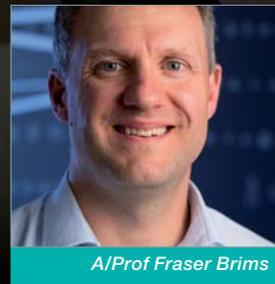




Asbestos Vigilance Still Needed

Despite banning asbestos 13 years ago, the deadly material still poses health risks that has clinicians, researchers and regulators ever vigilant.



A/Prof Fraser Brims

The discovery of asbestos in imported building materials on the construction site of the Perth Children's Hospital last month was a sobering reminder that despite the material being banned in WA since 2003 and the myriad agencies established to control it, the continued risk of asbestos exposure is real.

While two scientists from the National Centre for Asbestos Related Diseases, based at the Perkins Institute in Nedlands, write here of their treatment research focus, it's timely to look at the broader picture of how the use of the material is being monitored and how effective the asbestos-related disease surveillance has become.

Last year, A/Prof Fraser Brims wrote in *Medical Forum* about the Asbestos Review Program (ARP) based at SCGH and funded by WA Health. Its objectives are to monitor the health of people who have had a minimum of three months continuous exposure to asbestos and provide health and clinical advice with the aim of early detection of cancers.

WA's unique perspective

The program is unique to WA, which perhaps reflects the unique relationship the state has had with asbestos mining and the resulting rise of asbestos-related diseases over the decades. More than 5000 people since 1990 have visited the program at least once. Most attend annually (about 1200 people currently)

and cancers in about two patients a year are diagnosed.

"Collaboration with the University of WA over the years has meant that observations in this cohort have translated into world-renowned research and the SCGH respiratory clinic has unparalleled experience in managing mesothelioma and other asbestos-related diseases," Fraser said.

The ARP has been offering low dose CT scans and identifying treatable early stage lung cancer for four years and Fraser is hopeful that WA Health's commitment to the program will continue. He added that a grant from the NSW Dust Diseases Board is facilitating research to establish who is at raised risk of lung cancer following asbestos exposure.

"We are trying to look at the combination of other risk factors along with asbestos to help us understand who we should be concentrating on."

Sobering stats

According to the latest Australian Mesothelioma Registry (AMR) figures (2014), 641 people nationally were diagnosed with the disease that year. It was the lowest figure in the four years of the registry. In 2011 there were 692 cases diagnosed, 2012, 713; and 2013, 676. In WA 94 new cases were diagnosed in 2014 (77 men and 17 women) giving the state the highest rate of 3.6 people

per 100,000 population, with Queensland next with 3.1.

Of the 641 cases of mesothelioma, 597 (93.1%) were tumours of the pleura (a combined term used here to represent pericardium, pleura and mediastinum) and 38 (5.9%) of the peritoneum.

"The elderly workforce offers a natural decline in that respect but we are also recruiting new people into ARP every week," Fraser said. "The asbestos issue at the Perth Children's Hospital site is an opportunity to flag to the community that this program exists and people who have had an exposure to asbestos for more than three months are entitled to be part of it. It is all bulk billed."

"Text books and the internet give the impression nothing can be done but in WA we have a unique service so there is something doctors can do. You can refer people to the ARP where we will review them annually and treat lung cancer early. It makes a big difference to these people."

WorkSafe on Asbestos

WorkSafe was one of several government agencies (Comcare, the WA Building Commission and the Department of Environment Regulation were others) called in to the Perth Children's Hospital. We spoke to Ms Sally North, the Principal Scientific Officer of WorkSafe's Occupational Hygiene and Noise Control Team.

While she was not able to comment on the details of the hospital audit, which is being led by WA Building Commissioner Peter Gow, she said that awareness of the use of asbestos in WA needed to improve.

“There are still buildings, plant and equipment where asbestos is present. Workplaces must be able to manage it. If asbestos is maintained in good condition and people know where it is and don’t inadvertently disturb it when renovating or demolishing, it can be properly managed,” she said.

“While workplaces are heavily scrutinised and regulated, I think we tend to forget just how many asbestos products were used domestically in Australia. WorkSafe does not control unpaid DIY work, so people who embark on these projects need to consider the possibility of asbestos being present.”

Global perspective

When building panels supplied to the hospital’s builder John Holland by the Chinese company Yuanda were found to contain asbestos, it highlighted a problem that extended outside of Australia.

The Minister for Immigration, Peter Dutton, told *The Australian* newspaper it was “ridiculous” to suggest Australian Border Force could inspect all 2.4m containers entering Australia, while John Holland said Yuanda had provided certificates stating the 150 roof panels did not contain asbestos.

It reveals the dichotomy of views on the safety/efficacy of asbestos as a building material around the globe. While frantic alarm bells ring in countries such as Australia, the US and the UK when asbestos is detected,

Table 4.6: Trades JSM exposure assessment results (probability and estimated level of exposure only) for largest categories of job titles

Job title	No. participants allocated this JSM at least once	Assessed probability of exposure (no. participants for whom asbestos exposure was assessed)				
		Unlikely	Possible	Probable ^(a)		
				Low	Medium	High
Construction (carpenter, joiner, builder, bricklayer etc)	101	10	3	—	—	88
Electrician	36	7	4	—	—	25
Plumber	22	2	1	1	—	18
Boilermaker, welder	21	—	—	—	—	21
Other metal & mechanical trades (including fitters, turners, machinists)	67	11	6	—	2	48
Engineer	10	3	2	—	—	5
Telecommunications technician	9	5	2	—	—	2
Other	52	20	4	—	1	27
Total participants given Trades JSM	258					

(a) These categories refer to the estimated level of asbestos exposure.

Source: Australian Mesothelioma Registry Annual Report *JSM = Job-Specific Module

other countries continue to comfortably mine and manufacture Chrysotile (white asbestos).

“Many countries have banned asbestos industries but Russia and some Asian countries continue to mine and manufacture; it is perceived as a standard, cost-effective building material. Canada only stopped mining white asbestos in 2012,” Sally said.

It leaves regulation, awareness and education as the main weapons in the local fight being waged by a number of organisations in WA and Australia whose job it is to create systems

to keep the community safe and informed.

“If the systems are poor, the risks are greater. Isolated incidences in themselves may not be a big issue, depending on the circumstances. But where people work in an industry where they may have a number of exposures, the more that happens the more the risks are increased. Mesothelioma is a unique cancer – it is easy to count. We are still waiting for those numbers to turn around and decline.” ●

By Jan Hallam

A Gene Approach

Prof Gary Lee, head of the Pleural Medicine Unit at the Institute of Respiratory Health, is leading a team that is exploring a gene therapy to slow tumour growth.



Prof Gary Lee

Malignant pleural effusion (MPE) can complicate most cancers, especially lung and breast cancers. In addition, Western Australia has one of the world’s highest incidence of mesothelioma, and the majority of these patients present with an MPE.

The inpatient management of MPEs in WA alone involves over 2000 bed days and an estimated cost of over \$12m a year.

The Pleural Medicine Unit at the Institute of Respiratory Health and Sir Charles Gairdner Hospital (SCGH) leads several multi-national randomised trials to improve management of MPEs, including the AMPLE (Australasian Malignant Pleural Effusion) studies which involve centres in Australia, New Zealand, Hong Kong, Malaysia and Singapore.

Their recent work has shown that indwelling pleural catheters (IPC) are as effective as conventional pleurodesis in relieving symptoms and can significantly reduce time these patients have to spend in hospital throughout their illness. The latter is significant as patients with MPE often have a limited lifespan.

The ongoing AMPLE-2 trial now aims to optimise the drainage regime for MPE patients treated with IPCs to maximize the benefits in relief of breathlessness.

The unit is also active in its translational research for pleural malignancies. Together



Prof Jenette Creaney

with Profs Anna Nowak, Jenette Creaney and Michael Millward, the unit and the National Centre for Asbestos Related Diseases (NCARD) have recently begun a new phase II clinical trial for patients with malignant mesothelioma.

The FRAME (Fibroblast Growth Factor Receptor Antagonist for Mesothelioma) study is a product of an integrated laboratory and clinical research program and exemplifies the “bench to bedside” research pathway whereby original laboratory findings from WA can be brought through to human testing.

This work began with analysing the global gene expression profiles of over 22,000 genes on pleural biopsies the group collected during medical thorascopies. The results revealed that a specific growth factor, FGF-9, was overexpressed in mesothelioma but not in other cancers or benign pleural tissues.

Further analysis of pleural fluid samples

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New Trial to block Checkpoint Inhibitors

Perth trials combining Immuno and Chemotherapies will push boundaries in the mesothelioma treatment. **Prof Anna Nowak** from NCARD explains rights.

The asbestos-related cancer, mesothelioma, is a stealthy killer, usually developing between 30 and 50 years after exposure to the fibre. While only a small proportion of people exposed to asbestos will develop the disease, there is no screening or early detection which can alter the course of this invariably fatal cancer.

The mainstay of current standard treatment is palliative chemotherapy, which increases survival by a matter of only months. I have been working on improving chemotherapy for mesothelioma since 1999, when I started researching the effect of chemotherapy on the immune response to tumours, and how immunotherapies could best combine with chemotherapy.

Findings from early laboratory work with the National Centre for Asbestos Related Diseases (NCARD) included significant benefits of the combination of chemotherapy and immunotherapy in curing mice with mesothelioma. This work has led to several clinical trials of chemotherapy and immunotherapy, with the most recent being a national clinical trial led by me out of NCARD and run through the Australian Lung Cancer Trials Group.

In the past five years, immunotherapy has moved from early clinical trials to mainstream therapy for melanoma and non-small cell lung cancer, with a class of drugs known as checkpoint inhibitors leading this change.

Checkpoint inhibitors block negative regulators which normally come into play to limit an immune response. Whilst these negative regulators may play a useful role in avoiding potentially damaging autoimmunity, they can also switch off an anti-tumour immune response before it can usefully inhibit tumour growth.

Checkpoint blockade 'takes the brakes off' immune cells, potentially allowing an effective anti-tumour response to flourish. Unfortunately, only a small proportion of patients experience the dramatic responses



Prof Anna Nowak and Dr Joost Lesterhuis

to single agent immunotherapy which have captured the imagination of the public, the media, and the scientific community.

Increasing the number of responders to checkpoint blockade treatment, and thus long-term cancer survivors, is the goal of the next generation of chemo-immunotherapy clinical trials.

Durvalumab is a monoclonal antibody which blocks PD-L1, the inhibitory ligand (binding partner) expressed by both many cancer cells, and some lymphocytes. The upcoming clinical trial, which is likely to be open before the end of the year, combines standard chemotherapy for mesothelioma (cisplatin and pemetrexed) with durvalumab given at three weekly intervals, and continues durvalumab as maintenance treatment once chemotherapy has been completed.

The Australia-wide phase II trial will begin recruiting just over 50 patients soon, and will be focussing on outcomes of tumour response, progression-free survival, and toxicities.

Finding a treatment that works is not the only challenge. The high costs of checkpoint blockade, together with potential toxicities, make it particularly important to identify biomarkers and predictors of patient benefit.

NCARD, headquartered in Perth, will also be leading the correlative biomarker studies under the guidance of tumour immunologist Dr Joost Lesterhuis. He will be using a number of novel techniques in the hunt for biomarkers which can predict responses to combination treatment. ●

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A Gene Approach

collected in the UK and in Perth from over 1000 patients further confirmed this. With funding from the NHMRC and the Cancer Council of WA, the teams demonstrated that removal of FGF-9 from mesothelioma tumours stopped its growth in animal models.

In addition, antagonists of FGF-9 or its receptors were able to retard the tumour

growth in different types of mesothelioma models in mice.

These findings have led to the FRAME trial, a phase II study funded by the NSW Dust Diseases Authority designed to evaluate the clinical effectiveness of a receptor antagonist of FGF-9 in mesothelioma patients that have progressed despite conventional

chemotherapeutic treatments. The study will enrol up to 55 patients at SCGH.

The FRAME study also provides an opportunity for training new clinician researchers. (Drs Wei-Sen Lam and Sanjeevan Muruganadan, both recipients of the WA Cancer & Palliative Cancer Network Clinical Fellowships, will be involved.) ●