
Contemporary Themes

Long term transtracheal oxygen delivery through microcatheter in patients with hypoxaemia due to chronic obstructive airways disease

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Abstract

Transtracheal administration of oxygen is a new technique for long term treatment. Twenty patients with hypoxaemia due to chronic obstructive airways disease were studied while receiving oxygen through a microcatheter inserted percutaneously into the trachea. By bypassing most of the dead space and avoiding oxygen wastage at the face this method of delivery reduced oxygen requirements by roughly half compared with delivery through nasal cannulas, thus reducing costs and facilitating portable treatment. Twelve of these patients continued to use the system for up to 13 months in preference to using nasal cannulas. Two important complications were a staphylococcal infection and a fractured catheter. Transtracheal oxygen reduced breathlessness and helped patients with routine daily activities.

Transtracheal administration of oxygen is a practical method of treatment which may have an important role in rehabilitating patients with chronic lung disease.

Introduction

Long term oxygen treatment has been shown to reduce mortality in severe chronic obstructive airways disease associated with hypoxaemia.^{1,2} It has been estimated that between 13 000 and 107 000 people are eligible for long term oxygen treatment in England and Wales under Department of Health and Social

Security guidelines.³ The provision of oxygen concentrators for domiciliary use under the National Health Service drug tariff has been an important practical advance and this is currently the most economical way of providing long term treatment⁴; it does not, however, allow the patient to use oxygen outside the home or during exercise.

The usual method of administering oxygen at home or during exercise is through nasal cannulas at flow rates of 2-3 l/min. Many patients find these cannulas uncomfortable, cosmetically unacceptable, or that they interfere with daily activities. These problems may lead to poor patient compliance and a reluctance by doctors to initiate long term treatment. Oxygen administered through nasal cannulas has had a limited role in rehabilitating patients with chronic obstructive airways disease because cylinders that are light enough to be carried or wheeled by the patient contain only a short supply of oxygen.

The technique of supplying oxygen through a microcatheter implanted into the trachea was introduced by Heimlich in 1982⁵ and may overcome some of the problems associated with long term domiciliary and portable oxygen treatment. Heimlich's original study⁵ and studies in France by P Léger and colleagues (papers delivered to the Fourth Congress of the European Society of Pneumology in Milan/Stresa, 23 to 28 September 1985) suggested that substantial reductions in oxygen flow rates could be achieved with this technique. We have investigated the efficacy and acceptability of transtracheal oxygen given as long term treatment (including portable use) in a group of patients with dyspnoea and severe hypoxaemia due to chronic obstructive airways disease.

Patients and methods

We studied 17 men and three women aged 47-79 years (mean 66.4 years; three aged 47-59, 11 aged 60-69, six aged 70-79) with chronic obstructive airways disease—mean forced expiratory volume in one second (FEV₁)

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0.68 l (range 0.32-1.36 l); mean forced vital capacity 1.86 l (range 0.54-3.2 l). Eighteen had severe resting hypoxaemia with a mean arterial oxygen tension of 6.6 kPa (50 mm Hg) (range 4.9-7.7 kPa; 37-58 mm Hg) while in a stable clinical state and were recruited from outpatient clinics. One patient, a 47 year old man who had severe respiratory failure refractory to other treatment, was not in a stable clinical state. One other patient was a "pink puffer" with an arterial oxygen tension of 9.4 kPa (70 mm Hg) while breathing air who had been in hospital for three months for severe dyspnoea despite medical treatment. All patients complained of breathlessness on exertion. None showed appreciable reversibility in their airways obstruction (improvement in FEV₁ after inhaled salbutamol less than 15%). Four had been receiving oxygen through nasal cannulas for more than 15 hours a day before the study began and two had used oxygen for symptomatic relief. All patients were receiving inhaled β_2 agonists and nine were receiving inhaled ipratropium. Ten were receiving sustained release theophylline preparations and 13 a diuretic. Seven patients were using inhaled steroids and four were receiving oral steroids.

The study was approved by the ethical committee of Harefield Hospital and informed consent obtained from all patients.

Under local anaesthesia and using a sterile technique a Teflon "intravenous" catheter 13.3 cm \times 1.7 mm (16 gauge Angiocath, Deseret Medical Inc, Parke Davies Co, Utah, USA) was inserted percutaneously into the trachea in the midline between the second and third tracheal rings. The catheter was secured by gluing the hub to an inverted 3.5 mm paediatric tracheostomy tube (Great Ormond Street pattern; Franklin Medical Ltd, High Wycombe, Bucks) supported by a steel chain around the patient's neck (figure).



Transtracheal microcatheter retained by steel chain around patient's neck.

Two patients initially received a different microcatheter of an experimental design, which proved unsatisfactory and was later replaced by the Angiocath. Episodes of coughing in the first 48 hours after insertion were controlled with injections of 2 ml 1% lignocaine down the catheter every four to six hours. This produced no ill effects—for example, bronchospasm, which has been seen with nebulised lignocaine, did not occur.

The catheter was connected to a regulated supply of oxygen and blood gas values determined at flow rates of 0.5, 1.0, and 1.5 l/min. Before these measurements at least 30 minutes was allowed for equilibration at each flow rate. Blood gas values were also determined while breathing 2 l oxygen/min through nasal cannulas. All blood gas analyses were performed on a standard analyser (Radiometer ABL4, Copenhagen). The arterial oxygen tensions at each flow rate were compared with those measured while breathing air using a paired *t* test.

Patients were provided with two portable aluminium oxygen cylinders (Specialty Oxygen Service Ltd, Manchester), a flow regulator calibrated for low flow rates for use with portable cylinders, and a similar flow regulator suitable for use with the standard size F oxygen cylinders supplied for domestic use. Patients were also supplied with an adapter to allow recharging of the portable cylinder from the large domestic cylinder. Two patients were supplied with oxygen concentrators. Patients were taught to use the equipment and to flush the catheter regularly with 2 ml sterile saline three times a day and to clean the entry site daily with sterile saline. Each patient had an appropriate oxygen flow rate determined to raise the arterial

oxygen tension above 8 kPa (60 mm Hg). Patients were advised to use oxygen continuously or as near continuously as possible and were warned of the dangers of smoking. They were encouraged to use the portable oxygen cylinders when outside the home and during exercise.

The catheters were changed routinely every two months at an outpatient visit. A guide wire was used initially, but once a track became established the guide wire was no longer needed. After 1 February 1985 the tips of all catheters removed were sent for culture and patients systematically questioned about episodes of infection and antibiotic treatment since they were last seen.

By 1 August 1985 treatment had continued for up to 13 months and 11 of the 12 remaining patients anonymously completed a simple postal questionnaire (sample available on request) asking for their views on the treatment.

Results

BLOOD GAS MEASUREMENTS

Table I shows the effect of transtracheal oxygen on arterial oxygen tension compared with oxygen delivered through nasal cannulas in the 17 patients on whom full data were available. The increment in arterial oxygen tension achieved with 1 l of oxygen/min delivered by the transtracheal system was roughly equal to the increment produced by 2 l oxygen/min delivered through nasal cannulas, allowing a 50% reduction in oxygen flow rates.

Serious carbon dioxide retention did not occur with the system, though all the patients had a moderate increase in arterial carbon dioxide tension at rest (table II).

TABLE I—Arterial oxygen tensions (kPa) in 17 patients breathing air, oxygen by transtracheal delivery system, and oxygen via nasal cannulas

	Air	Transtracheal oxygen			Oxygen via nasal cannulas, 2.0 l/min
		0.5 l/min	1.0 l/min	1.5 l/min	
Mean (SEM)	6.6 (0.23)	7.8 (0.23)*	9.3 (0.39)*	10.7 (0.43)*	9.3 (0.36)*

*Paired *t* test for comparison with air: $p < 0.001$.

Conversion: SI to traditional units—Oxygen tension: 1 kPa \approx 7.5 mm Hg.

TABLE II—Arterial carbon dioxide tensions (kPa) in patients breathing air, oxygen by transtracheal delivery system, and oxygen via nasal cannulas

	Air	Transtracheal oxygen			Oxygen via nasal cannulas, 2.0 l/min
		0.5 l/min	1.0 l/min	1.5 l/min	
Mean (range)	6.4 (4.7-8.8)	7.0 (4.8-10.2)	6.8 (4.7-11.2)	7.2 (5.2-9.8)	7.0 (4.7-9.0)

Conversion: SI to traditional units—Carbon dioxide tension: 1 kPa \approx 7.5 mm Hg.

EARLY COMPLICATIONS

Two patients developed subcutaneous emphysema within a few hours after insertion of the transtracheal catheter. The catheters were removed and one patient had the catheter reinserted successfully one week later. The second patient refused further treatment. A third patient, a 47 year old man with severe hypoxaemia refractory to conventional oxygen treatment (arterial oxygen tension 4.8 kPa (36 mm Hg) while receiving 3 l oxygen/min by nasal cannulas), was treated with the transtracheal oxygen system, which also failed to relieve his hypoxaemia adequately (arterial oxygen tension 4.5 kPa (34 mm Hg) while receiving 1.5 l oxygen/min through the catheter). This patient died of respiratory failure.

SUBSEQUENT PROGRESS

Eighteen patients were discharged for follow up as outpatients, and during this period two further deaths occurred.

Case 1—Four months after insertion of the catheter a 73 year old man who had had a previous myocardial infarction and was treated with amiodarone for documented episodes of ventricular tachycardia was admitted to another hospital for an episode of collapse probably due to cardiac arrhythmia. Review of the clinical notes showed that he had subsequently developed a fever with an increase in white cell count from 5.9 to 9.9 $\times 10^9/l$ (96% neutrophils). The chest x ray picture was reported as showing "perivascular shadowing" at the left hilum. Sputum

culture was negative. One blood culture was sterile and another grew scanty *Staphylococcus epidermidis* (a probable contaminant). He was treated with amoxicillin and subsequently cefotaxime. Initially his condition improved, but he then became increasingly breathless and died 11 days after admission. Necropsy was not performed.

Case 2—A 66 year old man developed an episode of acute respiratory distress at home roughly six weeks after beginning treatment. His breathing rapidly deteriorated and he died before he could be admitted to hospital. At necropsy no problems could be found related to the transtracheal oxygen delivery system; examination of the lungs merely showed signs of chronic bronchitis with no evidence of infection. (This patient had had previous admissions because of severe breathlessness resistant to treatment.)

Four patients were withdrawn from the study. A 79 year old man inadvertently pulled the catheter out on several occasions; a 60 year old man with an early dementia could not cope with the system despite good family support; and a third patient did not think that the transtracheal oxygen delivery system was of benefit, and it was therefore discontinued after about a month. In the fourth patient the site of insertion became colonised with an antibiotic resistant *Staph aureus* causing a persistent purulent discharge. (The organism had previously been isolated from a nasal swab, suggesting self infection.) Bronchoscopy was performed because of a new shadow seen in a radiograph of the chest, which proved to be a bronchial carcinoma. The transtracheal catheter was removed before radiotherapy.

Two serious complications related to the system occurred during follow up. One patient (who had received one of the experimental microcatheters) suffered a fracture of the catheter five months after insertion. He was admitted to hospital and the distal fragment retrieved using a fiberoptic bronchoscope. An Angiocath was inserted and he was well enough to be discharged home the same day. He was still using the transtracheal system some 13 months after its original insertion. Another patient was admitted with drowsiness, fever, and worsening respiratory failure. Her chest x ray picture was clear but her symptoms failed to respond to amoxicillin. Cultures from her transtracheal catheter and sputum grew *Staph aureus*. She deteriorated and required mechanical ventilation for respiratory failure. Based on the culture results, flucloxacillin and gentamicin were prescribed. She made a good recovery and subsequently returned to transtracheal oxygen treatment.

RESPONSE TO TRANSTRACHEAL OXYGEN

The 12 patients who remained in the study in August 1985 were surveyed by means of a simple postal questionnaire. At the time they had had the system in place for an average of 6.4 months (maximum 13 months). Eleven patients replied. The patients were using oxygen for an average of 18.1 hours a day (range 10-24); 10 patients used oxygen at night (all 10 using the transtracheal delivery system). One patient was still breathing oxygen intermittently through nasal cannulas. Responses to the five questions about breathlessness and mobility showed that the system reduced breathlessness and made daily activities easier (table III). When asked whether they wished to continue with the system or be changed to oxygen given through nasal cannulas all 11 patients wished to continue with transtracheal oxygen. All used the portable oxygen cylinders at flow rates varying between 0.5 and 1.5 l/min. They found that a full cylinder lasted between one and a half and four hours depending on the flow rate. Two patients admitted they were still smoking.

TABLE III—Degrees of improvement recorded in answer to questionnaire. Figures are numbers of patients (total=11)

	Great improvement	Moderate improvement	Slight improvement	No improvement
Has transtracheal oxygen delivery system improved amount of walking you can do?	2	3	5	1
Has transtracheal oxygen delivery system improved your breathing (made you feel less breathless)?	5	5	0	1
Has transtracheal oxygen delivery system improved how you feel generally?	4	4	2	1
Has transtracheal oxygen delivery system helped you with essential activities at home (for example, washing, dressing, eating)?	7	1	1	2
Has transtracheal oxygen delivery system helped you to get out of the house more?	6	4	0	1

COLONISATION OF CATHETER AND INFECTION

During 1 February to 1 August 1985, 25 catheters were removed and the catheter tips cultured. Thirteen were sterile. Eight catheters from five patients grew *Staph aureus*; four of these patients grew *Staph aureus* from nasal swabs with identical antibiotic sensitivities and phage types. Two catheter tips grew *Pseudomonas aeruginosa*. One catheter grew a *Proteus* species and one an *Enterobacter* species. During this period eight chest infections occurred (56 patient months at risk). Three were treated by general practitioners (two successfully); the third patient was admitted to hospital after an allergic reaction to amoxicillin. Five episodes were treated in hospital. In three of these no pathogens were isolated from the sputum or transtracheal catheter. The fourth patient was successfully treated with ampicillin for an infection with *Haemophilus influenzae*. The fifth patient suffered a serious infection with *Staph aureus* (see above).

Discussion

Administering of oxygen through a microcatheter into the trachea leads to a reduction in oxygen requirements. This is achieved by bypassing most of the anatomical dead space and filling the upper respiratory tract with oxygen enriched air during expiration. Our finding of a 50% reduction in oxygen flow rate is similar to that of Heimlich.⁵ Transtracheal oxygen did not produce further carbon dioxide retention in these patients. The lower oxygen flow rate achieved using the transtracheal delivery system may be useful in three settings: firstly, where cylinders are used as the principal source of oxygen supply; secondly, for portable oxygen treatment; and, thirdly, in patients who require high oxygen flow rates.

In countries where oxygen concentrators are not readily available the principal mode of supply is by cylinders. In 1982 the yearly cost to the NHS of providing 15 hours of oxygen a day at 2 l/min through nasal cannulas using 1360 l (size F) cylinders was estimated to be at least £3500⁶; hence a 50% reduction in oxygen consumption would be very worth while. The cost of long term oxygen treatment using oxygen concentrators in Britain will not be altered greatly by the transtracheal oxygen delivery technique but the cost of providing intermittent treatment using oxygen cylinders for patients who continue to need symptomatic relief would be reduced.

Two practical problems with portable oxygen treatment have been the weight of the equipment and the limited supply obtainable from cylinders of reasonable size. In one study of portable oxygen treatment the beneficial effect of oxygen on exercise capacity was almost completely offset by the decrease in exercise capacity when the patients carried their own equipment.⁷ As a result, though domiciliary oxygen treatment improves survival in patients with severe hypoxaemia secondary to chronic obstructive airways disease,^{1,2} portable oxygen treatment has not been widely used in Britain. The low oxygen flow rates possible with the transtracheal delivery system should facilitate the development of smaller and lighter oxygen cylinders for use during exercise and while away from home. The system used in this study entailing filling portable oxygen cylinders from the standard cylinder is not ideal, as the filling process is very inefficient, and needs further research.

Occasionally patients are seen who require much higher oxygen flow rates through nasal cannulas to relieve their hypoxaemia adequately. These patients are a therapeutic problem, as the oxygen concentration delivered by most domestic oxygen concentrators falls off rapidly with increasing flow rates and the maximum flow seldom exceeds 5 l/min. For example, the oxygen concentration available from the De Vilbiss Mini DeVo2 concentrator is 95% at 2 l/min but falls to only 70% at 5 l/min. The manufacturers recommend a maximum flow of 4 l/min, which yields an oxygen concentration of 80%. Giving oxygen by the transtracheal technique may be effective in these patients by reducing their oxygen requirements to a level which can be met by the standard domestic oxygen concentrator.

The transtracheal oxygen delivery system is cosmetically more acceptable than conventional methods (figure). In addition, some of our patients found that it was more comfortable than nasal cannulas for continuous use and interfered less with daily activities—for example, washing, eating, etc. Good patient cooperation is essential to long term oxygen treatment, which inevitably produces

a dramatic change in the patient's lifestyle.⁸ It appears that increasing the number of hours of oxygen treatment a day reduces mortality in severely hypoxaemic patients with chronic obstructive airways disease and that ideally they should receive oxygen continuously.^{2,9} If the transtracheal oxygen delivery system proves to be more acceptable to patients and motivates them to use oxygen by reducing breathlessness on exercise it may help to improve survival by improving compliance with treatment. Twelve of our patients continued to use the transtracheal oxygen delivery system for a mean of 6.4 months (maximum 13 months), suggesting that the system will be acceptable to a substantial proportion of patients with hypoxaemia due to chronic obstructive airways disease who require long term treatment.

The potential advantages of transtracheal oxygen treatment must be weighed against the possible risks and the alternative methods of oxygen administration which are becoming available. In view of the known poor prognosis in this group of patients even with oxygen treatment several deaths were expected. Very few serious problems were encountered during follow up, however, and none of the deaths which occurred were related to the system. Fracture of the catheter can probably be prevented by improvement in design.

We were concerned by the high isolation rate of *Staph aureus* from the catheters, but this may in part be an artefact due to contamination of the catheter tip when this is withdrawn through the entry track. The overall incidence of infection (one episode every seven patient months) was acceptably low. Nevertheless, one serious infection with *Staph aureus* occurred during the study. The clinical picture was acute on chronic bronchitis with fever and worsening respiratory failure. No lesion was seen in the chest radiograph. Once a bacteriological diagnosis was made and appropriate antibiotics given the patient made a full recovery, but only after a period of mechanical ventilation. We do not know whether staphylococcal infection will prove to be an important problem with long term transtracheal oxygen treatment or whether this was an isolated incident. Awareness of this potential pathogen and including an antistaphylococcal agent when the patient fails to respond to standard antibiotic treatment or is seriously ill with a chest infection appears advisable. Further studies of transtracheal oxygen treatment will need to monitor patients closely for such problems. As most of the patients colonised with *Staph aureus* also carried it in the nose, prophylaxis with an antistaphylococcal agent (for example, fusidic acid ointment) before and perhaps intermittently during treatment might help.

Six of our patients were over 70 (the upper age limit in the Medical Research Council trial).¹ We may be criticised for initiating long term oxygen treatment in these patients on the grounds that their life expectancy was short and they were unlikely to improve with treatment. Our decision to treat, however, was based not only on the patient's age and physiological state but also on the severity of the breathlessness. In addition, many patients were highly motivated to try the system. Symptomatic improvement appears to be a more important consideration than prolongation of life in this elderly group.

We were disappointed that two of our patients continued to smoke. Every effort was made to discourage patients from smoking from the point of view both of safety and of reducing the rate of progression of the lung disease. We were not able to monitor carboxyhaemoglobin concentrations, which would have been helpful.

Our findings suggest that breathless hypoxaemic patients with chronic obstructive airways disease benefit from transtracheal oxygen. We were impressed by the enthusiasm of most of our patients for the treatment. Supplying oxygen during exercise may also benefit patients with disproportionate dyspnoea on exertion ("pink puffers").¹⁰ The one patient in this category whom we treated progressed well and had been an outpatient for four and a half months at the end of the study despite having spent three months in hospital before the start of treatment because of dyspnoea refractory to conventional management. Patients with other types of chronic lung disease associated with hypoxaemia such as fibrosing alveolitis or cystic fibrosis may also benefit from the procedure, though this remains to be studied.

Recently other methods of reducing oxygen requirements have been described.^{11,12} One device depends on the reservoir system,¹¹ and two others depend on delivering oxygen intermittently.¹² The reservoir system may be cosmetically unacceptable to many patients. The intermittent delivery valve systems may be expensive and may possibly be prone to malfunction and mechanical failure. We think that the transtracheal oxygen delivery system will compare favourably with these techniques, but further studies are necessary.

Transtracheal oxygen delivery through a microcatheter is a practical technique for long term oxygen treatment and has a potential role in rehabilitating patients with chronic obstructive airways disease. The low oxygen flow rates which can be achieved will be of particular advantage during portable oxygen treatment and when oxygen concentrators are not available. Many patients find its appearance more acceptable than with conventional oxygen treatment. Nevertheless, it requires more patient cooperation and motivation than conventional treatment and certainly requires closer hospital supervision. The potential risks of infection need to be evaluated further and the system should be directly compared with other forms of oxygen administration.

We thank Erie Medical, Milwaukee, Wisconsin, USA, for supplying the flow regulators and oxygen recharging adapters used in this study.

References

- 1 Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981;i:681-5.
- 2 Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Ann Intern Med* 1980;93:391-8.
- 3 Williams BT, Nicholl JP. Prevalence of hypoxaemic chronic obstructive lung disease with reference to long term oxygen therapy. *Lancet* 1985;ii:369-72.
- 4 Lowson KV, Drummond MF, Bishop JM. Costing new services: long term domiciliary oxygen therapy. *Lancet* 1981;i:1146-9.
- 5 Heimlich HJ. Respiratory rehabilitation with transtracheal oxygen system. *Ann Otol Rhinol Laryngol* 1982;91:643-7.
- 6 Anonymous. Oxygen in the home. *Drug Ther Bull* 1982;20:65-7.
- 7 Leggett RJE, Flenley DC. Portable oxygen and exercise tolerance in patients with chronic hypoxic cor pulmonale. *Br Med J* 1977;ii:84-6.
- 8 Anonymous. Long term domiciliary oxygen therapy. *Lancet* 1985;ii:365-7.
- 9 Anthonisen NR. Long term oxygen therapy. *Ann Intern Med* 1983;99:519-27.
- 10 Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in "pink puffers." *Lancet* 1981;i:907-9.
- 11 Moore-Gillon JC, George RJD, Geddes DM. An oxygen conserving nasal cannula. *Thorax* 1985;40:817-9.
- 12 Gould GA, Hayhurst MD, Scott W, Flenley DC. Clinical assessment of oxygen conserving devices in chronic bronchitis and emphysema. *Thorax* 1985;40:820-4.

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A 69 year old man who has never smoked got a unilateral pleural effusion that proved to have been caused by an adenocarcinoma of the lung. For 16 years he had worked in a chemical factory producing industrial catalysts, with nitric acid the principal agent used. Is there any link between adenocarcinoma of the lungs and industrial exposure to nitric acid?

Nitric acid fumes invariably contain oxides of nitrogen, particularly nitrogen dioxide (NO₂) and dinitrogen tetroxide (N₂O₄). These are highly irritant and may cause acute pulmonary damage. Neither nitric acid nor the oxides of nitrogen are mutagenic when subjected to the Ames test.¹ Furthermore, they do not appear to produce the covalent, strongly electrophilic metabolites that damage chromosomes and are associated with many known human chemical carcinogens.¹ Short term studies have failed to show an excess of cancers in animals exposed to nitric acid or oxides of nitrogen but these studies have been criticised because it has been difficult to maintain constant concentrations of these chemicals in the environment.² Although there is no evidence that nitric acid or oxides of nitrogen cause lung cancer, this does not exclude an occupational cause in this case. Compounds of arsenic, nickel, and antimony which are suspected lung carcinogens may be encountered in the manufacture of industrial catalysts. Further inquiry in the workplace is therefore suggested.—W R LEE, professor, and A R SCOTT, lecturer of occupational health, Manchester.

- 1 World Health Organisation. *Oxides of nitrogen. Environmental health criteria*. Geneva: WHO, 1978.
- 2 Gage JC. Nitrogen oxides. In: Parmeggiani L, ed. *Encyclopaedia of occupational health*. Geneva: International Labour Office, 1983:1459.