Ministry of Defence

Synopsis of Causation

Mesothelioma

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

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1. Definition

1.1 Mesothelioma is a tumour of the pleura, pericardium or peritoneum. It arises from embryonic mesothelium that forms the outer lining of the lungs, heart and intestine.

1.2 The tumour is almost always malignant although there is a rare form of fibrous mesothelioma that is benign. This document will consider the nature and aetiology of malignant mesothelioma.

1.3 Pathologically it can present in three forms:

- Epithelioid
- Sarcomatous
- Mixed (a combination of the above types)

1.4 The epithelioid type is most common and it is sometimes difficult to distinguish from adenocarcinoma secondary to a primary tumour from the lung or breast. Diagnosis is often difficult with routine histology. Specific chemical stains are needed to assist differential diagnosis.

1.5 The tumour develops and spreads as a white, pearly sheet along the tissue of the pleural cavity and invades adjacent tissue including the pericardium, and mediastinum. It is invariably fatal. At this stage treatment does little to alter the course of the disease. The tumour can present in the pericardium but pericardial involvement is more likely to be by invasive spread from the pleura. Primary peritoneal disease can occur, usually linked to high asbestos exposure, but invasive spread through the diaphragm is probably more common.

1.6 **Epidemiology**: Over recent years there has been a continuing rise in the incidence of mesothelioma which was previously considered to be a rare tumour. Incidence is increasing significantly in the United Kingdom and in other industrialised countries. The annual numbers of deaths from mesothelioma in the UK has risen from 153 cases in 1968 to 1631 cases in 2000 and 1848 in 2001.[1] It is more common in men with a ratio in the UK of around 8:1.[2] In the USA 200-300 new cases are diagnosed each year and internationally the frequency is 0.9 cases per 100,000 population.[3] Incidence is high in geographical areas where the mineral asbestos is mined and processed and also in communities near to where raw asbestos or asbestos products were used. The incidence continues to rise. In view of the long latent period between exposure to asbestos and development of the disease, estimates of future incidence in the UK predict an expected peak of between 1950 to 2450 deaths per annum by some time between 2011 and 2015, falling thereafter until 2050.[1]

2. Clinical Features

2.1 Mesothelioma develops insidiously and clinical presentation can be variable. Typically it presents with either onset of dyspnoea, chest pain or both. Dyspnoea is the most common initial symptom and is usually due to a developing pleural effusion compressing the lung. Progressive encasement of the lung by tumour causes further restriction of lung expansion and adds to the dyspnoea. Chest pain is described as dull and diffuse and worsens as the disease progresses. Mesothelioma can present as an acute illness with a sharp pleuritic pain on inspiration, fever, cough and pleural effusion. This is due to an acute pleuritic inflammatory reaction and can be mistaken for an episode of infection. This may resolve temporarily only for other symptoms including fatigue, sweats and weight loss as well as chronic chest pain and increasing dyspnœa to appear as it progresses.[4] Pleural effusion appears in at least 50% of cases and can become loculated. Unilateral loss of lung volume from compression by effusion and tumour and loss of chest expansion from rigidity of the chest wall may also be features. Distortion of the mediastinum from the pressure from build up of pleural fluid and invasion by tumour can also reduce respiratory function. Primary peritoneal disease presents with non-specific symptoms such vague abdominal discomfort, anorexia and malaise and can be difficult to identify in the early stages.

2.2 Unlike adenocarcinoma of the lung, metastatic spread is rare as is involvement of the cervical lymph nodes. Spread is by invasion and infiltration along the pleural cavity, into the chest wall and mediastinum and through the diaphragm. Initially there may be a period of inactivity before progress of the disease becomes inexorable, other than in a few patients who have undergone radical surgery. Increasing breathlessness, chronic debilitating pain, weight loss, fatigue and cachexia progress to terminal illness and death.

2.3 Diagnosis can be suspected coincidentally following routine chest X-ray when pleural thickening or peripheral mass may be noted. Mesothelioma should be excluded in any patient with either pleural thickening or effusion, particularly with persistent non-specific chest pain.

2.4 Where the presenting symptoms suggest mesothelioma, it is essential to get a full and detailed occupational and social history to establish any previous exposure to asbestos. This may have occurred either directly from contact at work or coincidently from contact with contamination from clothing. The possibility of indirect exposure through working in areas where asbestos was being used or where contamination could have been present should also be considered.

2.5 Physical signs are variable depending on the stage at presentation but may be those of clinical dyspnœa, pleural effusion or generalised signs of malaise or weight loss. Plain chest X-ray may show signs of effusion but it can be difficult to identify pleural thickening due to masking by pleural fluid. CT or MRI scanning is more likely to identify typical irregular pleural thickening with invasion of local structures. The disease tends to start in the lower zones of the lung and spread upwards and medially. Confirmation of diagnosis, particularly in early stages, is dependent on histological examination. The use of positron emission tomography (PET scanning) which is not yet widely available may give more accurate determination of the appearance to help to differentiate between benign pleural thickening, pleural disease due to spread of adenocarcinoma of the lung, and mesothelioma.

2.6 The British Thoracic Society Standards of Care Committee has devised a diagnostic algorithm for investigating suspicious clinical presentation or radiological findings. Mesothelioma should be considered in any case presenting with either pleural effusion or pleural thickening and with a history of possible exposure to asbestos. Cytological examination of pleural fluid aspirate and blind pleural biopsy are not reliable on their own and identify only 30% of cases but percutaneous needle biopsy identifies a larger proportion. Negative cytology results do not exclude the diagnosis. Equivocal or negative fluid cytology or blind biopsy should be followed by CT scanning. If there is a lesion suitable for biopsy, CT guided biopsy should be done. Thoracoscopic or surgical biopsy should be done where the lesion is not suitable for CT guided biopsy. A combination of thoracoscopy with full thickness biopsy (with appropriate staining techniques) together with examination of aspirated fluid can identify up to 98% of cases. MRI may be of value in identifying invasive spread to help differentiate between benign thickening and malignancy. Positron emission tomography (PET) is also now proving to be even more helpful in making the distinction. In frail patients with advanced disease at presentation with other typical clinical manifestations both on examination and on CT or MRI scanning, surgical biopsy is not indicated. Pathologists should attempt to specify the histological type to assist decisions on surgical intervention and a selection of specific staining techniques should be used to help differentiate mesothelioma from adenocarcinoma. It is important to do this as incorrect diagnosis of mesothelioma may deny adequate treatment of more responsive types of malignancy.[5]

3. Aetiology

3.1 Once rare, mesothelioma is becoming increasingly common. Malignant pleurisy was described in the late nineteenth century as a rare oddity. The commercial value of mineral asbestos was recognised by the beginning of the 20th century and both mining and processing of this substance began to escalate around the same time. The causal link with exposure to asbestos is now generally accepted.

3.2 **Asbestos.** Asbestos is the generic name for a group of fibrous silicate minerals. It has useful properties of chemical stability, thermal insulation and high tensile strength, making it an ideal material for use in construction and manufacturing industries. It differs from other minerals in its crystalline formation which takes the form of long thin fibres. It is divided into two mineral groups, serpentine and amphibole, which have different fibrous structures. Chrysotile, or white asbestos, is the only member of the serpentine group and makes up around 90-95% of all asbestos found in buildings. There are five types of asbestos in the amphibole group of which the commonest are amosite, known as 'brown asbestos', and crocidolite or 'blue asbestos'. The other three types (athophyllite, tremolite and actinolite) are rare and usually found as contaminants of the other forms. Asbestos fibres break down into a very fine dust which readily becomes airborne. The fibre particles are small enough to enter the smallest air passages of the lung if inhaled. These become trapped in the lung and cause irritation of the lung tissue and linings and can produce a variety of health problems including mesothelioma.

3.3 By 1930 it was recognised that there was a significant increase in the number of cases of mesothelioma, particularly in areas such as South Africa, Canada and Australia where asbestos was mined and processed. The potential causal link with asbestos was considered and investigated from 1927 but early research failed to establish any such link. Demand for asbestos increased rapidly after the Second World War and cases of mesothelioma, as well as other forms of asbestos related disease continued to rise.

3.3.1 In 1960 a study from South Africa laid the basis for the now widely held view that mesothelioma is caused by asbestos. This study reported an analysis of 33 clinically proven cases of mesothelioma that presented in a five-year period in a localised region around Witwatersrand. This area had large natural deposits of crocidolite asbestos. Mining and processing of this material had been a local industry over many years. Of these cases all but one had a well-documented history of asbestos exposure. Not all of the 22 men and 11 women worked in the asbestos industry. Nevertheless there was a direct link with asbestos in 32 cases including exposure from occupations such as boiler making and locomotive engineering, and childhood exposure from playing with asbestos waste on spoil tips. Mesothelioma in other parts of Africa was extremely rare. This investigation reviewed all the clinical and pathological evidence including variations of histological type. Other possible causes and confounding factors were considered by the authors. However, the history of exposure, the pathology and pattern of presentation and the frequent presence of asbestosis of lung tissue supported the causal link between mesothelioma and exposure to dust from blue asbestos.[6]

3.3.2 These findings have been reproduced in many other studies, particularly in Quebec, Canada where the relationship between mesothelioma and amphibole asbestos as compared with serpentine asbestos was established. The strong link

with amphibole types of asbestos has also been demonstrated by a study of a cohort of 11,000 asbestos miners and millers in Quebec,[7] whilst another from the same region described differences in fibre content of the lungs between locations where differing types of asbestos predominated, and linked these to mesothelioma development.[8] Several studies of the effect of asbestos exposure among factory workers in the East End of London and the workers in the Royal Dockyards have also confirmed the link between exposure to asbestos and chest disease, including mesothelioma.[9,10]

3.3.3 A British study in 1995 gave results of an analysis of mesothelioma mortality in Britain since 1968.[11] The study involved analysis of cohorts of male workers in age-bands starting with dates of birth in 1893. In the group born between 1893 and 1948 there was a significantly high level of mesothelioma. The incidence fell in cohorts born between 1948 and 1958 but in view of the long latency for developing the condition, if the age profile for this group follows the same pattern, their predicted lifetime mesothelioma risks will be between 1.3% and 0.6%. Predictions based on these figures suggest that by 2020, male deaths from mesothelioma will be between 2700 and 3300 per annum. This study confirmed that the rates of mesothelioma mortality formed a clear pattern in relation to age. Many other studies involving asbestos miners and workers in different industries have irrevocably confirmed the causal association with asbestos.

3.3.4 There is good evidence that the risk of mesothelioma varies according to the different types of asbestos used. A study in 1980 looked at the lung pathology of 93 cases of mesothelioma who died in 1976. This found that mesothelioma patients had more amphibole fibres than controls and chrysotile fibres were not found in greater numbers than in controls. Four had no amphibole fibres and of these, two had no asbestos fibres identified. This suggested the much stronger relationship of mesothelioma to amphibole types of asbestos.[12]

3.3.5 A more recent study reviewed mortality reports that had information on asbestos exposure on exposed cohorts. From this it was estimated that the specific risk of developing mesothelioma from exposure to the three most common commercial forms of asbestos are 1:100:500 for chrysotile (white asbestos), amosite (brown asbestos) and crocidolite (blue asbestos) respectively. The latter two, although less commonly used, are clearly much more of a risk for mesothelioma. Peritoneal tumour risk was also proportional to exposure and the overall risk was cumulative with increased levels of exposure. The effect of contamination with other forms of asbestos, particularly amphibole types has prompted studies to examine the possibility that it is the contaminant rather than the crocidolite that has the causal effect but little difference has been found between risks from contaminated and pure crocidolite.[13]

3.3.6 Many thousands of workers have been exposed to asbestos due to the widespread use of asbestos in building and engineering work following the Second World War. Another study in 1997 looked at the occupational, clinical and pathological aspects of 272 cases of mesothelioma in south east England. Asbestos exposure was documented in 87% of cases. The mean time between first exposure to asbestos and onset of symptoms was 40 years and mean survival was 14 months. Many previous studies had highlighted the long latent period between exposure and development of tumour but this investigation helped to confirm it. It is rare for mesothelioma to develop within 20 yrs of

exposure but the reasons for the long latent period are not evident. Clinical features of the condition were similar in those with clearly documented asbestos exposure and those with no confirmed link.[2] An American case control study included 208 cases of confirmed mesothelioma and 533 controls. Direct and indirect exposure to asbestos was determined and results showed a clear link between mesothelioma and asbestos exposure in men. The link in women was less definitive, probably due to the lower background incidence rate and lower asbestos exposure for the women in the study.[14]

3.3.7 **Occupational Risks.** Asbestos was widely used before 1970 for a large variety of purposes. Its heat resistant and insulating properties made it an ideal material for use in pipe-work insulation, jointing, boiler insulation and electrical conduit. It was extensively used for fireproofing of buildings, ships, domestic heating and insulation and was compounded into various forms of panelling, corrugated sheeting and flooring tiles. Prefabricated buildings were made of asbestos panels and sheeting of various sorts. Anyone involved in manufacture, construction and installation would have been exposed by mixing raw asbestos, applying and moulding insulation, sawing, drilling and cutting the products.

3.3.8 Legislation to control the use of asbestos began to be introduced from 1970 in the UK and the USA, initially with regulations to prohibit the use of spraying of material containing asbestos. These regulations have been regularly updated since with the most recent in the UK being the Control of Asbestos at Work Regulations 2002. Control is now stringent in many industrialised countries but there are still those where this is less apparent and asbestos is still being produced and marketed. Attempts to implement a worldwide ban on its use are still a matter of contention. Disposal of existing asbestos material also still presents a major international problem in many areas, particularly the scrapping of older ships built before controls came into effect. Demolition of buildings containing large amounts of asbestos in panelling and lagging also has caused considerable concern.

3.3.9 It is possible but very unusual to be able to demonstrate asbestos fibres within the tissue of the tumour.[15] Pathological association is usually made from fibre counts in general lung tissue at autopsy. Asbestos fibres can be isolated from lung tissue in most people from background environmental presence of fibres but a relationship between fibre counts in the lung and degree of asbestos exposure has been established. An editorial in Thorax 1996 described a scale which relates lung fibre counts to asbestos exposure. Very high fibre counts are associated with the presence of asbestosis (fibrosis) of the lung. The risk of mesothelioma increases with higher exposure and can occur in the presence of asbestosis but many cases are associated with lower fibre levels in the lung than seen in asbestosis.[16]

3.3.10 **Threshold of exposure.** Recent opinion in the British Thoracic Society statement on mesothelioma (2001) is that there is no evidence of a threshold dose of asbestos below which there is no risk. However, the risk at low levels of exposure is small and there is no significant risk from asbestos that is already present in buildings or equipment so long as it is well sealed, is not giving off dust particles and not disturbed by removal, repair or maintenance.[5]

3.3.11 Miners and millers of the raw asbestos were exposed to some of the highest levels. Areas of Canada, South Africa and Australia where asbestos is mined have some of the highest incidences of asbestos related disease. Indirect exposure to environmental asbestos dust and contaminated clothing have lead to a high incidence of asbestos disease in individuals who were not directly working with asbestos but living in communities near to asbestos mines or processing plants. Other occupations with a high incidence of mesothelioma and accepted exposure to asbestos include:

- Dockyard work – Loading/unloading raw asbestos
- Shipbuilding
- Locomotive manufacture and repair
- Building and construction industry
- Power station construction and maintenance
- Motor manufacture – including component manufacture
- Manufacture of flooring tiles and other asbestos products[17]

3.3.12 Many workers whose jobs did not involve handling asbestos were exposed by environmental contamination from working in the vicinity where asbestos was being used and even office workers and canteen assistants may well have inadvertently suffered exposure. People working in locations where asbestos materials were being removed or replaced as part of normal maintenance and repair also may have suffered inadvertent exposure.

3.3.13 Asbestos was used extensively in shipbuilding and particularly in warships where it formed lagging for boilers and pipe work, fireproofing of bulkheads and electrical installation. Some armoured vehicles made prior to 1970 had asbestos insulation around gun barrels and lining of internal panels. As elsewhere, asbestos was once widely used in military buildings although the MoD is now required to follow all health and safety regulations in controlling any asbestos risk. Anyone involved in maintenance and repair work on board ship or repair or demolition of buildings was likely to have been exposed to asbestos. An increased incidence of death from mesothelioma among naval personnel was shown in a report from 1990 which studied mortality in the armed forces, based on a group of 30,619 personnel who had served abroad in the 1950s and 1960s. This showed that among Royal Navy personnel there was a statistically significant increase in standard mortality ratio for mesothelioma.[18] This may well reflect the potential risk from exposure to asbestos aboard ship for some personnel.

3.4 **Mesothelioma without asbestos exposure.** Mesothelioma can occur with no documented history of asbestos exposure. Mesothelioma in childhood is not considered to be due to asbestos, although it is a rare tumour in this age group. One survey of 80 cases with a mean age of onset of 9.7 years showed evidence of asbestos exposure in only two cases. Mesothelioma can occur spontaneously probably due to some other environmental factor. Reports of malignant pleural tumours are recorded from the end of the nineteenth century before asbestos was used. Most studies show that between 75%-90% of cases of mesothelioma have accepted histories of exposure but also point to the difficulty in excluding contact with asbestos in the remainder, in view of its ubiquitous nature in the middle part of the last century.[19]

3.4.1 **Local epidemics** of mesothelioma have occurred in Turkey and Greece where other indigenous mineral fibres such as zeolite or erionite are mined. Other factors implicated by anecdotal reports include sugar cane, ionising radiation and pleural disease following empyema but these associations are not supported by valid scientific research.

3.4.2 **Virus infection.** There has been interest in the role of simian (monkey) virus SV40, which has been shown to cause mesotheliomas in hamsters. SV40 was a contaminant of early polio vaccine administered in the late 1950s to early 1960s and the virus has recently been identified in tumour tissue. The period when this contamination occurred and the latent period for developing mesothelioma are consistent with the onset of escalation of incidence. This has lead to much speculation that this is a factor in precipitating the tumour. Carbone et al suggest a relationship between SV40 and mesothelioma and propose possible mechanisms, including the possibility that the virus may be a factor in increasing susceptibility to asbestos.[20] There are many reports supporting this theory but there is much inconsistency between various studies. For example, results of a Belgian study where DNA was extracted from frozen tissue in 12 patients diagnosed with mesothelioma showed that none of the samples was positive for SV40 DNA sequences.[21] The National Cancer Institute (NCI) recently reviewed the current evidence for this association and concluded that despite studies involving decades of observation no increased cancer risk from exposure to SV40 has been established.

3.5 **Peritoneal mesothelioma.** Primary peritoneal presentation is less common. It is rare in the UK but is more common in workers in mining and milling of asbestos. Most studies in this group show primary peritoneal disease forming no more than 15% of cases.[22] Invasive spread to the peritoneum through the diaphragm constitutes a proportion of the cases. The causal association with asbestos exposure can still be made but the relationship with exposure is not linear. Documented evidence of previous asbestos exposure reflects a similar pattern to pleural disease although higher exposures are usually involved. Direct ingestion of fibres from contaminated saliva or swallowed sputum has been postulated as the cause but documented evidence of the presence of fibres in intestinal tissue has not been found. However it is generally accepted that this moiety is also caused by asbestos exposure.

3.6 Overwhelming evidence supports the probability that mesothelioma is caused by amphibole asbestos. Some cases still occur where the only known exposure is from chrysotile (white asbestos) although contamination of chrysotile with amphiboles is common and may be a factor in those cases. Even in those patients with mesothelioma who have no obvious history of exposure to asbestos it may still be a factor in view of its ubiquitous presence in the environment in past years. Mesothelioma developing at a time within twenty years of possible exposure is less likely to be due to asbestos.

3.7 Although the incidence of this tumour is increasing only a proportion of the large numbers that were exposed to asbestos develop the disease, so it has been considered that some other factor may play a part. This may be due to a genetic predisposition or the effect of some other environmental factor that enhances the carcinogenic effect of asbestos. Apart from the debate about the influence of simian virus SV40 (see section 3.4.2), as yet no such factor has been identified.

4. Prognosis

4.1 Mesothelioma is not curable and is invariably fatal. Disability and death occurs from constriction of the lung due to encasement by tumour and pleural effusion. Invasive spread to the mediastinum and its vital organs leads to death. It can spread through the chest wall and diaphragm but rarely spreads by distant metastasis.

4.2 The epithelial type of tumour has a better prognosis than the sarcomatous or mixed types but median survival rate overall from time of presentation is poor, varying from 8-14 months in different studies. Patients who do develop systemic involvement have a particularly poor prognosis.

4.3 Radical surgery, chemotherapy and radiotherapy all form part of the treatment strategy. Clinicians are encouraged to enter new patients into suitable trials of innovative therapy.

4.4 **Surgery.** Radical surgery to excise the tumour and strip the pleura may be considered and those potentially suitable would be those with low bulk early stage epitheliod disease who are otherwise fit for a major operation. Staging is used to help select those suitable for surgery. The system proposed by Butchart has been commonly used.[23] The tumour is classified into four stages:

Stage 1: Tumour confined to one side of the chest – pleura, pericardium or diaphragm
Stage 2: Tumour invades chest wall, mediastinal structures and or thoracic lymph nodes
Stage 3: Penetration of diaphragm with/without lymph node involvement outside the chest
Stage 4: Distant metastases

Staging is essential for correct selection of patients for surgery and provides important prognostic information. Further systems of staging have been developed recently to define more distinct prognostic groups with a view to planning and evaluating the effect of treatment. Subgroups with the best overall physical fitness at presentation in the younger age group (below 49 yrs) show better survival although best survival rates were no better than 13.9 months.

4.4.1 Further trials based on more refined staging are ongoing.[24] Multimodal treatment using surgery, radiotherapy and chemotherapy is being studied. A trial known as the Mesothelioma and Radical Surgery (MARS) study, currently at the feasibility stage, is planned to evaluate the benefits of radical surgery (extrapleural pneumonectomy or EPP) and compare the effects of this with multimodal treatment excluding EPP.

4.5 **Chemotherapy.** There is some evidence that chemotherapy can reduce tumour bulk in up to 20% of cases. Most chemotherapeutic agents have been used in a variety of regimens but none has consistently resulted in a response rate of more than 20%. Doxorubicin, epirubicin, mitomycin and several others have consistently given response rates of between 10-20%. Trials of combinations of these substances have so far not shown improved results. Symptomatic improvement has been demonstrated in some cases even without reduction in tumour bulk.

4.5.1 A current trial by the British Thoracic Society and the Medical Research Council will compare the effects of active symptom control alone with either symptom control plus a combination of three agents (mitomycin, vinblastine and cisplatin) or symptom control plus a single agent (navelbine).[5] Trials of the drug pemetrexal disodium (Alimta) in combination with cisplatin have also shown promise with an increase in median survival time of around 3 months for those treated with this combination.

4.6 **Radiotherapy.** Because of the widespread nature of the tumour, large areas of the chest need to be irradiated with the potential of extensively damaging healthy lung tissue. Newer techniques are being developed which allow a greater dosage to be given directly to the pleura but the effects of these are still under investigation and there is presently nothing to support the use of radiotherapy as a single method of treating mesothelioma. Radiotherapy to the port site of invasive access has been shown to prevent tumour spread through biopsy areas and incisions. Port site radiotherapy is essential for all who have an invasive investigation. It has been shown to significantly reduce chest wall implantation following invasive procedures.

4.7 **Palliative treatment.** Palliation is usually needed from the time of presentation and onwards with early implementation of symptom relief. Breathlessness and pain are the most common causes of distress although anorexia, weight loss, fatigue and general debility occur frequently. The diagnosis carries significant social and psychological consequences as well as physical illness and all need to be addressed to ensure that specific treatment has the most favourable effect.

4.7.1 Palliative care aims to reduce the predominant symptoms of pain and breathlessness, control other symptoms, including those from the side effects of therapy and reduce the psychological impact and social consequences of the condition. Involvement of the family and other agencies in emotional and social support is essential. All patients need to be under multidisciplinary specialist care. It is important to ensure that the patient and family members have access to relevant information including written information on the condition and details of organisations that support patients with advanced malignant disease. The diagnosis needs to be communicated to the patient and carers with care and sympathy with emphasis on the expectation and benefits of treatment. It may be difficult for some to accept that palliation is the only option but an encouraging, positive approach is needed to maintain the patient's morale and compliance. The GP should be kept regularly informed of the progress of treatment and should be fully involved in the ongoing management.

4.7.2 Pain relief should be implemented as soon as possible balancing the type and dosage of analgesia to the severity of pain. The most effective form of pain relief is still based on the use of suitable medication. Simple analgesics may be sufficient in early stages but stronger opiate-based preparations should be introduced as the pain progresses following the standard "ladder" of treatment advised by the World Health Organization (WHO). Non-steroidal anti-inflammatory drugs, amitriptyline, corticosteroids, laxatives and anti-emetics may need to be included in the regimen. Referral to a pain management clinic may be needed for other pain relief techniques such as use of TENS or local anaesthetic blockade of nerves or spinal roots.

4.7.3 Breathlessness is due to a combination of pleural effusion compressing the lung, rigidity of the chest wall and distortion of the mediastinum. It can be alleviated by drainage of pleural effusion and pleurodesis. Drugs and oxygen are of limited use although opiates or benzodiazepines may be used in advanced stages. Chronic cough due to lung compression is often a feature of the condition and treatment with opiate-based cough linctuses, corticosteroids or inhalation of local anaesthetic by nebuliser may help.

4.7.4 Radiotherapy is typically used palliatively, aimed at improving symptoms by reducing pleural effusions, reducing tumour bulk, slowing spread and relieving pain. It provides pain relief in about half of all patients and can reduce the size of palpable masses. It does not help breathlessness or mediastinal obstruction. Trials of differing palliative regimens using different doses of radiation are also being undertaken.[5] Because of its damaging effect on viable tissue widespread palliative radiotherapy is only appropriate in end-stage disease when there is little remaining healthy tissue to be affected. The role of chemotherapy in palliative reduction of pain or breathlessness has yet to be fully established.

4.7.5 Anorexia, weight loss and fatigue are common, particularly in the later stages of disease. Dietary advice and supplements may helpful in this context. Depression may also be a feature and nausea, together with other side effects of chemotherapy or radiotherapy may need to be treated with suitable medication.

4.7.6 Compensation may be available under both civil law and the Industrial Injury Disablement Benefits scheme administered by the Department for Work and Pensions. Guidance on opportunities for compensation also forms part of the general support of the patient and family, and the physician is usually well placed to advise on these matters.

4.7.7 The overall management of the widespread effects of this condition requires well-planned and co-ordinated multidisciplinary action to sustain the wellbeing and quality of life of the patient as well as to give sympathetic and optimistic encouragement to the family.

5. Summary

5.1 Mesothelioma is a malignant tumour of the pleural lining of the chest cavity, the pericardium or the peritoneum.

5.2 It is almost exclusively due to inhaled or ingested asbestos fibres and is most commonly associated with the amphibole type of asbestos. The crocidolite form is most commonly associated with mesothelioma but tremolite contamination may be a factor in those cases with only chrysotile exposure. The condition was extremely rare before commercial use of asbestos and, for anyone who has had an occupational exposure to asbestos, it is difficult on probability to deny a direct causal link to the disease.

5.3 There is a long latent period between exposure and presentation of mesothelioma, and incidence is increasing steadily with an expected peak of between 1950 to 2450 cases per annum in Britain at some point between 2011 to 2015.

5.4 Disability is rapidly progressive and prognosis remains very poor with the usual survival from presentation being between 8-14 months, although there have been some longer-term survivors.

5.5 Recent innovative treatment regimes particularly with chemotherapy are having some effect in improving symptoms and quality of life in the shorter term but treatment is still essentially palliative and mainly aimed at reducing pain and breathlessness. A few cases detected in early stages may be suitable for radical surgery with the hope of more promising long-term results. However there are as yet no randomised trials to confirm the efficacy of surgery and the limited available evidence only reports the effects of surgery within an overall treatment strategy. It is hoped that continuing research into the diagnosis and management of the condition may provide longer-term benefits in future. Although no effective cure is currently available, it is important to stress that much can be done to improve quality of life for the patient.

6. Related synopses

Cancer of the Lung

7. Glossary

adenocarcinoma	A tumour arising from glandular cells. In the lung this is a tumour that arises from the cells lining the air passages of the lung.
cachexia	The appearance of widespread wasting of the body, pale wrinkled skin and debility caused by a wasting disease.
diaphragm	A curved muscular membrane in humans and other mammals that separates the abdomen from the chest. Assists the action of breathing by contracting and relaxing.
DNA sequences	In this context - evidence of genetic material from SV40 virus.
dyspnoea	Difficulty in breathing or laboured breathing – breathlessness.
empyema	A collection of pus trapped within the cavity between the lung and the chest wall.
epithelioid	Having a microscopic cellular form of cells from the membranes that line the glandular surfaces of the body.
extrapleural pneumonectomy	Removal of a diseased lung together with the pleural lining of the chest wall.
histology	The study of the microscopic structure of tissues.
mediastinum	The area of the chest that lies between the lungs and which contains vital organs such as the heart and major blood vessels.
mesothelium	Tissue arising from an embryonic layer called the mesoderm forming part of the lining of the chest cavity.
metastatic spread	Spread of a malignant tumour to a distant site in the body.
percutaneous biopsy	A method of taking a sample of tissue by passing a needle through the skin into the diseased area.
pericardium	The double layered membrane that encloses the heart.
peritoneum	The transparent membrane that lines the outer layer of the intestine and the inner abdominal cavity.
pleural effusion	Formation of fluid in the chest between the pleural linings of the chest wall and the lung.

pleuritic pain	Pain arising from the pleural lining of the lung. Typically its character is of a sharp, stabbing pain on inhalation.
pleurodesis	A procedure which causes adhesion of the lining of the lung to the lining of the chest wall. Used in this instance to reduce the pleural space and formation of pleural effusion.
sarcomatous	Having the appearance of cells derived from connective tissue such as muscle or bone.
transcutaneous electrical nerve stimulation (TENS)	A method of relieving pain by passing a low voltage current through the skin to deaden nerves that transmit pain impulses.
thoracoscopic	Pertaining to thoracoscopy, the use of a fibreoptic scope through a small incision in the chest wall for the purpose of directly observing the organs of the chest.

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