Therapeutic whole lung lavage for inhaled plutonium oxide revisited

IOP Publishing Journal of Radiological Protection

J. Radiol. Prot. **30** (2010) 735–746 doi:10.1088/0952-4746/30/4/007

Therapeutic whole lung lavage for inhaled plutonium oxide revisited

C Morgan[1], D Bingham[2], D C B Holt[3], D M Jones[2] and N J Lewis[2,4]

[1] Anaesthesia and Critical Care Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK
[2] Atomic Weapons Establishment, Aldermaston RG7 4PR, UK
[3] Institute of Naval Medicine, Alverstoke, Gosport PO12 2DL, UK

E-mail: nick.lewis@awe.co.uk

Received 22 October 2009, accepted for publication 17 August 2010
Published 8 December 2010
Online at stacks.iop.org/JRP/30/735

Abstract

Two reviews in the last 12 years have differed widely in their indications for the use of whole lung lavage (WLL) to remove plutonium from the lung, one recommending its use at relatively low radiation doses to prevent stochastic effects and the other recommending restricting its use to high doses to prevent deterministic effects only. Since the publication of these reviews significant data have accumulated demonstrating the increased safety of WLL, and there are additional data on stochastic and deterministic effects. We discuss deterministic and stochastic risks and the practical aspects of undertaking WLL. We recommend that each case be assessed individually.

1. Introduction

Whole lung lavage (WLL) formerly known as bronchopulmonary lavage (BPL) can be used to remove insoluble oxides of plutonium-239 ($^{239}PuO_x$) which have been inhaled into the lung as a result of an incident. In a review in 1997, Dean [1] recommended considering WLL if the annual limit of intake (i.e. 20 mSv integrated over 50 years, but 'credited' in the year of intake) was likely to be exceeded. In contrast, however, Wood *et al* [2] recommended WLL only to prevent deterministic effects and if the lung dose were likely to exceed 5 Sv (sic) within a timescale of 'a few weeks'. It is understood [3] that this recommendation was influenced by the low stochastic risk evident in the follow-up of the Los Alamos workers [4].

Dean [1] noted that WLL was becoming increasingly safe, provided it was done by a specialist team, and in a specialist centre. In the UK, a division within Pulmonary Medicine at the Royal Brompton Hospital led by Dr Cliff Morgan (CM) acts as a national referral centre for performing WLL for the rare condition pulmonary alveolar proteinosis (PAP). Since that review, CM has acquired considerable additional experience of the WLL procedure.

[4] Author to whom any correspondence should be addressed.

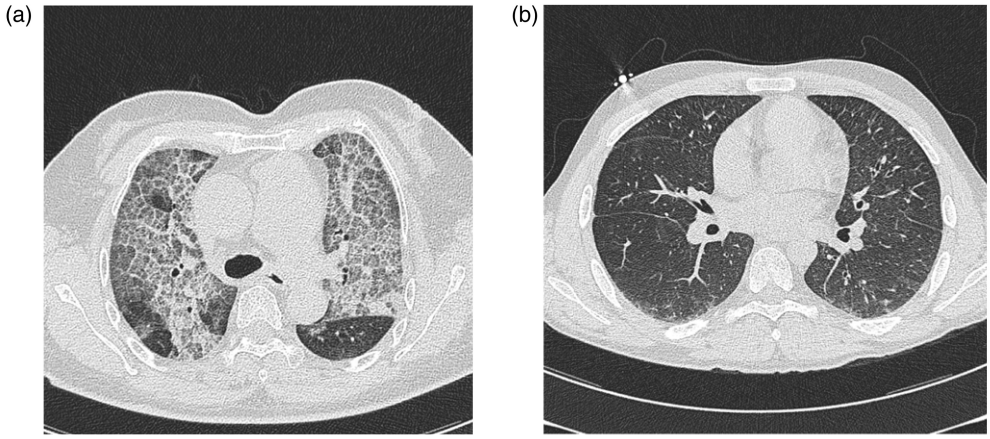

Figure 1. (a) This image shows the typical CT appearances of severe PAP with the 'crazy paving' effect, extensive airspace filling and some 'geographic' sparing of relatively normal looking lung. (b) Relatively normal CT appearance of healthy lung after successful treatment (different patient).

Dean also noted increasing risk aversion in society. This trend has continued and has been noted by physicians working at the Atomic Weapons Establishment (AWE). In the past, workers who suffered minor contamination remained relaxed and open to explanations that residual risks of persistent contamination and committed effective dose were low: now they request that contamination be removed regardless of the personal cost [5]. In addition, since Dean's and Wood's papers, evidence has emerged from the Russian Federation of the stochastic effects of plutonium inhalation in man [6, 7] from chronic exposure of accumulating high dose. This is in marked contrast to Los Alamos workers of the Manhattan Project followed for 50 years [4] but whose intakes were mostly single rather than chronic in nature.

Although it has not yet been found necessary to consider WLL for any specific incidents at AWE, WLL is part of the AWE's emergency planning and in view of the issues raised above, it seemed pertinent to conduct a review into the circumstances in which WLL could be used. At AWE, the main inhalation hazard is from plutonium.

2. WLL and pulmonary alveolar proteinosis (PAP)

While WLL might be considered a novel technique for the treatment of plutonium inhalation, it is routinely used for the treatment of the medical condition, pulmonary alveolar proteinosis (PAP). PAP is an extremely rare lung disease affecting less than one in 1 million of the population in which the alveolar airspace gradually fills with a combination of lipo-proteins derived from normal surfactants and immature and dysfunctional macrophages. This airspace filling causes a progressively worsening gas exchange failure across the alveolar capillary membrane which explains the symptoms of breathlessness and exercise limitation and the radiological findings of diffuse airspace shadowing on the plain chest radiograph and the almost unique appearances on the chest computed tomography (CT) scan (figure 1(a)).

Recent developments in the understanding of PAP have led to improvements in clinical management through selective drug therapy to regain functional control of the alveolar macrophage [8]—which appears to be the central defect in the majority of cases, but the mainstay of treatment is still the physical removal of the abnormal material from the alveoli by therapeutic lavage [9–11] figure 1(b). There has been some interest in using the basic

technique of WLL in other medical conditions where there is a removable accumulation of some target material in the alveolar space. There were no clinical benefits in patients with mucus plugging secondary to asthma, nor in patients with alveolar cell carcinoma and only worsening of general sepsis in patients with cystic fibrosis. However, some patients with lipoid pneumonia secondary to Niemann–Pick syndrome have had significant clinical improvement after a series of WLL treatments [12] and successful treatment of lipoid pneumonitis due to ingestion and inhaling coconut oil has been reported [13]. Also, and perhaps more intriguingly relevant to the context of risk reduction in occupational health, is the reported use of WLL to reduce the dust burden in pneumoconiosis [14], although complicated by a hydropneumothrax possibly caused by decreased compliance of a lung with pneumoconiosis. Interestingly the silica dust recovered was mostly engulfed in alveolar macrophages.

Ramirez-Rivera is generally recognised as the pioneer in treating PAP in the early 1960s [15]. Therapeutic, massive WLL was first attempted in the early 1960s and has gradually evolved in terms of safety and efficacy since. A small number of centres worldwide have had significant experience in performing WLL in patients with PAP and there are variations in the detailed technique employed but the essence of the treatment is to ensure separation of right and left lungs by the placement, under general anaesthesia, of a double lumen endobronchial tube and then to ventilate one lung with 100% oxygen while the other lung is irrigated with large quantities of body temperature, sterile, saline until all the moveable material is lavaged out of the target lung. In some cases the other lung is then treated during the same anaesthetic, in other cases this is delayed to another day and in many patients, the treatment has to be repeated a variable number of times before a long lasting and satisfactory remission is achieved. There were reports of series of cases treated in the 1960s, 70s and 80s but few since because the use of WLL in PAP is established and no longer newsworthy. The exception is the relatively recent publication of the effectiveness and complete safety of WLL in PAP by Beccaria *et al* in Pavia, Italy [10], and unpublished discussions between experienced providers of WLL at specialist PAP conferences. The overwhelming view is that when WLL is conducted in an experienced centre, it is safe and effective.

The safe and reliable separation of the two lungs is the critical factor in ensuring both the safety and the efficacy of the treatment. Fortunately, while PAP and its treatment by WLL is extremely rare the use of double lumen endobronchial tubes to facilitate lung surgery is not. Subtleties of the detailed conduct of the WLL are probably important but not nearly as crucial as this simple, central cornerstone of safety. It should be stressed that while slightly suboptimal placement of the double lumen tube may not be a significant issue in most instances of lung separation for lung surgery, the position and function of the double lumen tube must be absolutely perfect for the safe conduct of WLL. The Royal Brompton Hospital WLL technique is briefly described in box 1.

In 1997, Dean [1] noted that CM had performed 63 WLLs in 16 patients with no deaths or complications. This figure is now 521 WLLs in 68 patients. Three adverse events have now been seen: one post-operative urinary retention, one possible episode of partial awareness during the WLL and one failed intubation. The failed intubation was predictably difficult resulting in a tracheostomy, but it was still possible to proceed to segmental fibre-optic lavage. These adverse events were not attributable to WLL. There is thus increased evidence of the safety of WLL since 1997.

3. WLL: effectiveness and practical aspects

Experimental data give guidance as to how many lavages should be done, at what frequency and how soon after an intake.

Box 1 The WLL technique at Royal Brompton Hospital.

Preparation

Standard pre-operative anaesthesia preparations include discussion, consent, premedication (where appropriate) and thrombo-prophylactic precautions (e.g. low molecular weight heparin and antithrombotic stockings).

General anaesthesia
GA is induced using standard agents (e.g. propofol and vecuronium) and maintained with remifentanil by infusion (0–0.1 μgm kg^{-1} min^{-1} plus 0–2% inhaled isoflurane in oxygen).

Double lumen endobronchial intubation is effected with left sided disposable Robert Shaw type endobronchial tube (size chosen on basis of size of patient and inspection of pre-operative chest CT scan).
Placement and function of the tube carefully checked using fibre-optic bronchoscopy before committing to treatment.
The patient is tilted so that the target lung is lower than the ventilated lung—this provides protection of the ventilated lung in the event of spillage past the endobronchial tube cuffs but tends to increase the gravitational bias of continued perfusion to the non-ventilated lung, thus exacerbating the ventilation/perfusion mismatch and fall in blood oxygen saturation (a 30° tilt is a good compromise).

WLL

Both lungs ventilated with FiO_2 1.0 $\times$ 20 min to remove all nitrogen from the target lung and then the target lung excluded from ventilation at the end of expiration (thereby leaving the target lung full to its functional residual capacity (FRC) with 100% oxygen and no nitrogen).
The sterile, closed lavage circuit then connected to the target lung lumen of the double lumen tube.
Aliquots of sterile saline at 37 °C and from no higher than 45 cm (45 cm H_2O drive pressure) are gradually allowed into the target lung at around 100 ml min^{-1} as the FRC of remaining oxygen is gradually absorbed by residual pulmonary perfusion of the target lung—at around 100 ml min^{-1}.
This continues until the target lung is full to its total lung capacity (TLC) and no further saline can flow in at the drive pressure limit.
A ‘tidal volume’ of initially around 500 ml is let out of the target lung into the graduated collecting cylinder (and the fluid balance carefully monitored) and replaced with a fresh input tidal volume of around 500 ml.
Samples of the effluent fluid are collected for biochemical and microbiological analysis and the degree of severity of the PAP is obvious from the lipo-protein load in the effluent.
Tidal volumes are let in and out of the lung in this way. It is usually possible to gradually increase the tidal volume to up to 1000 ml and this may improve efficacy (through lung recruitment) and efficiency (by reducing total treatment time for a given WLL volume). There should be a gradual but exponential decrease in lipo-protein load in the effluent as the WLL proceeds and this can be confirmed by measurement but is usually apparent by simple inspection.
When the effluent returns are clear, the therapeutic endpoint has been reached.
All residual fluid is drained passively though this can be encouraged by tilting the operating table through cycles of lateral tilting and longitudinal (head up then head down) tilting. Then suction catheters are passed down the lumen to the target lung to aspirate all remaining liquid before re-ventilating both lungs.
In a single lung WLL, this is the end of the procedure; the double lumen tube is changed for a standard endo-tracheal tube and the patient then ventilated in Recovery or Intensive Care Unit for at least 2–3 h (with continued sedation). During this time, residual fluid that could not be recovered will be absorbed and the treated lung will re-stabilise. A trial of spontaneous breathing then demonstrates when the patient is judged safe to be woken and extubated.
In bilateral sequential WLL—after lavage of one lung, both lungs are ventilated for at least 30 min. There is then a trial of ventilation of the recently treated lung. If this is judged satisfactory, it is safe to proceed to WLL of the second lung (exactly as for the first target lung). When both lungs have been lavaged, the period of post-operative ventilation should be at least 4–6 h before a trial of spontaneous breathing—to ensure that most of the residual saline has been safely absorbed.

The circuit diagram is shown in figure 2.

How many lavages and how frequent: Nolibe *et al* [16] conducted lavages in beagle dogs and baboons over a period of 1–56 days with gaps of 3–14 days between lavages. They found that the first lavage removed almost 25% of plutonium oxide and five lavages removed a total of 40% in dogs and 50% in baboons. They found little value in more than eight lavages. They also mention one human case which was treated with two lavages of the right lung and one to the left removing 13% of material. However the aerosol was partly soluble and also treated with chelating therapy (DTPA) which removed a further 17%. A report following the Chernobyl accident [17] noted that 'therapeutic bronchoalveolar lavage led to elimination of a large percentage of the radioactive dust which was present in the alveolar macrophages'. Sanders [18], in work on 90 rats, noted a stable amount removed by repeated washings during the 16 days following exposure and then decreasing.

As a guide, taking the above work of Nolibe [16] and Sanders [18] into account, it is recommended that about five lavages are done over 16 days. A pragmatic approach should also be used whereby lavages continue while the arisings show a reduced content of plutonium and stop when plutonium is no longer being removed. The minimum gap between lavages and the total number performed will be governed by the condition, comfort and consent of the patient.

How soon after an incident lavage should be started: Dean recommended starting lavage at day 3, to allow time for mucociliary clearance from the upper airways to occur. This is supported by European physicians [19] who also prefer to allow two days to ensure adequate uptake of plutonium oxide by alveolar macrophages. Sanders [18] however, quoting work on rats, cites that particles are removed from the trachea, bronchi and bronchioles during the first day following exposure. Pfleger *et al* [20] found best results in beagles at day 0, 8 and 16. However, Nolibe [16] showed little difference in effectiveness at day one when using baboons or day two when using dogs.

Sanders [18] showed greatest accumulation in macrophages between days 1 and 5 and stated, 'the effectiveness of plutonium removal by washing decreases with time following inhalation. This decrease is more rapid after deposition of larger quantities of plutonium, an effect which is probably related to the radiation dose delivered to the lung'.

Ellender *et al* [21] cite little difference in results in starting lavage in hamsters at one week, one month or six months after exposure. However they designed the radiation intake of the hamsters in their study to be at a level not to cause damage to macrophage function. They noted the risk of reduced macrophage activity if radiation damage occurred and thought that delay in WLL could cause greater absorbed dose.

The optimal time to start WLL is thus unclear. However, time will be needed to assess intake and dose (see section 5) and we conclude that an optimum time to start WLL for insoluble $^{239}PuO_x$ inhalation is on day four after intake.

The gold standard of any novel treatment is a randomised clinical trial, with a group of treated patients to be compared with a placebo-treated control group. This would require a significant number of patients to achieve statistical significance. To date this has not been possible for WLL for inhaled PuO_x, nor is it likely in the future. In these circumstances we must rely on comparing the risks of intervention with the risks of doing nothing, as described in the following paragraphs.

4. Hazards of plutonium inhalation

4.1. Deterministic effects

There is a lack of clarity in published work as to which dose is relevant in considering deterministic effects such as lung pneumonitis and fibrosis. Traditionally the gray has been

used. The International Commission on Radiological Protection (ICRP) included the term gray-equivalent (Gy-Eq) [22] to adjust absorbed dose by the appropriate relative biological effectiveness (RBE) for the specified biological endpoint, i.e. radiation pneumonitis/pulmonary fibrosis. Effective and equivalent doses (in units of sievert) are relevant only to occupational and environmental exposures to inform stochastic risk in exposed populations and have no relevance to deterministic effects not withstanding equivalence to the gray (Gy) for low LET radiations with a radiation weighting factor (w_r) of unity. The w_r may be seen as an example of RBE specifically for risk of stochastic outcomes, but with no application to deterministic effects. For the purposes of this paper we use gray-equivalent.

There is a further difference between calculating dose to the lung for deterministic effects and for stochastic effects. In calculating equivalent dose to the lung (taken to be the thoracic region) for stochastic effects, the equivalent doses to the bronchial, bronchiolar, alveolar interstitial (AI) and lymphatic regions are assigned weighting factors of 0.333, 0.333, 0.333 and 0.001 based on their contribution to detriment [23]. The differing deposition and clearance of material among these regions means that doses between these regions will vary in a time-dependent manner. In the first few weeks after an intake, a higher dose will be received by the bronchial and bronchiolar regions, but over longer periods the dose to the alveolar interstitial region will be highest. For the endpoint of pneumonitis or pulmonary fibrosis, it would appear most appropriate to either calculate the dose to the AI region only, or to calculate the mass-weighted average of dose to the regions, noting that most of the mass is in the AI region (1100–1200 g compared to 1.3 g and 1.9 g for the bronchial and bronchiolar regions).

Wood *et al* recommended WLL to prevent deterministic effects if lung doses were to exceed 5 Sv of alpha radiation. Perhaps 5 Gy-Eq was intended by the authors, but if not, the committed equivalent dose to the lung, in Sv, must be divided by the w_r of 20 to establish the absorbed dose in Gy and then multiplied by the RBE for the particular biological endpoint of radiation pneumonitis/pulmonary fibrosis. The clearest figure we have found for RBE for alpha radiation for the endpoint of lung pneumonitis or fibrosis is 7 [24]. On this basis, 5 Sv would equate to a dose of 1.75 Gy-Eq. Also, if the 5 Sv dose represents the integrated dose over 50 years, then it may be noted that the integrated dose over the period of interest (the first few weeks) would be very much smaller.

Scott and Peterson [25] took RBE and dose rate into account when generating risk distributions for plutonium oxide inhalation based on Nuclear Regulatory Commission (NUREG) reports' risk models [26] and time-dependent dose conversion factor data from publication 30 of the ICRP [27]. They used both absorbed and adjusted doses (taking into account RBE and dose rate). They calculated median absorbed and adjusted threshold doses for respiratory dysfunction of 38 Gy and 473 Gy-Eq respectively, implying an RBE of about 12.5. The median threshold doses for death from pneumonitis were 54 Gy and 672 Gy-Eq respectively. However, they noted that the NUREG data were based largely on animal data of 1.5–3 year follow-up and suggested revision in the light of later animal and epidemiological data. Their derived absorbed and adjusted doses seem excessively high for threshold doses although the dose rates assumed are not disclosed but must be expected to be very low.

ICRP31 [28] notes that death from fibrosis in several species of experimental animal occurs with a dose of 370 Bq g^{-1} of lung tissue. If we take a reference human male as having a lung mass of 1200 g [29]—the analogous measurement to that in the experimental studies—lung fibrosis would be expected at a deposition of 440 kBq in the lung. Assuming exposure of a worker to a particulate aerosol of 5 μm AMAD particle size, which means that about 6.4% would be deposited in the alveolar interstitial and bronchiolar regions [23], then this amount of deposition would be caused by an initial intake of 7 MBq. Dose to the AI region of the lung from exposure to this activity of insoluble (Type S) $^{239}PuO_x$ would be 4.5 Gy-Eq over a 30 day

period and 39.2 Gy-Eq over one year (assuming an RBE of 7). More recent data includes Muggenburg *et al* [30] who report death from radiation pneumonitis in dogs at 6.3–95 Gy lung dose.

Caution is needed when extrapolating animal doses to human subjects. Persuasive human work is provided by Okladnikova [31] reporting pneumosclerosis (pneumonitis and lung fibrosis) in Mayak workers exposed to plutonium aerosols at over 1.4 Gy lung dose. In nuclear weapon plutonium workers cumulative equivalent occupational doses to the lung of 10 Sv (=3.5 Gy-Eq) conferred a five-fold risk of having an abnormal chest x-ray consistent with pulmonary fibrosis [32].

The above are also consistent with clinical data: Oya *et al* [33] noted pneumonitis in 20% of bone marrow patients receiving 8–12 Gy x-ray lung dose.

Coggle *et al* [34] cite pneumonitis occurring within six months of exposure to a lung dose of 8 Gy of X or gamma rays. The ICRP [35] cites pneumonitis occurring at a whole body gamma ray exposure of 6 Gy.

In summary, the range of doses over which deterministic effects to the lung can occur reflects the different radiation types, dose rates, species and biological endpoints involved. Having studied all the above we consider the possibility of deterministic effects should be considered at a lung (AI) dose of 6 Gy-Eq or more from $^{239}PuO_x$ exposures. This dose would be incurred over periods of 30 day and one year following intakes by inhalation of 9.2 and 1.1 MBq respectively of insoluble (Type S) $^{239}PuO_x$ of 5 μm AMAD.

4.2. Stochastic effects

50-year follow-up of a small sample of plutonium workers from the Manhattan Project [4] showed a low standardised mortality ratio and no statistical elevation in the incidence of all cancers although there was one bone cancer excess. Early work from Russia [6] on male Mayak workers exposed to alpha radiation from plutonium has shown an excess relative risk (ERR) of lifetime lung cancer of 0.23–1.36 per sievert equivalent lung dose giving a lifetime risk in the dose range below 30 Sv as 1.21% Sv^{-1}. Later work [7] showed an ERR of 7.1 for males.

The 2007 recommendations of the ICRP [35] provide a lifetime risk coefficient for lung cancer in the working population of 1.27% Sv^{-1} lung dose. Bearing in mind the wide range of doses above, this is taken as the most authoritative figure.

4.3. Psychological effects

As noted above, intakes of radioactive material are unlikely to be tolerated by the modern workforce. Notwithstanding attempts to explain the possibility of deterministic and stochastic effects to the worker, it is highly likely that a worker who has inhaled plutonium oxide will request any treatment available. However, in those for whom no treatment is possible or justifiable, repeated biodosimetry followed on each occasion by the provision of information about the dosimetry, explanation about the inferred risks and reassurance to the greatest extent possible will be required [36].

5. Assessment of Intake

5.1. Dosimetry assessments

Following inhalation of $^{239}PuO_x$, initial dose assessments would be based on alpha activity in nose blows, nasal swabs and lung monitoring for americium-241 (^{241}Am) associated with the

plutonium. Faecal and urinary monitoring would also be initiated, with rapid measurement of ^{241}Am in faecal samples. An assessment of the magnitude of the intake and dose could be made in the first three days, based on the nose blows, lung monitoring and faecal data.

The most accurate assessment of dose will be in cases where ^{241}Am is present and ^{239}Pu:^{241}Am ratios are known. The limit of detection for lung monitoring of ^{241}Am is about 10 Bq. Thus if 10 Bq of ^{241}Am is detected, at ratios of ^{239}Pu:^{241}Am of 2:1 and 20:1, and assuming an intake of insoluble (Type S) $^{239}PuO_x$ of 5 μm AMAD, then total intakes would be of 480 and 3400 Bq respectively, resulting in dose to the AI region over 30 days of less than 1 and 2 mGy-Eq respectively. Alternatively in these cases, AI doses may be assessed directly from energy deposited in the mass of tissue based on simple predictions regarding the retention of activity. Lung monitoring also has the advantage that it may give some indication of the spacial distribution of activity throughout the lung. Lung monitoring for ^{239}Pu is much less sensitive than for ^{241}Am with a limit of detection of a few kBq. If lung monitoring results are not available, then assessments of lung activity and dose can be made based on faecal and nose blow measurements, although there will be much greater uncertainties in the assessments.

5.2. Diagnostic bronchoalveolar lavage

Diagnostic bronchoalveolar lavage of a segment of a lung (but not of the whole lung) has an established role in the diagnosis of a range of serious pulmonary conditions including PAP. The procedure is well tolerated in most cases and is based on the use of fibre-optic bronchoscopy and selective, limited volume lavage of a target lung segment supplied by a segmental lobar bronchus. Saline is instilled through the procedure channel of the fibre-optic bronchoscope and aspirated back. The sample thus collected can be used for microbiological, biochemical or cytological analysis. The same technique could be used to collect a sample to estimate the size and mobility of the plutonium intake as a preliminary to committing to WLL, as an adjunct to traditional health physics assessments.

As noted above, dose assessment will take three days and there is conflicting evidence about when to start lavage. A pragmatic approach would be to start lavage four days after an intake, which allows time for dose assessment, time to talk to the employee concerned and time to organise transfer to hospital. If deterministic effects are suspected from the circumstances of the incident, WLL should be done as soon as possible.

6. WLL: radiation protection aspects

Pre-planned arrangements should be in place to ensure that the contamination control arrangements, both during and following WLL, are suitable and sufficient. These should cover transportation of the patient, monitoring the clinical environment, sampling and disposal of contaminated arisings and contingencies for dealing with contaminated equipment and components. The arrangements should include the patient and staff who may come into contact with the patient.

Modifications to the WLL are required to ensure that PuO_x is not exhaled from the patient into the treatment room or ventilator unit. The circuit for WLL is shown in figure 2 with the lavaged lung shown as hatched and the ventilated lung in white. Modifications of standard WLL to allow lavage of PuO_x are:

(1) Addition of a type P (particulate) class 3 (high efficiency) filter to exhaled oxygen to ensure that no PuO_x is being exhaled. Breathing out significant activity would be highly unlikely as most particles will have been taken up by macrophages by day 4. In addition, ventilators with their own disposable breathing circuit are available.

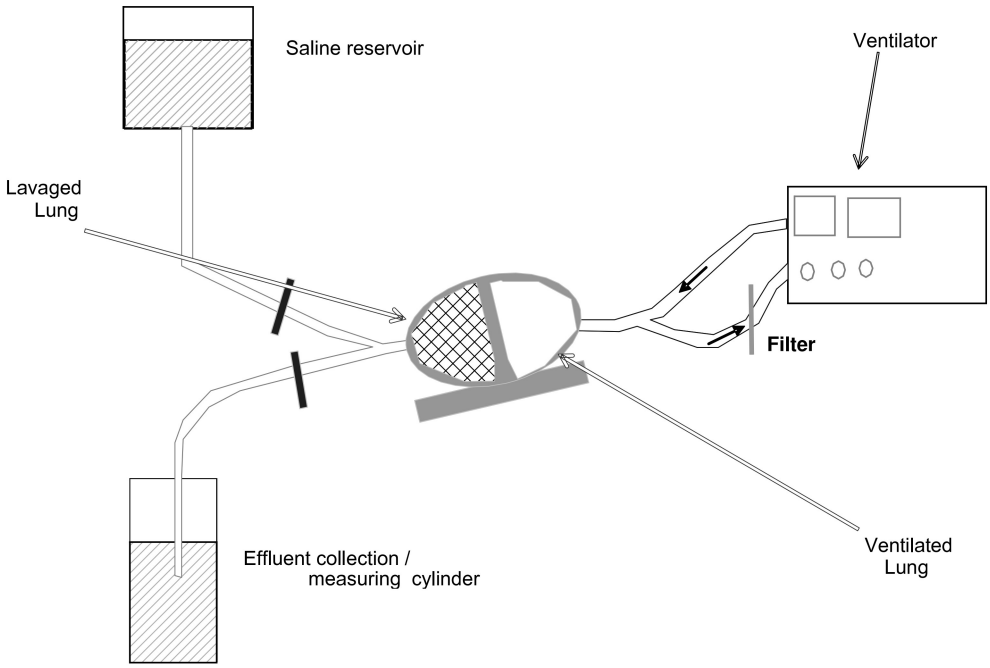

Figure 2. WLL circuit.

(2) Provision of health physics monitoring support during the procedure. This will ensure that staff, the treatment room and equipment will not become contaminated. Full monitoring of the treatment area will be needed before returning to general use.
(3) Monitoring of the arisings using an instrument to detect ^{241}Am. The most appropriate we have identified is the plastic scintillant BM185 small article monitor. This will allow the effectiveness of the WLL to be assessed to determine if it is worthwhile continuing lavaging in any one session.
(4) Collection and disposal of the arisings and equipment.

7. WLL: anaesthetic and other risks

Risks associated with WLL are risks associated with the WLL procedure, risks associated with hospital admission and those due to giving an anaesthetic.

Risks associated with the WLL procedure: CM's series and the Pavia series [10] demonstrate that in experienced hands, in a centre with experience in the management of PAP, the intrinsic risks of the WLL procedure are effectively zero.

Risks associated with hospital admission: all hospital admissions carry a risk of infection and venous thrombo-embolism but these risks are contained by appropriate measures and have not occurred in the 521 WLLs in 68 patients at the Royal Brompton Hospital, nor are they reported in any of the recent PAP literature [10]. Also PAP patients are often very ill and prone to infectious complications by the nature of their illness and are possibly at greater risk of venous thrombo-embolic events than the general population. Thus the absence of any such complications bodes well for healthy workers who have inhaled PuO_x.

Anaesthetic risks: the 1987 CEPOD study (the confidential enquiry into perioperative deaths) put the mortality rate attributable to anaesthesia alone at 0.0005% [37] and this mortality rate has not changed significantly since [38].

Assuming that it is decided to try to reduce stochastic risk and that stochastic effects are as previously described: 1.27% lung cancer risk per sievert lung dose [35] then taking an intake of insoluble (Type S) plutonium oxide giving rise to an effective dose of 20 mSv, the equivalent dose to the lung is 112 mSv. This gives a lifetime extra lung cancer risk of $1.27/1000 \times 112 = 0.14\%$. If 50% of the plutonium is removed the extra cancer risk is halved to 0.07%. This is 140 times greater than the risk of anaesthetic death of 0.0005%. If five lavages are done, then the anaesthetic risk could be said to multiply by 5, to 0.0025%, so that the cancer risk is now 28 times the anaesthetic risk. Similarly, if only 25% of the plutonium is removed, the cancer risk is still 14 times the anaesthetic risk. However, the anaesthetic risk in experienced hands at the Brompton Hospital, as shown by CM's series, is almost certainly much lower than 0.0005%. It should also be noted that these lung cancer risk estimates are average figures for a working population and if possible it would be better to produce a risk estimate tailored to the individual, which would take into other risk factors such as age and smoking history.

As noted earlier, deterministic effects should be considered at a dose of 6 Gy-Eq or more over a 30 day period. The principal aim of WLL is to remove as much insoluble PuO_x as possible, but notwithstanding its insolubility, it may be that a degree of translocation to other tissues over time may occur and hence WLL may reduce some committed equivalent dose to those tissues, also.

Notwithstanding the very small anaesthetic risk of WLL, the risk is, nonetheless, effectively immediate while that of cancer is not. Radiation-induced cancers do largely seem to have long latencies and it may be relevant to consider the advances in cancer medicine leading to earlier diagnosis and progressively more effective treatment that may be realised in the much longer term—of possibly decades. Of course, cancer may not ensue at all. It will be important to compare the risks and benefits of WLL and non-intervention. This will be particularly relevant in the case of the younger patient with a predictably longer life expectancy in which to express risk. The older patient may, after consideration, elect to do nothing.

8. Conclusion

Since Dean [1] and Wood *et al* [2] published their work further evidence has accumulated as to the safety of WLL. In order to obtain fully informed consent of the patient when discussing the risks of WLL versus its benefits it will be necessary to explain that there are uncertainties about all the following: dose assessment, the efficacy of WLL, anaesthetic risk and the risks of developing deterministic and stochastic effects.

In conclusion, it is recommended that WLL is considered a viable treatment option for PuO_x intakes. Potentially, it could also be used to treat contamination following inhalation of other insoluble radioactive materials. We feel that intervention with WLL should be conducted to avoid deterministic effects at lung doses of above 6 Gy-Eq anticipated within a 30 day period and that WLL should be considered carefully, on a case by case basis, to reduce the risk of stochastic effects at lower committed equivalent doses to the lung.

Each case will need to be assessed individually. Pre-planning and close co-operation between health physicists, occupational physicians, radiation medicine specialists and hospital specialists will be of critical importance.

Acknowledgments

Our thanks are due to: Dr K C Edsall, former tri-service Head of Radiation Medicine, Drs R G W Anderson and D Bruce, Consultant Occupational Physicians, Mr P Cooper and Ms R Dinning for secretarial support. Dr Edsall deceased during the preparation of this paper.

References

[1] Dean M R 1997 An evaluation of the use of bronchopulmonary lavage in the treatment of plutonium oxide Inhalation *J. R. Nav. Med. Serv.* **82.3** 188–96
[2] Wood R, Sharp C, Gourmelon P, Le Guen B, Stradling G N, Taylor D M and Henge-Napoli M-H 2000 Decorporation treatment—medical overview *Radiat. Prot. Dosim.* **87** 51–7
[3] Sharp C 2001 Personal communication with Holt D C B
[4] Voelz G L, Lawrence J N and Johnson E R 1997 50 years of plutonium exposure to the Manhattan Project plutonium workers: an update *Health Phys.* **73** 611–9
[5] Jefferies S J, Dolan M J, Stewart P, Thompson P J and Anderson R G W 1999 Plutonium and americium contaminated puncture wound—initial treatment, monitoring, dosimetry and medical aspects *Society for Radiological Protection Mtg (Southport)* pp 415–8
[6] Koshurnikova N A, Bolotnikova M G, Illyin L A, Kerim-Markus I B, Menshikh Z S, Okatenko P V, Romanov S A, Tsvetkov V I and Shilnikova N S 1998 Lung cancer risk due to exposure to incorporated plutonium *Radiat. Res.* **149** 366–71
[7] Sokolnikov M E *et al* 2008 Lung liver and bone cancer mortality in Mayak workers. *Int. J. Cancer* **123** 905–11
[8] Seymour J F, Dunn A R, Vincent J M, Presneill J J and Pain M C 1996 Efficacy of granulocyte-macrophage colony-stimulating factor in acquired alveolar proteinosis *N. Engl J. Med.* **335** 1924–5
[9] Trapnell B C, Whitsett J A and Nakata K 2003 Pulmonary alveolar proteinosis *N. Eng. J. Med* **349** 2527–39
[10] Beccaria M, Luisetti M, Rodi G, Corsico A, Zoia M C, Colato S, Pochetti P, Braschi A, Pozzi E and Cerveri I 2004 Long-term durable benefit after whole lung lavage in pulmonary alveolar proteinosis *Eur. Respir. J.* **23** 526–31
[11] Morgan C 2004 The benefits of whole lung lavage in pulmonary alveolar proteinosis *Eur. Respir. J.* **23** 503–5
[12] Nicholson A G, Wells A U, Hooper J, Hansell D, Kelleher A and Morgan C 2002 Successful treatment of endogenous lipoid pneumonia due to Niemann–Pick Type B disease with whole-lung lavage *Am. J. Respir. Crit. Care Med.* **165** 128–31
[13] Chang H Y, Chang-Wen C, Chiung-Yu C, Tzuen-Ren H, Cheng-Ren C, Wu-Wei L, Min-Ho W and Ying-Tai J 1993 Successful treatment of diffuse lipoid pneumonitis with whole lung lavage *Thorax* **48** 947–8
[14] Wilt J L *et al* 1996 Reduction of lung dust burden in pneumoconiosis by whole-lung lavage *J. Occup. Environ. Med.* **38** 619–24
[15] Ramirez-Rivera J, Schultz R B and Dutton R E 1963 Pulmonary alveolar proteinosis a new technique and rationale for treatment *Arch. Int. Med.* **112** 419–31
[16] Nolibe D, Metivier H, Masse R and Chretien J 1989 Benefits and risks of bronchopulmonary lavage: a review *Radiat. Protect. Dosim.* **26** 337–43
[17] Tatarsky A R and Marachev A V 1996 Results of combined treatment of respiratory diseases in subjects exposed to radiation after the Chernobyl accident *Ter. Arch.* **68** 30–3
[18] Sanders C L 1969 The distribution of inhaled plutonium-239 dioxide particles within pulmonary macrophages *Arch. Environ. Health* **18** 904–12
[19] 2007 Personal communications at training course: 'Treatment Initiatives after Radiological Accidents' *CEA Fontenay-aux-Roses*
[20] Pfleger R C, Wilson A J, Cuddihy R G and McClellan R O 1969 Bronchopulmonary lavage for removal of inhaled insoluble materials from the lung *Chest* **56** 524–30
[21] Ellender M, Hodgson A, Wood K L and Moody J C 1992 Effect of bronchopulmonary lavage on lung retention and clearance of particulate material in hamsters *Environ. Health Perspect.* **97** 209–13
[22] ICRP (International Commission on Radiological Protection) 2003 Relative biological effectiveness (RBE), quality factor (Q) and radiation weighting factor (wr) *ICRP Publication 92*; *Ann. ICRP* **33** (4) (Oxford: Pergamon)
[23] ICRP (International Commission on Radiological Protection) 1994 Human respiratory tract model for radiological protection *ICRP Publication 66*; *Ann. ICRP* **24** (1–3) (Oxford: Pergamon)
[24] NRPB (National Radiological Protection Board) 1996 Risk from deterministic effects of ionising radiation *Doc. NRPB* **7** (3) 15

[25] Scott B R and Peterson V L 2003 Risk estimates for deterministic health effects of inhaled weapons grade plutonium *Health Phys.* **85** (3) 280–93
[26] US Nuclear Regulatory Commission 1993 Health effects models for nuclear power plant accident consequence analysis part 1: introduction integration and summary *Report NUREG/CR-4214 ITRI-141 Rev. 2 Part 1* (Washington, DC: USNRC)
[27] ICRP (International Commission on Radiological Protection) 1979 Limits for intakes of radionuclides by workers *ICRP Publication 30*; *Ann. ICRP* **3** (1–4) (Oxford: Pergamon)
[28] ICRP (International Commission on Radiological Protection) 1980 Biological effects of inhaled radionuclides *ICRP Publication 31*; *Ann. ICRP* **4** (1/2) (Oxford: Pergamon)
[29] ICRP (International Commission on Radiological Protection) 2002 Basic anatomical and physiological data for use in radiological protection: reference values *ICRP Publication 89*; *Ann. ICRP* **32** (3–4) (Oxford: Pergamon)
[30] Muggenburg B A, Guilmette R A, Hahn F F, Diel J H, Mauderley J L, Seilkop S K and Boecker B B 2008 Radiotoxicity of inhaled ^{239}PuO2 in dogs *Radiat. Res.* **170** 736–57
[31] Okladnikova N D, Pesternikova V S, Sumina M V and Doschchenko V N 1994 Occupational diseases from radiation exposure at the first nuclear plant in the USSR *Sci. Total Environ.* **142** 9–17
[32] Newman L S, Mroz M M and Ruttenber A J 2005 Lung fibrosis in plutonium workers *Radiat. Res.* **164** 123–31
[33] Oya N *et al* 2006 Influence of radiation dose rate and lung dose on interstitial pneumonitis after fractionated total body irradiation: acute parotitis may predict interstitial pneumonitis *Int. J. Hematol.* **83** 86–91
[34] Coggle J E, Lambert B E and Moores S R 1986 Radiation effects in the lung *Environ. Health Perspect.* **70** 261–91
[35] ICRP (International Commission on Radiological Protection) 2007 Recommendations of the ICRP *ICRP Publication 103*; *Ann. ICRP* **37** (2–4) (Oxford: Pergamon)
[36] Holt D C B 2007 Risk assessment and decision making. Training course: treatment initiatives after radiological accidents *CEA Fontenay-aux-Roses* http://www-carmin.cea.fr
[37] Buck N, Devlin H B and Lunn J N 1987 *The Report of a Confidential Enquiry into Perioperative Deaths* (London: The Nuffield Provincial Hospitals Trust and the Kings Fund)
[38] Cashman J and Grounds M 2007 *Recent Advances in Anaesthesia and Intensive Care* (Cambridge: Cambridge University Press)