

## Radical surgery for mesothelioma

*The epidemic is still to peak and we need more research to manage it*

One in every hundred men born in the 1940s will die of malignant pleural mesothelioma, which is almost exclusively a consequence of exposure to asbestos, with a lag time that is rarely less than 25 years and often more than 50 years from first exposure. Half of all cases are now aged over 70, with 80% in men. For a man first exposed as a teenager, who remained in a high risk occupation, such as insulation, throughout his working life, the lifetime risk of mesothelioma can be as high as one in five.<sup>w1</sup> There are now over 1800 deaths per year in Britain (about one in 200 of all deaths in men and one in 1500 in women), and the number is still increasing.<sup>1 w2</sup> As exposure in the United Kingdom continued until 1980 the peak of the epidemic is still to come, and we need a strategy to manage these patients.

Asbestos was a valuable and versatile material and imports rose after the second world war when it was widely used as an insulator, in the manufacture of filters, cements, friction products, and as a fire retardant. It found a place in shipbuilding and industry and was used extensively in building in the form of light workable boards.<sup>2</sup> It was a convenient partitioning material that combined insulation and fire proofing. The Health and Safety Executive statistics indicate that 25% of deaths will be in men who worked in the building industry and that carpenters and joiners are most commonly afflicted.<sup>w3</sup> These men have often been self employed in small enterprises or engaged in do it yourself home improvements. About 90% of deaths due to mesothelioma are due to exposure to asbestos in unmonitored settings. Wives and daughters who washed the overalls of asbestos workers are among those who have died.

Imports were at their highest from about 1955 to 1980 in the UK.<sup>3</sup> The Asbestos Licensing Regulations came into force in the United Kingdom in 1983 and Control of Asbestos at Work Regulations in 1987 (both amended in 1988). The peak of the epidemic is expected in 2015 to 2020 when the death rate is likely to be 2000 per year in the United Kingdom. The situation in Europe is similar.<sup>4</sup> Australia had the highest pro rata asbestos usage,<sup>w4</sup> and asbestos imports continue in the developing world.<sup>w5</sup> The epidemic in the United States has probably peaked because of earlier awareness and action on asbestos imports.<sup>5</sup> Many countries are seeing the rising tide of an epidemic, and all doctors need to know how to recognise and diagnose this disease and what treatments are available.<sup>6</sup>

Mesothelioma is a relatively slow growing tumour that most commonly originates in the parietal pleura but can also arise in the abdomen and the tunica vaginalis. It presents with pain in the chest wall or breathlessness due to increased pleural fluid, but symptoms may be absent or develop insidiously. Not infrequently, at the time of first awareness, a thick rim (1 cm or more) of hard dense tumour encasing and restricting the lung may already be present. The diagnosis can be difficult to prove. When pleural disease is found it has to be distinguished from pleural plaques and malignant effusion from adenocarcinoma.<sup>6</sup> Cytological examination of pleural fluid and small needle biopsies are often inconclusive because adequate tissue is required and it may take several attempts, culminating in surgical biopsy—each time with a risk of infection and needle or drain track seeding to which mesothelioma is particularly prone. Biopsy and drain tract radiotherapy is recommended.<sup>6</sup>

Once made there is tendency for the diagnosis to be met with a sense of hopelessness—not without good reason for it is a horrible disease, often with months of unremitting pain, progressively diminishing pulmonary performance, cachexia, and the inevitability of death. Median survival from diagnosis is usually under a year, but individual series vary markedly<sup>7-8</sup> as is not surprising in a cancer with such a long lead time and in which the known phase of the disease is a small proportion of its natural history.

How can we think about it positively? The best we can offer at present is stage specific treatments, which should whenever possible be within clinical trials.

As with most solid tumours the first consideration is surgery—can we cut it out and get rid of it? The operation, extrapleural pneumonectomy, entails removal of all the parietal pleura, the pericardium, and the diaphragm in addition to the whole lung on that side.<sup>9</sup> It is usually considered as part of trimodality treatment with various combinations of preoperative and postoperative chemotherapy and radiotherapy to the empty hemithorax after surgery.<sup>10</sup> This is associated with survival figures of up to 48% at five years in highly selected subsets of patients with the more favourable epithelioid (as opposed to sarcomatoid) histology and no lymph node metastases.<sup>w6-w9</sup> Radical surgery has been performed infrequently in the United Kingdom, with an average of only 20 patients per year in the past

five years. Some patients and their doctors desperately seek radical surgery as their only hope, but others have doubts about the evidence.<sup>11</sup> A trial is needed, and a pilot feasibility study (the mesothelioma and radical surgery "MARS" trial, funded by Cancer Research UK) is now under way. To answer the question 670 patients will be required over three years with five years' follow up. If achieved this would give an answer by about 2012 in time for the peak of the epidemic.

Irrespective of whether radical surgery will be considered much needs to be done in the care of these patients. The diagnosis should be made early and efficiently. Without it we cannot have meaningful discussions with the patient or plan treatment, and the patient's legal position in terms of compensation remains unclear. At the same time we try to control any pleural effusion to maintain breathing as long as possible.<sup>6</sup> This is best done by thoracoscopic talc pleurodesis, which can usefully be combined with surgical biopsy. Then with the diagnosis made the disease can be staged. If the pathological stage is early extra-pleural pneumonectomy should be considered, and we would recommend that this is done in the context of multimodality treatment and within a study.<sup>11</sup> If the

tumour is inoperable management can be with chemotherapy, and again it would be preferable that this is within a study.<sup>12</sup>

This disease is increasing in frequency. There is nothing we can do now to prevent it in workers exposed to asbestos throughout the 1950s, 1960s, and 1970s. What we can do is recognise it early, treat it actively, and learn about best treatment with carefully thought out studies because we will be seeing many more mesotheliomas in the next 25 years. In the developed world alone 100 000 people alive now will die from it.

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## Pandemic risks from bird flu

*The risk to humans is small, but we need to be better prepared*

An outbreak of avian influenza is ravaging the poultry industry in South East Asia. This carries a devastating economic toll for the communities affected, but what of the associated risk to human health? At least seven people in Vietnam have been infected by the strain of H5N1 subtype influenza found in poultry. Of these six are dead. In Thailand three boys contracted the virus; two are dead. These numbers are small, and investigations and case studies so far suggest that the virus does not transmit from human to human but is acquired directly from close contact with infected chickens. How likely is it that these events signify the emergence of a new human pandemic, and what measures do we have to deal with the global threat?

Although we think of influenza as a human disease, the natural reservoir for influenza A viruses is aquatic birds and wildfowl. Many different strains circulate at any one time, and most are not associated with disease in wild birds. Influenza strains are divided into subtypes depending on the antigenic nature of the H (haemagglutinin) and N (neuraminidase enzyme) proteins. A

limited subset of influenza subtypes H1N1, H3N2, and H1N2 cause annual epidemics in humans, but all had their origins in avian species. They adapted for transmission in people following zoonotic events. Influenza virus has several options for creating genetic diversity. Firstly, it can shuffle genetic material derived from two different virus sources in an event known as reassortment. This was certainly the origin of the influenza pandemic strains of 1957 and 1968. Secondly, being composed of ribonucleic acid rather than deoxyribonucleic acid, influenza virus is error prone. Stepwise single mutations accumulate, and these can eventually alter the properties of the virus. This happened early after the H3N2 virus was introduced into the human population in 1968. Some changes occurred during replication of avian viruses in people during zoonotic events in Hong Kong in 1997, where six of 18 infected individuals died,<sup>1</sup> and in the fatal case of a veterinarian infected during a poultry epidemic of H7N7 influenza in the Netherlands last year, although these changes were luckily not sufficient to allow transmission between people.

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