen season, and a postseasonal assessment by the patients and a doctor. Conjunctival and skin sensitivity to local allergen provocation was measured before and after eight months of treatment.**

***Results*—There was a highly significant decrease (median Alutard SQ *v* median placebo (95% confidence interval for difference between medians)) in total symptom scores ($p=0{\cdot}001$) in the Alutard SQ treated group (360 *v* 928 (238 to 825)). Significant differences were also found in total drug use ($p=0{\cdot}002$, 129 *v* 627 (178 to 574)). Visual analogue symptom scores were also reduced in the active group ($p=0{\cdot}02$, 2·2 *v* 5·5 (−4·8 to −0·5)). The postseasonal assessment, by either the doctor or the patients, showed a large improvement ($p<0{\cdot}001$) in favour of Alutard SQ. Provocation tests showed a greater than 10-fold reduction for the active group in immediate conjunctival allergen sensitivity ($p=0{\cdot}001$), a 40% decrease in early phase response ($p=0{\cdot}02$), and a 57% decrease in the late phase ($p=0{\cdot}001$) cutaneous response after intradermal allergen. A total of 523 active injections were given. There was one systemic reaction at 10 minutes after injection, which was rapidly reversed with intramuscular adrenaline. There was one mild delayed urticarial reaction at 2½ hours.**

***Conclusion*—Immunotherapy is effective in patients with severe summer hay fever, but immediate anaphylactic reactions limit its use to specialised centres. Patient selection is extremely important, and chronic perennial asthma should be specifically excluded. As serious reactions occur within minutes a two hour wait for all patients after each injection seems unnecessary.**

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Introduction

Over the past 30 years there has been a substantial increase in the prevalence of summer hay fever in the United Kingdom.[1] At the same time there have also been considerable improvements in treatment, particularly with the introduction of non-sedating selective histamine H_1 antagonists[2] and local nasal corticosteroids. Nevertheless, a minority of people with hay fever have extreme hypersensitivity to grass pollen and respond poorly to standard antiallergic drugs. In these people immunotherapy (hyposensitisation) would be the treatment of choice in many countries throughout the world, including the United States, Scandinavia, and the continent of Europe.[3,4]

In the United Kingdom allergen injection immunotherapy for treating disease mediated by IgE, including summer hay fever, has been largely discontinued on the recommendations of the Committee on Safety of Medicines in October 1986.[5] The committee's report questioned the efficacy of immunotherapy and expressed concern about the number of deaths from severe bronchospasm and anaphylaxis. The committee recommended that injections should be given only where facilities for full cardiorespiratory resuscitation were immediately available, and that patients be kept under medical observation for at least two hours.

Generally, the committee's ruling was welcomed because it highlighted the potential dangers of immunotherapy, particularly in asthmatic patients. Nevertheless, the two hour waiting period has made this treatment impracticable for both patients and doctors.

For immunotherapy to retain a place in the treatment of summer hay fever we thought that a double blind, placebo controlled study in highly sensitive patients who were inadequately controlled by standard treatment was necessary in the United Kingdom. Previous studies have been described,[6-8] but we are unaware of any double blind, placebo controlled studies using a biologically standardised extract. Such a study would re-evaluate the important issues of side effects and their timing along with efficacy. We chose the Alutard SQ vaccine as this is a biologically standardised depot preparation with a reported low incidence of systemic side effects and high efficacy.[9-11]