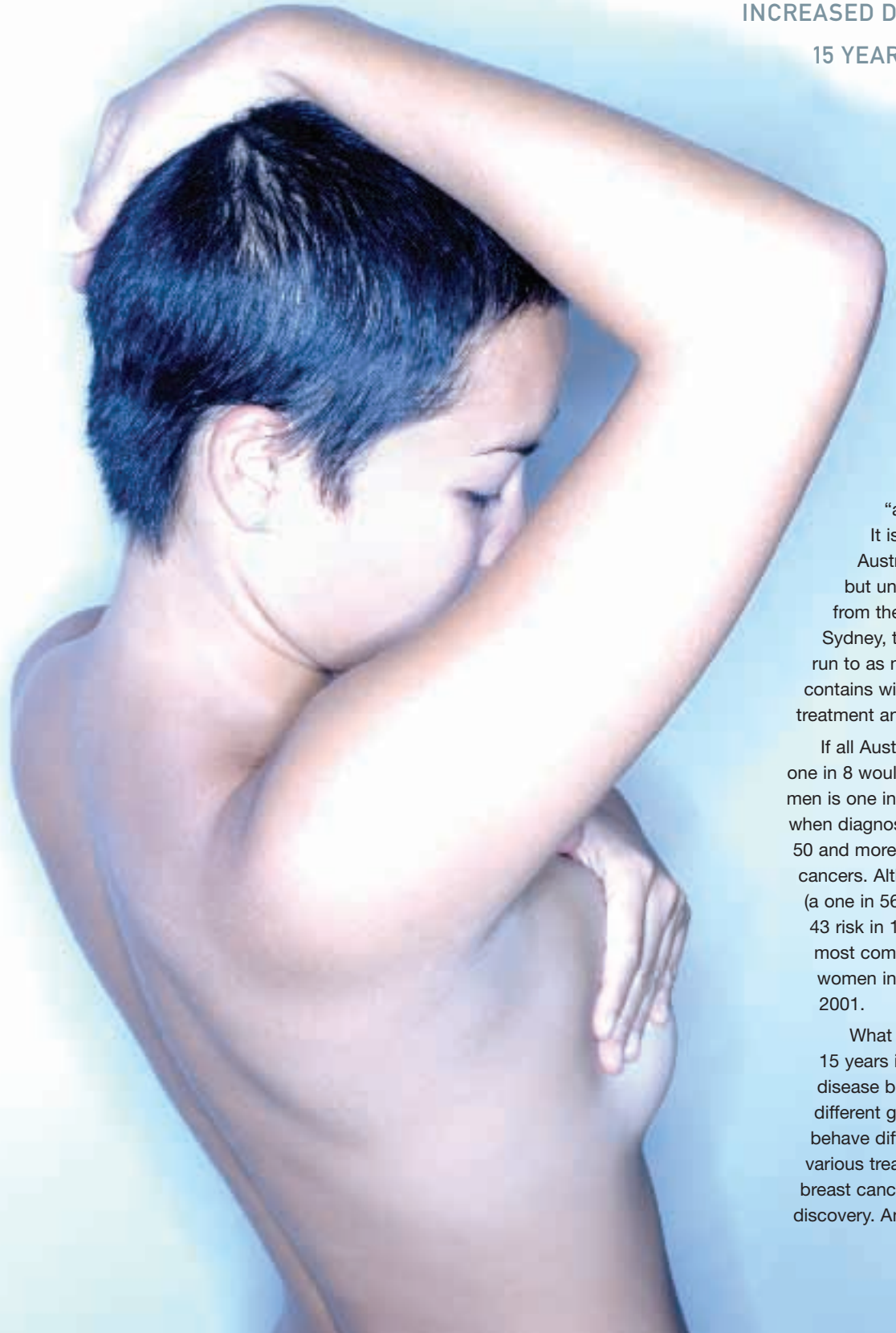
Breast cancer: unlocking the secrets

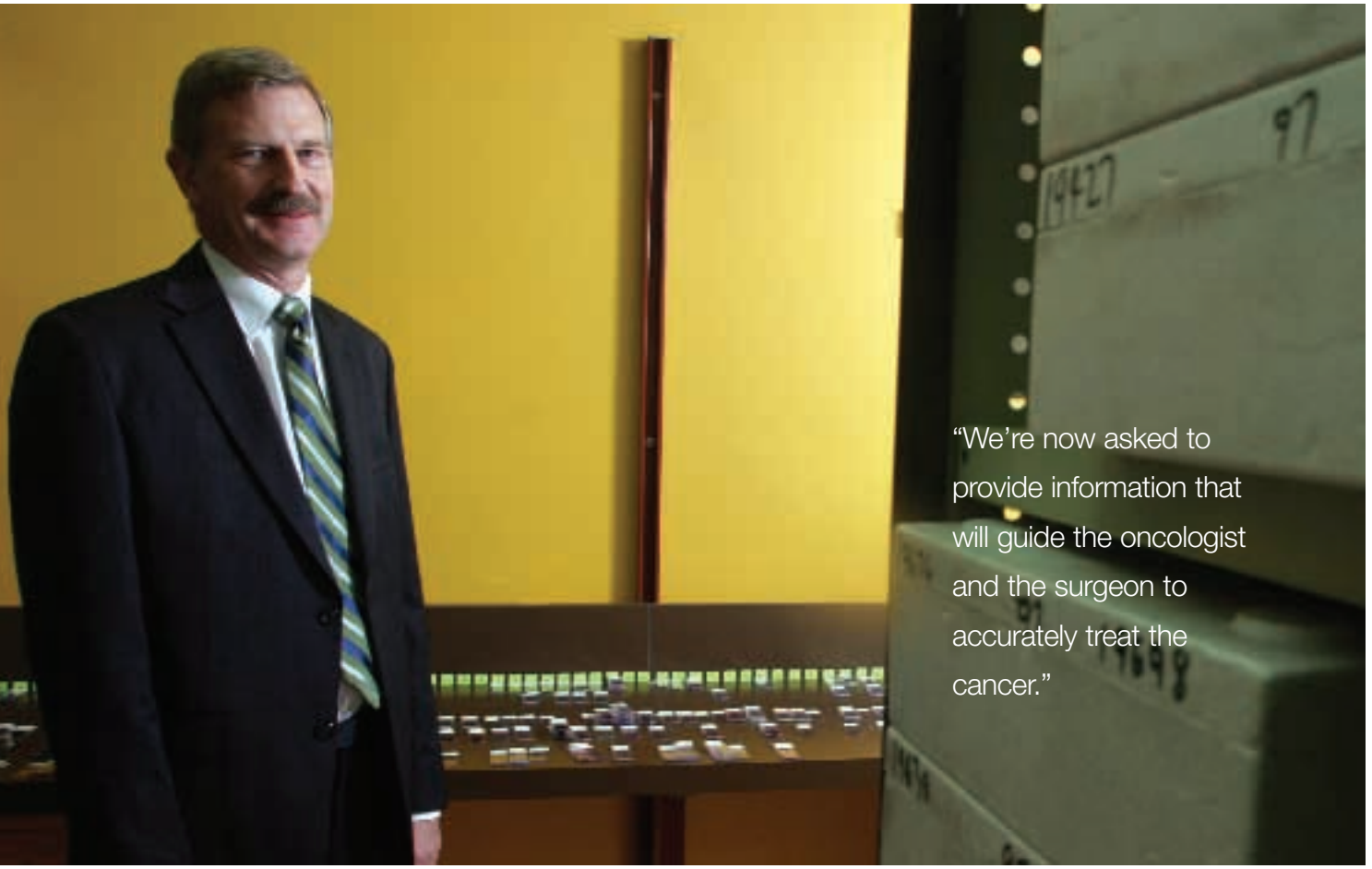
PATHOLOGISTS' ROLE IN THE DETECTION AND TREATMENT OF THIS COMMON ILLNESS HAS INCREASED DRAMATICALLY IN THE PAST 15 YEARS, WRITES **MATT JOHNSON**.



It is brutally short and cruelly definitive but offers almost no information. Just two lines stating, "adenocarcinoma of breast is present". It is a diagnosis more than 13,000 Australian women will receive this year, but unlike this 70-year-old pathology report from the archives of St Vincent's Hospital in Sydney, the report women now receive can run to as many as five pages, and what it contains will have a profound effect on their treatment and prognosis.

If all Australian women lived to the age of 85, one in 8 would develop breast cancer. The risk in men is one in 763. The average age of women when diagnosed is 60, but one-third will be under 50 and more likely to suffer larger and aggressive cancers. Although the survival rate is improving, (a one in 56 risk in 2004 compared to a one in 43 risk in 1983), breast cancer remains the most common cancer-related cause of death in women in Australia, claiming 2594 lives in 2001.

What has been discovered over the past 15 years is that breast cancer is not a single disease but a group of diseases linked to different genetic mutations, each of which may behave differently and respond unpredictably to various treatments. Pathologists working in breast cancer research have been central to this discovery. And a consequence of their findings



has been an increased role for pathologists in breast cancer detection and treatment.

Clinical Associate Professor Michael Bilous, an Anatomical Pathologist at the Institute of Clinical Pathology and Medical Research at Westmead Hospital in Sydney, has not only witnessed much of this evolution but has also played a role in researching and assessing the data that has driven it

"The basic change that has occurred is that once the pathologist was simply asked to assess the tissue they had been sent, to see if cancer was present," he says. "Now the pathologist is expected to provide information about the likely behaviour of a particular breast cancer: whether it's likely to spread, to recur, respond to a particular therapy or need extra therapy.

"We're now asked to provide information that will guide the oncologist and the surgeon to accurately treat the cancer."

Breast cancer is usually slow growing, so it can be several years before it becomes large enough to detect. It usually starts in the lobules where milk is made or in the ducts that carry milk. In the worst cases it can spread into the lungs, other organs and bones. Chances of survival are related to how early the cancer is detected and how far it has spread.

Australia's National Breast Cancer Centre program to provide women with free mammograms has been a remarkable success, but most investigations rely on women going to their doctor after they have noticed something unusual.

The doctor will conduct the first stage of what is known as the "triple test". After gaining a family history, he or she will conduct a clinical examination. If there is concern about the findings, patients will be advised to undergo two further tests. Taken alone, none of the tests in the "triple test" can reliably detect breast cancer, but used together they will find more than 99 per cent of cases.

The second test involves mammography or ultrasound imaging of the breast. A mammogram is a low-dose X-ray that can find changes too small to be felt through physical examination. In women under 35 (or who are pregnant or breastfeeding) breast tissue is too dense for changes to be obvious using mammography, and an ultrasound may be required. For some women both tests may be needed.

If an area of concern is found, a sample of cells can be extracted from the lump with a needle. This is known as a Fine Needle Aspirate or FNA. It is here, once the sample is collected, that the pathologist's work starts.

"Despite all the changes of the past decade, most of the work is still done looking down a microscope," Professor Bilous says. "The samples are taken, processed, prepared onto glass slides and then assessed by the pathologist looking into a microscope."

The cells are graded and the stage of the cancer is assessed, but the sample is also prepared for more tests.

"Once we've looked at the cells, we then want to test the properties of the cancer cell, to see what stimulates its growth. This information is very important to determine which patients are eligible for hormone therapy or the newer

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treatments such as Herceptin," Professor Bilous says.

"All this information – all the observations and measurements – is put into a report for the surgeon and oncologist. We then meet weekly with the team and discuss each patient to formulate an approach for their treatment.

"It's a multi-disciplinary team that will include people from all aspects of medicine: the surgeon, the oncologist, the pathologist, the breast care nurse, the geneticists, and we discuss the findings in context of the patient's needs, wishes and circumstances. At end of the meeting, one person from the team will speak to the patient and discuss ongoing management."

The aim of treatment for early breast cancer is to remove the cancer from the breast and nearby tissue by surgery, and then to destroy any individual cancer cells that may be left behind, usually with radiotherapy and/or chemotherapy.

A crucial part of Professor Bilous' role is providing the patient with information to make a choice about what type of treatment they have.

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Even once the cancer has been diagnosed and the surgical phase of treatment has begun the pathologist remains part of the team, firstly to assess the surgical margin. When surgeons remove the cancer they also try to take some of the healthy breast tissue around it: this healthy tissue is called the surgical margin. It's the pathologist's role to assess the tissue in the margin to see if all the cancer has been removed. If not, more surgery may be required.

The second role for the pathologist is to assess if the cancer has spread to the lymph nodes. Lymph vessels drain excess fluid from the breast and run into lymph nodes in the armpit. The nodes are the most common sites that invasive cancer cells will be found and in the past they were routinely removed. Painful at the time, the surgery also affected the limb's ability to drain lymph fluid, and some patients had to permanently wear pressure dressings on their arm to reduce swelling or lymphoedema.

Dr Adrienne Morey, an associate professor at the University of NSW and director of anatomical pathology at St Vincent's Hospital in Sydney, explains the role of the pathologist in reducing the number of unnecessary axillary lymph node dissections.

"We call it a 'sentinel node biopsy'. The lymph nodes are the first place where cancer cells will metastasise to, the first port of call, but different parts of the breast will drain to different nodes, so before the operation the patient's breast is injected with a radioactive colloid. The colloid gets into the first draining node and then during the surgery the surgeon will pass a Geiger counter over the area.

"If they find a 'hot' node, they take it out and send it to pathology for assessment. We prepare a frozen section to see if cancer cells are present in this 'sentinel node', and if they are, the surgeon will remove additional nodes. If the sentinel node is negative, it saves an unnecessary axillary dissection, but it relies on the pathologist to look for microscopic deposits of cancer."

With the surgical phase completed, the management team will look at preventing the cancer from recurring. For this they will return to the pathologist's original report about what influences the growth of the patient's particular type of cancer cells.

Firstly, they will consult the report for the cancer's hormone receptor status. Two hormones produced by the ovaries, oestrogen and progesterone, can stimulate the growth of abnormal breast cells. Cancer cells stimulated by hormones can be identified by testing them for a receptor: a protein found on the surface of cells that hormones attach to to cause growth and repair.

Breast cells can be positive or negative for either hormone, but knowing a breast cancer contains receptors helps direct treatment as cancers positive for receptors are more likely to respond to hormone therapy. The other receptor the pathologist is searching for is the HER-2 receptor. HER-2 is a gene that helps control how cells grow, divide and repair themselves, and about one in four breast cancers have too many copies of the HER-2 gene and produce excess HER-2 protein on the outside of the cancer cells.

Cancers with too many copies of the HER-2 gene tend to grow fast and have an increased risk of spreading, but Herceptin (*trastuzumab*), one of the first generation of targeted cancer therapies, binds to the HER-2 protein and reduces the effect.

Herceptin does not cure breast cancer but does reduce the risk of recurrence by about 30 per cent in patients with an early-stage breast cancer who are HER-2 positive. It is, however, extremely expensive, so before it can be prescribed patients must be tested for the gene.

"At the moment breast cancers are so different that treating two patients the same may only work for one. If we can target therapy to that type of cell, tailor the therapy to the patient's genes to knock out the cancer cells by knocking out the genes that make them grow, then we might be able to control the disease."

Until recently there were two main tests for HER-2: the IHC (ImmunoHistoChemistry) test and the FISH test (Fluorescence In Situ Hybridisation). The IHC test looks for the protein on the cell's surface while the FISH test uses fluorescent gene probes to look for the gene itself to see if it is present in high numbers ("amplified").

On October 1 this year the Federal Government accepted a recommendation from the Pharmaceutical Benefits Advisory Committee to list Herceptin on the Pharmaceutical Benefits Scheme for the treatment of patients with HER-2 positive early stage breast cancer following surgery, provided they tested positive for gene amplification. The advisory committee estimates this will be about 2100 patients each year.

The committee rejected the IHC test as the standard test for determining treatment eligibility despite it being cheaper and more widely available, after data from Australia and overseas indicated there were serious problems with its accuracy.

The use of fluorescent dyes, however, restricts the FISH test to laboratories with fluorescence microscopes and doesn't allow the results to be preserved for future reference (the fluorescent signal quickly decays).

"There are a number of problems with the FISH test: it is certainly a time-consuming, labour intensive and expensive technique, but there is a new alternative that satisfies the (committee's) requirement," says Dr Morey, who is referring to the CISH test.

Using peroxidase enzyme to detect HER-2 gene amplification under a normal light microscope, the Chromogenic In Situ Hybridisation (CISH) test allows slides to be stored at room temperature without loss of signal. It correlated well when tested in five Australian laboratories against breast cancers where the HER-2 status was already known.

Roche, the maker of Herceptin, is funding the establishment of several CISH testing laboratories over the next four years, and pathologists will continue to assess and research new tests and treatments.

"The discovery of the importance of hormone receptors and, now, the HER-2 gene have made it very apparent that breast cancer is not just one disease," Dr Morey says. "Recent research suggests there are at least five or six subtypes based on molecular profiles, and in the future we will need additional molecular assays to sub-classify breast cancer and be able to provide more accurate prognostic information."

For Professor Bilous the hope is to one day develop a test that will detect cancer without requiring the pathologist to examine cells.

"A lot of people want to look at a breast from the outside and detect the cancer and know what type it is, but we're not even close to that," he says. "Unfortunately, at this stage the only reliable way to diagnose the disease is to get a sample of the cells and then try to quickly and accurately prepare the report and, hopefully present it the same day.

"The cutting-edge research is really focussed on what makes breast cancer cells act the way they do: looking at the genes that control their growth. At the moment breast cancers are so different that treating two patients the same may only work for one. If we can target therapy to that type of cell, tailor the therapy to the patient's genes to knock out the cancer cells by knocking out the genes that make them grow, then we might be able to control the disease."

BREAST CHANGES – WHAT TO LOOK FOR

- A lump or lumpiness.
- Any change in the shape or appearance of the breast such as dimpling or redness.
- An area that feels different to the rest.
- Discharge from the nipple.
- Change in the shape or appearance of the nipple: pulling in or scaliness.
- Pain.

The vast majority of women who undergo the triple test are negative for breast cancer but it is vital that all breast changes are carefully investigated. If it is cancer, early detection will drastically improve the chances of effective treatment.