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A REVIEW OF RESEARCH IN MESOTHELIOMA AND OTHER ASBESTOS-RELATED DISEASES

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A Review of Research in Mesothelioma and other Asbestos-Related Diseases

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PREFACE

The catalyst for this review was a request from the Department of Health (DH) to the NCRI in March 2010 asking for a review of the current state of play in relation to mesothelioma and other asbestos-related disease research and advice on capacity, infrastructure and important research questions. At about the same time, the British Lung Foundation (BLF) received a donation of £3m over 3 years from the insurance industry to support new research in asbestos-related disease. The BLF agreed to support this review so that it could be completed to coincide with the announcement of their research funding opportunity in November 2010.

The approach taken was to email everyone in the UK known to be involved with asbestos-related diseases asking them to submit ideas for research (with a request to forward the email to relevant colleagues). This report is therefore a synthesis of views from translational scientists, clinicians, nurses, pharmacists, pathologists, patient support groups, and individual patients and carers; a number of overseas experts were also included. Efforts have been made to balance differing views where necessary, though there will always be scope for debate where such a diverse community is concerned.

We present the review in 2 parts: firstly an overview of the current position and then a consideration of opportunities, priorities and potential barriers in relation to future research. Our aim is to stimulate ideas and enthusiasm for research in this challenging field, not to impose restriction on funding opportunities. In addition to the £3m over 3 years available from the insurance industry, we have also been assured by research funders that they are willing to fund high quality research in this field, through existing funding streams, especially if there is a clear prospect of benefit to patients.

In the time available, we have focused mainly on the most serious asbestos-related disease, mesothelioma.

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EXECUTIVE SUMMARY

This review has identified that all the ingredients exist in the UK to give a boost to research in mesothelioma and other asbestos-related diseases. The key components are expertise, research ideas, enthusiasm and a modest amount of dedicated funding which can be used to seed a larger effort if managed skilfully. The boost could be even greater if it is possible to increase the availability of tissue and clinical data from mesothelioma patients. In the first instance the latter would need a more detailed study of feasibility.

Research is needed across the full spectrum of epidemiology and aetiology (including tumour biology), screening, diagnosis and prognosis, treatment, and symptom control. Key issues and questions are highlighted in each of these areas and while the greatest patient need is in relation to mesothelioma, all asbestos-related diseases would benefit from a similar range of studies.

If new research is successfully funded across these areas then networking and coordination will be important to ensure effective cross-disciplinary communication, implementation of results, and the continuing generation of novel research ideas.

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PART 1: THE CURRENT POSITION

1.1 Introduction to asbestos

The term “asbestos” refers to a number of naturally occurring fibrous minerals that have been commercially exploited. The 3 main types of asbestos are white (chrysotile), brown (amosite), and blue (crocidolite). By far the most commonly used, chrysotile, consists of fine silky curly fibres formed in sheets, and comes from serpentinite rocks, which are common throughout the world. Amosite and crocidolite have straight brittle fibres with a chain-like structure. Amosite mainly occurs in South Africa, whereas crocidolite occurs in many locations such as Australia, South Africa, Bolivia, the former Soviet Union, and Canada.

Asbestos is remarkable for its resistant to heat, electrical and chemical damage, its sound absorption properties and tensile strength, and for the fact that it can be spun and woven into fabric. It can also be mixed with cement and used in construction (garage roofs, gutters, partition walls, pipe lagging, bath panels, floor tiles, fire doors, etc), and in the past has widely been used in shipbuilding, in household appliances, as a soil conditioner, in cigarette filters, brake linings, theatre curtains, and even tablemats and crayons.

Its use in the UK increased dramatically in the late 30’s as part of the increased manufacturing associated with the war effort, but for nearly 4 decades around 150,000 tons were being imported annually, and overall it is estimated that a total of over 5m tons of asbestos was imported into the UK.

However, inhalation of asbestos fibres causes a number of diseases.

Although the ancient Greeks and the Romans noted that the material damaged the lungs of slaves who wove it into cloth, it was not until the 1950’s that reports linking asbestos and cancers of the lung were published, which led to the definitive investigation of insulation workers[1] and the first paper officially establishing mesothelioma as a disease arising from exposure to blue asbestos[2].

Asbestos causes pleural mesothelioma (a cancer of the membrane surrounding the lungs), asbestosis (a form of lung fibrosis or scarring), diffuse pleural thickening (pleural plaques are localised areas of pleural thickening), and lung cancer, as well as non-pleural mesothelioma (usually in the peritoneum, occasionally in the pericardium). However, the latency period (especially for mesothelioma) can be very long, often taking 40 years from exposure to diagnosis.

Asbestos is relatively safe *in situ*. With appropriate precautions, it can be safely removed and disposed of, but when buildings burn asbestos fibres are released into the atmosphere. In 1994 the empty British Leather tanning factory in Birkenhead blazed out of control for hours, resulting in a wide area being covered with asbestos dust and debris from the old corrugated roof. Soot showered the neighborhood making it look as though it had snowed. In New York, 5,000 tonnes of asbestos-containing material were sprayed on to the first 40 floors of one of the Twin Towers before it was banned in new construction in New York in 1970. It was also used heavily in ceiling tiles. The explosive collapse of the Twin Towers blanketed a region of several square miles with a fine powder. An analysis of dust within three days of the attack found that some of the dust was 4% asbestos.

In the UK, regulations were introduced in 1986 banning the import of blue and brown asbestos, and in 1999 covering white asbestos. However it was not until 2006 that the Control of Asbestos Regulations brought together all the previous sets of regulations to cover the prohibition of asbestos.

Globally however, because of its remarkable properties, the use of asbestos continues unabated (at least 85% being used in corrugated asbestos-cement sheets for building construction), and its use is increasing in parts of Asia, South America and the former Soviet Union[3]. Although the use of asbestos peaked in the 1970’s (when worldwide production exceeded 5m tons per year), currently 2m tons per year are still mined and shipped around the world, and it is estimated that 125m people are currently still exposed to asbestos in the workplace[4]. In the year 2000 the largest asbestos producers were Russia, China, Canada, Kazakhstan, Brazil and Zimbabwe, and the biggest users were Russia, China, Brazil, India and Thailand. Canada dominates world trade with an annual export of around 300,000 tons of white asbestos (chrysotile).

1.2 Epidemiology and Aetiology of asbestos-related disease

1.2.1 Incidence

The UK has the highest incidence per head of population of mesothelioma worldwide (and only the US has more absolute numbers per year). The latest figures from ONS[5] reported 1960 new cases in England and Wales in the year 2008, and the HSE reported 2156 cases in England, Wales and Scotland in the year 2007[6].

The annual incidence figures can be used to predict the future incidence pattern and in 2005 Hodgson et al[7] predicted that this will follow a similar pattern to that of the annual import of asbestos, albeit displaced by about 50 years, with a peak incidence in the years 2011 and 2015. However, the Thames Cancer Registry (the lead National Cancer Intelligence Network Cancer Registry for lung cancer and mesothelioma) have recently modelled the likely trend in numbers of new cases for the South East of England and predict the peak incidence will occur in the year 2022 for men and 2027 for women[8], and a recent Bayesian analysis[9] predicts a peak in the year 2016. Nevertheless the impact of secondary asbestos exposure (e.g. the deterioration of asbestos-containing products, maintenance, alteration, removal and demolition of asbestos-containing buildings), and the long latency period will continue to represent a risk, albeit relatively small, for many decades.

The incidence of other asbestos-related diseases is collected by the Health and Safety Executive (HSE)[10]. The incidence of diffuse pleural thickening has remained relatively stable for the past 2 decades. In 2008, there were 1063 reported new cases of benign pleural disease, and 400 cases of disablement due to pleural thickening. Asbestosis resulted in 96 deaths in 2007, and there were 795 disablement benefit cases in 2008. However, the number of lung cancers caused by asbestos can only be estimated, as the disease is indistinguishable from that caused by other agents (most notably tobacco), but it is thought that asbestos may be implicated in around 2000 lung cancers a year.

The cohort of men working in shipbuilding and construction in the 1930s-40s represents the high exposure and high-risk group, which continues to influence the overall demographic. Thus around 95% of asbestos-related diseases occur in males, and the age at presentation has risen inexorably. However it is predicted that this will change as the disease affects increasing numbers of individuals who have had medium or low-exposure, and already mesothelioma is being seen in more women, younger patients and in areas which were not connected to ship-building or other asbestos-related industries. This trend is confirmed by an HSE analysis[11] that indicates death rates decreasing in previously high rate areas (e.g. Yorkshire, Humberside, Scotland), and increasing in previously low rate areas (e.g. West Midlands), and in male carpenters, plumbers and electricians, and female cleaners, shop assistants and office workers.

1.2.2 Causal epidemiology

The MALCS (Mesothelioma and Lung Cancer Study) study is jointly funded by Cancer Research UK and the Health and Safety Executive, and has shown, in specific high-exposure occupations, a linear relation between asbestos fibre burden and the risk of developing mesothelioma and other cancers[12].

The MALCS study is also comparing the asbestos fibre burdens in the lungs of mesothelioma, lung cancer, and pneumothorax patients (the latter are considered to be a random control group) who have been interviewed to obtain a full occupational and environmental history, to try and identify the relative risk factors, and provide evidence on the contribution to current lung cancer risk caused by past occupational asbestos exposure.

There is now sufficient evidence to link asbestos to cancer of the larynx and ovary[13], as cohort studies of women who were heavily exposed to asbestos in the workplace (e.g. women who made gasmasks in World War II) consistently report increased risks of ovarian cancer, and limited evidence for a link with colorectal cancer.

1.2.3 Tumour biology

There are substantial gaps in our understanding of the fundamental mechanisms of the development of malignant mesothelioma that hinder the development of effective treatment strategies. Developing targeted

treatments depends on identifying aberrant pathways that can then be blocked, or alternatively, immunological pathways that can be amplified. Research into all diseases relies on basic discovery of genes and proteins, understanding how these genes and proteins cause or effect a particular disease and finally delivering this discovery in a package that can improve patient care (whether a treatment or biomarker).

New technology now allows the comparison of abnormal tissue to normal tissue. These techniques can analyse all the genes expressed by tissues (approximately 27,000) in one sitting. These techniques are extremely powerful and can be used to generate new therapies to previously unknown targets. These approaches now include genomics, transcriptomics and proteomics depending on whether the genes themselves or their products are analysed.

Understanding factors that promote mesothelioma growth

The use of drugs that block specific growth factors has been successful in several cancer types including a subgroup of lung cancers. Using tissue-profiling approaches (transcriptional profiling, micro-RNA profiling, and translational profiling) that can show the genetic and protein changes within mesothelioma or asbestosis may reveal targets that include growth factor pathways as well as others. Considerable expertise exists in the UK in this systems biology approach which can be used to investigate cancer dependence on growth factors (or other molecules) and to screen for genetic mutations.

Deep sequencing, an approach that looks at mutations in the genetic sequence of known oncogenes, to try and find susceptibility to agents that block the pathways activated by these mutations, could also be performed on mesothelioma specimens. This would allow the identification of potential drivers for carcinogenesis and open up the possibility of using known compounds or drugs against these oncogenes. This data would inform future work and provide new markers for early/better diagnosis of mesothelioma and potentially contribute to a more personalized approach in treatment (e.g. prognostic markers for successful/unsuccessful surgery or chemotherapy).

Previous work has been smaller scale generally examining small sets of cell lines or tumour samples. However several candidates for therapy are being pursued including VEGF, src, C-met, IGF-IR, AKT, aurora kinases, ephrins, mesothelin, WT-1, NF2, ink4a and TRAIL. Similarly synthetic and medicinal chemistry approaches have led to drug development with potent anti-mesothelioma effects in vitro, for example a molecule called JBIR-23

Understanding factors that promote mesothelioma cell death

Blocking or promoting the normal cell death pathway in cells (apoptosis) is a traditional approach exploited by chemotherapies and radiotherapies. The growing understanding of the apoptosis pathway is leading to new small molecule therapies that target particular proteins that may be specific to mesothelioma, minimising systemic effects. These include agents that target, for example, HDAC, MET, SRC, WNT, IAP2, and the prosurvival BCL-2 family proteins. An alternative strategy is the ‘synthetic lethal’ induction of cancer cell death, where a known defect in cancer cells is exploited by blocking a second pathway that the cancer relies on.

Stopping expansion of mesothelioma by inhibiting tumour blood vessel formation

Angiogenesis is the growth of new blood vessels. Blocking new blood vessel formation in mesothelioma and hence starving the tumours is an avenue that has had some success in other cancers.

Using immune cells to attack mesothelioma cancers using vaccines or immune cell delivery strategies

Modifying the immune system to fight and eliminate cancer cells, with the use of agents to boost immune responses, or vaccines, is an important avenue of study across all tumour types. Mesothelioma has been one of the most studied cancers in this area with its high expression of a number of markers making the cancer cells potentially amenable to attack using these methods.

Development of new cellular and combined cellular and gene therapy treatments.

Stem cell therapies are a rapidly expanding area of study and their use as vectors for delivery of gene therapies has recently been successful in animal models of several cancer types. Mesothelioma growing within a pleural cavity may lend itself to this type of therapy. Other routes of study include targeting gene therapies to cancer cells, which on activation lead to chemotherapy activation and targeted destruction of the tumour.

Understanding the effect of the tumour microenvironment

Tumour cells proliferate in an environment containing inflammatory and stromal cells secreting various factors (cytokines, chemokines, growth factors) and macromolecular components such as extracellular matrix. There is an interaction and interplay between tumour cells and these different entities. Interactions between extracellular matrix and tumour cells, as well as circulating factors modulate cell migration and invasion. So far, the tumour microenvironment in mesothelioma is not well described. A better characterisation is needed.

Understanding mechanisms of resistance to chemotherapy

Targeting current therapies to specific individuals identified as sensitive to the therapy (and thus avoid giving ineffective treatment to resistant patients) is an important goal. With current standard chemotherapy, perhaps two thirds of patients are receiving a toxic treatment that will not benefit them. Argininosuccinate synthetase (ASS1) has been shown to be a robust marker of cisplatin sensitivity/resistance in ovarian cancer[14], and in the ADAM trial[15] (due to start late 2010) the role of ASS1 as a predictive biomarker will be examined prospectively. Evidence is also emerging that BRCA1 may be a marker for vinorelbine and cisplatin sensitivity[16]. Alternatively understanding drug mechanisms may lead to the discovery of new ways of sensitising cancer cells to the current therapies by blocking their resistance mechanism.

1.2.4 Asbestos in the carcinogenesis of non-thoracic cancers.

Given the production of pro-tumour endocrine cytokines and growth factors in response to asbestos exposure, asbestos may contribute to carcinogenesis of other, non-thoracic tumours. Further research is required to examine the contribution of asbestos responses to the carcinogenesis of other, non-thoracic tumours."

1.3 Screening, diagnosis and prognosis

1.3.1 Screening

Given the known cause of mesothelioma, and the individuals at high-risk, screening (with CT and possibly serum biomarkers) is a theoretical possibility[17]. However, no likely method of screening has yet been identified, and because treatment options are limited, the potential benefits are, at best, uncertain. Nevertheless, there are a number of promising therapeutic options on the horizon, so work needs to start sooner rather than later to find ways of identifying patients earlier in the natural history of their disease. Such a patient group would be an ideal population in which to trial new therapeutic approaches. In addition the long latency period provides a particularly good model for both early detection, and for early intervention.

1.3.2 Diagnosis

Patients rarely exhibit symptoms of asbestos-related disease sooner than 2 decades after exposure, and mesothelioma may present with breathlessness, chest pain, cough, chest wall mass, weight loss, fever and excessive sweating. Such symptoms make it difficult to distinguish mesothelioma from other more common respiratory problems.

Older markers of mesothelioma (such as hyaluronic acid, various cytokeratin fragments and other cancer antigens) are not considered sufficiently reliable, and although newer molecular markers have been proposed, the sensitivity of mesothelin and the specificity of osteopontin have been questioned[18].

Delays in diagnosis cause patients and carers considerable anxiety, often discomfort, and ultimately may result in patients not being able to receive optimal treatment, and miss out on early compensation. Referral

to an experienced multidisciplinary team is recommended by all recent guidelines for the management of mesothelioma[19-22], and the Department of Health Mesothelioma Framework 2007[23] has provided advice for SHAs, cancer networks, PCTs and NHS Trusts on how to organise services for mesothelioma patients. To date only a handful have been established, and the value of specialist MDTs in this disease needs to be evaluated.

1.3.3 Staging and Response

The current staging system for mesothelioma is contentious, poorly evidence-based and not consistently applied. However, the International Association for the Study of Lung Cancer Mesothelioma Staging Project has recently defined datasets for retrospective and prospective data collection. One problem is the assessment of tumour bulk, but ongoing work is exploring the computerised assessment of radiological tumour bulk that could be used both to develop staging and to assess response to treatment.

The SWAMP trial (South West Area Mesothelioma and Pemetrexed trial) is investigating whether PET for TGV, dynamic MRI and/or mesothelin blood tests can identify metabolic responders from non-responders early in order to inform management. To date this study has recruited approximately half of the 85 patients required.

1.4 Treatment

1.4.1 Surgery

The surgical options for mesothelioma are limited.

Extra-pulmonary pneumonectomy (EPP) involves the removal of the pleura, lung, ipsilateral diaphragm, and often pericardium. Although it has been strongly promoted in the US, this has been on the basis of case series of highly selected patients, and there has been no randomised evidence to support its use[24]. However the UK MARS (Mesothelioma and Radical Surgery) feasibility trial[25] successfully randomised 50 patients to (a) a triple therapy of chemotherapy, EPP and radiotherapy or (b) the same chemotherapy and radiotherapy with no surgery. The results are not yet available, although the global enthusiasm for EPP now appears to be diminishing.

Tumour decortication involves opening of the chest, stripping the pleural lining of the outer parietal pleural layer and, where possible, the inner visceral layer. During the healing process, the lung adheres to the chest wall, effectively obliterating the pleural space. Lung-sparing total pleurectomy aims for total macroscopic clearance of tumour, and the MARS2 trial is aimed to evaluate this approach, though its feasibility may depend on the results of MARS.

Video-assisted Thoracoscopic Surgery (VATS), in which the lung is approached through a number of small incisions between the ribs can also be used to perform a palliative debulking pleurectomy, and the ongoing MesoVATS trial[26] is comparing this with medical pleurodesis, which involves the insertion of talc to stick the lung to the chest wall to prevent further collection of fluid. Currently the trial has accrued 151 patients of the target of 196, and accrual could be completed by September 2011. However the final result may not be available before early 2013.

Photodynamic therapy[27], which potentially kills cancer cells, damages blood cells and stimulates an immune response, is being used in some centres, usually in conjunction with radical surgical decortication, with reportedly good results.

1.4.2 Chemotherapy

Mesothelioma has proved to be extremely resistant to chemotherapy drugs. In 2006 Ellis et al[28] pooled the results from 111 phase II studies and indicated that only single agent cisplatin and combinations containing cisplatin resulted in response rates of >20%. In terms of survival, 3 randomised clinical trials[29-31] have suggested that pemetrexed, raltitrexed, and vinorelbine might increase survival by a median of 8-10 weeks. Mainly as a result of the Vogelzang trial, the first line treatment of cisplatin and pemetrexed has become the standard worldwide, and is the only NICE approved chemotherapy in the UK. A phase II study of cisplatin and

bortezomib (velcade) is ongoing at the Royal Marsden Hospital, but future trials are likely to add novel agents to the cisplatin/pemetrexed regimen.

There is no agreed standard 2nd line chemotherapy, and results from phase II studies of new agents for 2nd-line therapy have been disappointing (for example, at ASCO 2010 studies of sunitinib, sorafinib, and dasatinib all showed very few responses[32-34]), and currently a policy of re-challenging with the same drug combination (as with many other cancers) may be the most effective treatment[35].

1.4.3 Radiotherapy

Historically, radiotherapy has had limited use in mesothelioma. This is mainly due to the diffuse nature of the disease (and that it surrounds normal lung tissue), but it is widely used prophylactically to radiate surgical intervention sites (biopsies, chest drains for pleural effusions, etc) as tumour seeding can occur along the tract and cause subcutaneous chest wall metastasis. However there is little standardisation of the practice of prophylactic radiotherapy and its efficacy has not been demonstrated[36]. The proposed PIT trial (a phase III randomised trial comparing (a) prophylactic irradiation of tracts following invasive chest wall intervention with (b) no irradiation would potentially change practice as there is no consensus as to its use. The PIT trial has to date failed to secure funding but there is known international interest in such a study and collaboration with an organisation such as the EORTC may allow for rapid recruitment and the availability of a practice-changing result in a relatively short period of time.

Modern radiotherapy techniques (such as Intensity Modulated Radiotherapy (IMRT). Tomotherapy, and Rapid Arc Radiotherapy) and better understanding of how to deliver chemotherapy and radiotherapy sequentially, are now being explored to see whether they can be used as high-dose palliative treatment for patients with intractable symptoms that cannot be controlled with opiate analgesics, and potentially as alternatives to surgery.

1.5 Symptom control

1.5.1 Palliative care

Patients with mesothelioma usually experience a long latency period from exposure to diagnosis (of up to 40 years), and then a swift decline, with the median time from diagnosis to death being around 9-12 months. During these last few months they often experience severe breathlessness, pain, fatigue, sweating and weight loss[37,38], all of which require specialised individualised management, yet many patients suffer from a lack of access to palliative measures.

Palliative care needs to be individualised, and might involve a panoply of therapies, including: palliative surgery, 2nd or 3rd line chemotherapy, tunnelled intrapleural catheters for trapped lung, cordotomy for pain, etc. A key issue is ensuring that patients receive all the supportive and palliative care they need, as soon as they need it, and that they have easy access to the best investigations and treatment. A recent study in non-small lung cancer[39] showed that in patients with advanced disease, early referral to palliative care resulted in better quality of life, lower rates of depression, less aggressive end-of-life care, and, surprisingly, increased survival.

Patients with mesothelioma often experience pleural effusions, and a small pilot study in Bristol (funded through several small pharmaceutical industry grants) is looking at the value of zoledronic acid for such patients. This leads on from animal studies showing zoledronic acid reduced malignant pleural fluid and tumour production and improved survival.

1.5.2 Breathlessness

Breathlessness is recognised as the major symptom experienced by mesothelioma patients, but very little research has been undertaken to find ways to alleviate the distress that breathlessness causes, although the value of opioids in dyspnoea (from any cause) was confirmed in a systematic review[40], and a further paper confirmed their value in dyspnoea from cancer[41].

A trial in lung cancer by Bredin et al[42] looked at the effectiveness of a nursing intervention for breathlessness

(which included assessment, advice, support, training and goal setting), and showed that this intervention not only improved patients breathlessness, but also their overall performance status and level of depression.

The ongoing Time2 (funded by the BLF) is randomising 114 patients to either talc or an indwelling catheter to see how well breathlessness from pleural effusions is controlled.

1.5.3 Pain

Alongside breathlessness, the main symptom experienced by mesothelioma patients is pain, which is often severe and chronic, and reported to be significantly worse than that experienced by lung cancer patients[43].

The role of neurodestructive and neuromodulatory techniques in the management of pain due to cancer is acknowledged; and quantitative evidence exists for some, e.g. coeliac plexus block for carcinoma of the pancreas[44], but the best evidence for others is limited to case reports and small, uncontrolled case series.

Percutaneous cordotomy (severing the nerves in the spinal cord that carry the nerve signals from the area affected by the mesothelioma to the brain) is used in some centres, and a retrospective review[45] indicates that this significantly reduces the dependence on strong analgesics. The value of cordotomy has not been established, but a systematic review, survey, and the development of a guideline for the use of cordotomy is ongoing[46].

1.5.4 Psychosocial issues

Unfortunately mesothelioma is often combined with lung cancer in psychosocial studies, although it is a different disease affecting a different cohort of patients. The very nature of mesothelioma means that patients and their families have to cope with anxiety (pre and post diagnosis), traumatic investigations and interventions, receiving bad news, lack of effective treatments, facing terminal illness, self-blame, as well as claims, benefits, and medico-legal procedures, and all of these put considerable strain on relationships.

1.6 Asbestos-related diseases other than mesothelioma

1.6.1 Diffuse pleural thickening and pleural plaques

A diagnosis of pleural plaques can give rise to an understandable sense of anxiety and unease as it indicates exposure to asbestos and therefore being at risk of more serious disease[47]. However, the current evidence is that in the great majority of cases pleural plaques do not in themselves produce any significant physiological change or loss of lung function, and only very rarely give rise to physical symptoms. There is also currently no available medical evidence to show that pleural plaques become malignant or lead to mesothelioma or other asbestos-related diseases, the suggestion being that it is a person's exposure to asbestos that produces any increased risk of developing a serious asbestos-related disease rather than the pleural plaques themselves.

1.6.2 Asbestosis

Asbestosis is classed as an interstitial lung disease, and is a potentially fatal fibrosing condition of the lung parenchyma. The HSE report that there were 96 deaths in the UK in 2007, but acknowledge that many cases are undiagnosed or mis-diagnosed. It has a long time lag from exposure and is a progressive disease, although little is known about the speed of progression or prognostic factors. There is no treatment, and the advice on the NHS website[48] is not considered helpful. It appears that asbestosis and smoking have a synergistic effect on the risk of developing lung cancer, which is greatly increased if asbestosis patients continue to smoke. Patients often experience severe breathlessness on a par with that of mesothelioma,

1.6.3 Lung cancer

It is well documented that there is an excess risk of lung cancer in individuals exposed to asbestos and that this risk is hugely elevated if the individual is also a smoker. The mechanism for this effect is unknown.

1.6.4 Peritoneal mesothelioma

Little is known about this form of mesothelioma, which appears to be more aggressive than pleural mesothelioma. The number of cases is reported as small in the UK, but this may be because patients are being seen by gastroenterologists and abdominal surgeons, and the condition is not recognised as mesothelioma. In the US (where there appears to be a greater proportion of peritoneal mesothelioma than elsewhere) a consensus for treatment has emerged, with many patients having cytoreductive surgery and intra-peritoneal chemotherapy, though this regimen is rarely available in the UK.

PART 2: PROMOTING NEW RESEARCH

2.1 Research Capacity

The UK has the highest recorded incidence rate per head of population of asbestos-related diseases in the world, and thus has an opportunity to take the global lead in the understanding and treatment of these diseases.

Despite being a serious problem, asbestos-related diseases are still relatively uncommon, and as a result the clinical and research community in the UK is also relatively small, though generally well-networked and, as evidenced by the response to this review, very enthusiastic.

In the consultation for this review, no evidence was presented that there is a lack of necessary skills for research in asbestos-related diseases. What is needed is the application of generic basic, translational and clinical approaches. The pressure in academia to raise research income, and the competitive nature of research funding, creates an incentive to tackle what are perceived as more tractable research questions, or in the case of cancer research, tumour types which are considered easier to study and where it is possible to build on past progress. Counter-incentives are therefore needed which might include targeted funding (as in the case of the current BLF initiative) and the sign-posting of generic funding schemes which could be tapped by the research community.

The relative unattractiveness of the field to researchers historically, and the relatively small amount of research undertaken, has to some degree fed a perception that research funders are uninterested in, or unwilling to fund, research in asbestos-related disease. However, research funders have stated that this is not the case and that they are limited by the small number of high quality proposals that they receive.

The ring-fenced funding now being made available represents a unique opportunity to attract some high-quality research and to establish a foundation on which future work can be built. The research community (both researchers and funders) should aim to use this as a magnet to attract experts from other areas, as well as bright young scientists taking early steps in their careers.

Building from this foundation, research funders and the research community should work together to develop strategies that help both to increase the number of research proposals coming forward and the success rate within open competitive funding streams. This should cover the full range of studies from basic science to palliative care, and should include consideration of how to encourage originality rather than only research which is safe but unadventurous. Research on mesothelioma in particular is in need of a step-change and this will not come from a wholly cautionary approach.

In Part 1 of this report we clustered current research into 5 areas all of which are needed if we are to offer better hope to mesothelioma patients in particular. Since the areas require different expertises, we do not see them as being in competition with each other, neither would it be helpful to place them in a rank order of priority. We now consider each again in turn to highlight key research issues and priorities within each, and also discuss a need for more mesothelioma tissue and more complete clinical information. We recognise that the full range of needs identified well exceeds what can be achieved with the dedicated funds for research on asbestos-related disease that are currently available. Some of this research can and should be supported through existing competitive funding channels.

2.2 Epidemiology, aetiology and basic science

In the UK it is estimated that the peak incidence of mesothelioma will not be reached until between the years 2015 and 2025, and also that the patterns of incidence and the populations at risk are changing. Monitoring these changes is essential, to better understand the disease, and for allocating resources.

Research needs to be directed towards exploring risk factors involved in mesothelioma, for example, estimating the risks associated with moderate and low exposure populations, investigating the current increase in mesothelioma in people (especially women) without an occupational history of asbestos exposure (such disease may relate to other inhaled agents or a genetic susceptibility), as well as looking at why some people with high exposure do not succumb to asbestos-related diseases.

There is still wide disagreement on the differences in lung cancer and mesothelioma risks between fibre

types, and further work to clarify these is important for the UK and for the countries that are still using large amounts of asbestos.

Continuing to monitor the incidence rates, to identify high-risk subgroups, and to estimate the risks for different populations, is essential in order to better understand the disease, and inform the allocation of resources.

The last decade has seen considerable progress in the basic understanding of mesothelioma biology and within the UK there are several high quality groups pursuing this area of research and testing new targets. This research however appears hampered by low numbers of patient specimens and hence putative targets often have poor validation. Further, genome wide approaches seeking common abnormalities across mesotheliomas are lacking due to this poverty of specimens. A greater availability of UK tissue samples which would help enable identification and validation of key targets that might be manipulated by either new or existing drugs, hence speeding delivery to patients (discussed further in 2.7).

There are many interesting areas in basic and translational science that may deliver improvements in therapy, including:

- the identification of somatic genetic alterations leading to activating mutations in oncogenes
- the amplification of oncogenic signalling pathways that can be targeted with known compounds;
- improvement in our understanding of chemoresistance that can lead to the identification of patients who will respond to therapies and those in whom toxic expensive therapies are futile
- the development of sensitising therapies that improve the efficacy of current treatments, and to
- developing and assessing both novel therapies and established therapies used in other tumour types for the treatment of mesothelioma.

2.3 Screening, diagnosis and prognosis

Screening only makes sense if there are treatments available for those patients identified with early disease. For this reason, and because a reliable screening tool has not yet been identified, screening for mesothelioma is currently not a viable option. However, studies involving the surveillance of cohorts of individuals from particular industries could be used to evaluate techniques for early diagnosis. This group, in turn, could provide a pool of patients with early stage disease for the trial of newer therapeutic options.

Delays in diagnosis can cause patients (and their families) considerable anxiety and may delay optimum treatment and compensation. Thus, better methods of expediting and simplifying the diagnosis of mesothelioma need to be developed, especially to clarify the difference between benign and malignant disease. The standardisation of the diagnostic pathway to ensure a high level of tissue diagnosis with good quality biopsy specimens is important but good quality pleural biopsy remains a relatively invasive process and new, less invasive methods of diagnosis could make a major impact on the speed of diagnosis.

2.4 Treatment

Mesothelioma has proved very resistant to treatment, and novel approaches need to come out of basic science, for example to identify new drug targets (see 2.2 above).

International collaboration is essential in order to run clinical trials of sufficient size to reliably detect benefits. Lessons need to be learned from the experience in diseases such as non-small cell lung cancer, where meta-analyses of thousands of patients were required to confirm even the most basic concept (e.g. that chemotherapy was beneficial).

Research into optimal surgical techniques and the related patient reported outcomes are important, and the role of radiotherapy needs to be defined.

While chemotherapy with cisplatin and pemetrexed is now accepted as standard frontline treatment, there are numerous questions remaining about chemotherapy, including when to start (in patients with minimal symptoms), what to give as 2nd (or 3rd) line treatment, and the role of maintenance chemotherapy. The wide variation in current second-line treatment indicates that this is an area that needs clarification. More innovative trial designs (such as multi-arm multi-stage trials[51]) to eliminate less effective treatments may be the best way forward, although deciding on the endpoint (possibly symptom control) would need discussion. Establishing

a standard second-line chemotherapy would potentially improve symptoms and quality of life and could increase survival.

In addition, different ways of delivering chemotherapy might be investigated (e.g, with chemo-embolisation the drugs are injected directly into an artery that supplies blood to the tumour, thus theoretically, attacking only the cancer cells, and potentially reducing toxicity). Finally, reliable markers for response to therapy are urgently required, principally to avoid non-responding patients continuing chemotherapy unnecessarily.

2.5 Symptom control

Many patients experience severe and intractable symptoms and better methods of symptom control would greatly improve patients' lives, especially in respect of breathlessness and pain. In terms of breathlessness, a number of options could be explored, including tunnelled drains, [1]VATS decortication, pleurodesis agents other than talc, and non-medical management such as breathing techniques etc. For pain, understanding how genetic variations of opioid receptors affect responses to drugs such as morphine, and whether levels of cytokines may be used as a biomarker of pain, could have major implications for treatment.

Given the slow progress with treatment, and the time-frame for development of novel molecular therapies, the area that would have the most immediate impact on patients would be symptom control. Repeating the trial that showed, in lung cancer, that early referral to palliative care improved quality of life, decreased depression, and increased survival, would certainly be worth considering. In addition, exploring new ways of helping patients (with mesothelioma, and with asbestosis) with their breathlessness (e.g. simple solutions like hand held fans[59], and their pain (e.g. assessing the use of intrathecal pumps and epidural port devices), and developing a standard pathway for palliative care would all improve the lives of patients, their carers, and their families.

Little has been done to explore patients' and carers' experience of being diagnosed with and living with mesothelioma, or how patients were given information about their prognosis and how this affected their treatment decisions.

2.6 Other Asbestos-related Diseases

Many of the outstanding research issues relating to mesothelioma are also germane to other asbestos-related diseases: understanding the epidemiology, confirming the risk factors, developing screening techniques, improving the diagnostic accuracy, developing a pathway for palliative care, and exploring interventions for breathlessness.

In particular research could include: An epidemiological study looking at the natural history (symptoms and prognosis) and disease risks associated with pleural plaques,
improving the diagnostic accuracy of asbestosis, particularly for mild asbestosis, which is radiologically indistinguishable from ageing changes of interstitial fibrosis[52], exploring the links between asbestos and lung cancer, and auditing the incidence, treatment and prognosis of patients with peritoneal mesothelioma.

All the above may require collaboration with other clinical communities.

The small, but generally neglected group of patients with peritoneal mesothelioma needs investigation. The incidence is probably under-reported, and there is little expertise in the UK in this area. Compared to the US where there is consensus regarding the standard treatment, in the UK treatment is rarely available. A starting point would therefore be an audit to establish the incidence, treatment and prognosis.

2.7 Infrastructure needs: Biobank and National Registry

Many contributors to this review cited the lack of tissue and of good clinical data as the major obstacle to research. The most commonly suggested priority was the setting up of a National Asbestos Related Diseases Register and Bio-bank to underpin research, and put the UK at the forefront of work in this field. The value of such biobanks/registries in other cancers (such as the Liverpool Lung Project[53]) are now being seen, as

[1] Video-assisted thoracoscopic surgery

not only can national studies be supported, but also collaborations can be set up internationally (either by passing data to requesting groups or combining data with other databases).

The value of collecting tissue (together with the related clinical data) on all asbestos-related disease patients in the UK cannot be overestimated, and was a recommendation of the NCRI Strategic Planning Group Report in 2006[54]. No one centre in the UK can provide enough patients to do reliable translational research, but pooling tissue would provide the infrastructure for the translational aspects of clinical trials, the ability to rapidly examine novel targets for drug therapy, and be a unique resource for novel technologies such as deep sequencing proteomics.

The setting up of a new biobank cannot be undertaken lightly and would require a sizeable commitment of resource. A feasibility study would need to be the next stage to examine such questions as:

- How tissue is currently sourced and what the limitations are
- Whether to have a 'virtual' bank (using local pathology department archives as the storage facility), or a 'central' bank (which would be very expensive and time-consuming to set up from scratch, and would have to overcome the reluctance of pathology departments to centralise material), or to piggy-back onto an existing tissue bank.
- What material to bank: frozen tissue (sometimes thought of as the ideal, but expensive to do well), paraffin blocks, pleural fluid etc.
- Whether to include autopsy tissue as it has been shown that it is feasible to harvest material, and that DNA can be extracted from such specimens recovered within a week of death[55].
- How to ensure sufficient tissue is available, as usually only small biopsy samples are taken, and it is often all used in diagnosis, and/or has to be made available to the courts (considering compensation claims)
- How to ensure reliable retrievability (which is the key to an effective bank), which includes the ability to search the database, and for samples to be logged in and out.
- Ownership, responsibility, ethics, consent, intellectual property, etc.
- How to ensure sustainability.

In addition, tissue banks are most valuable if supported by clinical, linkable data, and thus another (or the same) group would need to consider the feasibility of setting up a National Asbestos-Related Diseases Registry.

Such a Register would support the analysis and understanding of incidence and mortality trends as well as underpin the improvement in the staging of the disease. The CHIMP study (an audit of chemotherapy use in mesothelioma) [56] has shown that such data collection is feasible, and a number of groups already collect some data on asbestos-related diseases. The Cancer Registries collect data on mesothelioma, but at least in the past, the lack of histological confirmation of the diagnosis in many cases has led to some under-reporting. The National Lung Cancer Audit (LUCADA)[57], has been collecting data on mesothelioma since 2005 but there would need to be a significant expansion of the dataset to cover all that would be needed for a tumour registry. The Centre for Health and Environmental Health collects data on all respiratory disease thought to be due to occupational or work-related factors through its SWORD project[58] though this only covers a sample of incident cases. In addition, the NHS, HES and NCIN represent a unique unified framework to help identify and follow patients. Thus establishing a proper National Asbestos Related Diseases Registry would place the UK as world leader (only Western Australia has one at the moment) and would ideally build on the existing resources rather than attempt to establish an independent register.

2.8 Coordination

This review has identified that all the ingredients exist in the UK to give a boost to research in mesothelioma and other asbestos-related diseases. The key components are expertise, research ideas, enthusiasm and a modest amount of dedicated funding which can be used to seed a larger effort if managed skilfully.

To ensure the most effective use of research resources and the translation of research results into practice, some structured coordination would be helpful. This would ensure that different disciplines are brought together to share data and to tackle the more difficult questions, and that research across the whole spectrum from basic science to palliative care is integrated in such a way that researchers understand their own contributions within the context of the full picture. It would also maximise the opportunities given to patients

to participate in research through clinical trials or tissue donation.

Consideration should be given to establishing a means of communication in the UK, which would bring together all the component parts under one badge, and encourage collaboration. The need for such nationwide coordination has been highlighted by the extensive work already done in this area by the NCARD development group[61], though we believe much could achieved with relatively modest investment in a coordination function. Activities could include:

- Bringing together stakeholder groups to share information and ideas. This would include the NCRI Mesothelioma Sub-group, research funders, scientists, clinicians, patient groups, mesothelioma charities etc
- Holding scientific conferences that cross all relevant disciplines
- Working with the National Cancer Research Network to increase the uptake of mesothelioma trials
- Maintaining a website that points the way to relevant funding schemes and other web-based resources aimed at helping researchers secure funding
- Publishing reports on progress
- Facilitating dialogue and collaborative strategy setting between researchers and funders
- Ensuring close contact between researchers and the provision of clinical service through the NHS
- Fostering international links

2.9 Summary: the way forward

There is scope for new research in all the areas discussed in this report, and some important research questions have been highlighted accordingly. The review also found no evidence of a lack of research capacity – what is needed is the application of generic basic, translational and clinical approaches. There is therefore a need for established investigators in other areas of cancer or respiratory disease research, to apply their expertise to the challenges in mesothelioma and other asbestos-related diseases. Some dedicated funding is now available and this should act as an incentive, and a nucleus around which to build a larger body of work supported through competitive funding streams. Challenges do remain in making available mesothelioma tissue for research, together with associated clinical data. These require more detailed exploration than was possible within the scope of this report. Particularly with new funding coming on stream, research funders and the research community should consider the need for enhanced coordination, which could be built on existing structures in a cost-effective manner.

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