



PathWay

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA



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Issue #031

In This Issue

- Male 'Pap smears' help detect anal cancer earlier
- Brain cancer needs some happy endings
- Philanthropists fund two fellowships to help find dementia cure
- HbA1c helps pin down 'medical flibbertigibbet' but it has its moments

Interesting Facts

1 per
100,000

The incidence of anal cancer in the general population in Australia

Introduction

Here's a term you don't hear every day – male Pap smears! Our article explains why they are so useful in detecting early signs of anal cancer, and why they will help create more happy endings.

Happy endings are unfortunately few and far between when it comes to brain cancer, and our article explains why. We also look at how two fellowships worth almost \$2 million could take us one step closer to finding a cause and potential cure for two forms of dementia - Alzheimer's disease and frontotemporal dementia. And finally, the limitations associated with a popular test for diabetes – the HbA1c – are explained.

Thank you to all of the people who have 'liked' our Facebook page. You've already discovered the wealth of information available such as a link to watch an episode of ABC's Catalyst where Professor David Sullivan (one of our Fellows) lends his expertise to the debate about cholesterol and saturated fat and its association with heart disease.

If you haven't 'liked' our Facebook page yet, and want to join the online pathology community, then go to www.facebook.com/TheRoyalCollegeOfPathologistsOfAustralasia, or follow our CEO Dr Debra Graves (@DebraJGraves) or the College (@PathologyRCPA) on Twitter.

Male 'Pap smears' help detect anal cancer earlier

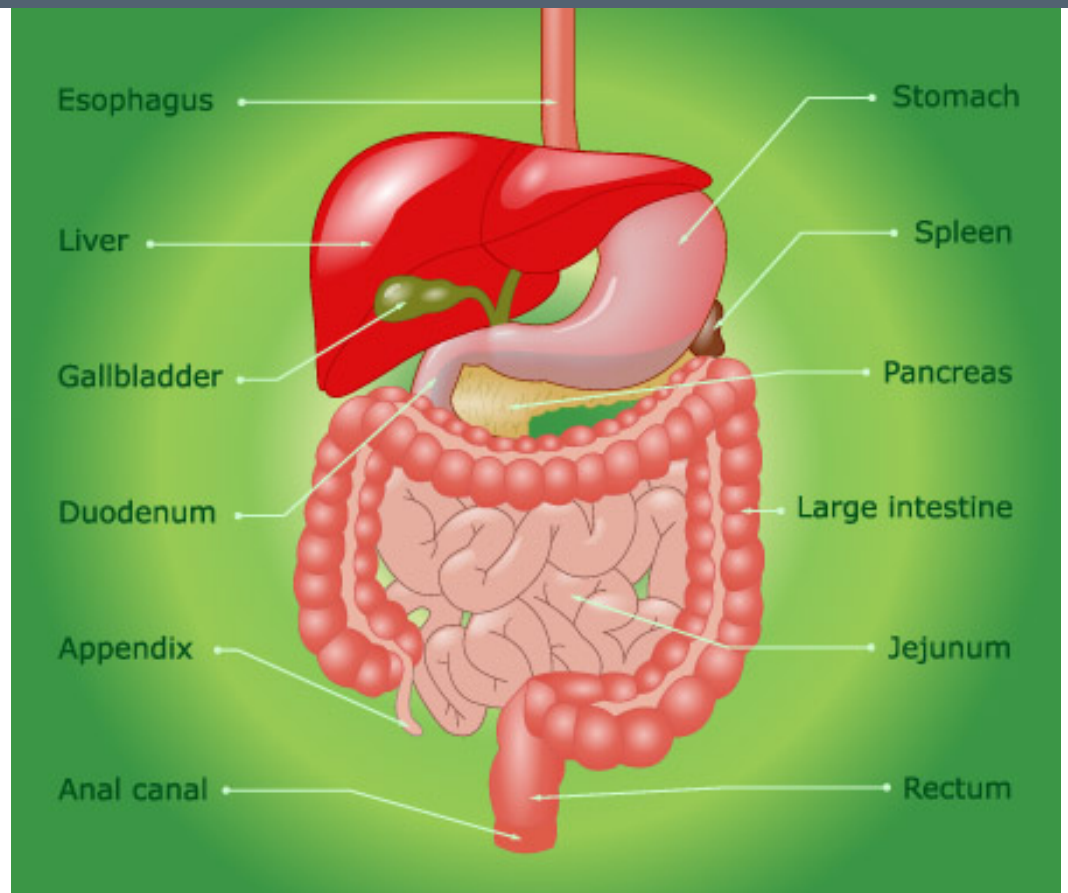
35 per
100,000

The incidence of anal cancer in "never married" men (pre-HIV) in Australia

60 per
100,000

The incidence of anal cancer in HIV-positive men who have sex with men (MSM) in Australia

Source: The University of Sydney – Western Sydney Sexual Health



This article has more than its fair share of uncomfortable words such as anal cancer, male 'Pap' smears, cervical cancer, human papilloma virus^[1] (HPV), anoscopy and human immunodeficiency virus^[2] (HIV). But if you join the dots between what these words represent, you'll find a picture of an uncommon form of cancer able to be detected early.

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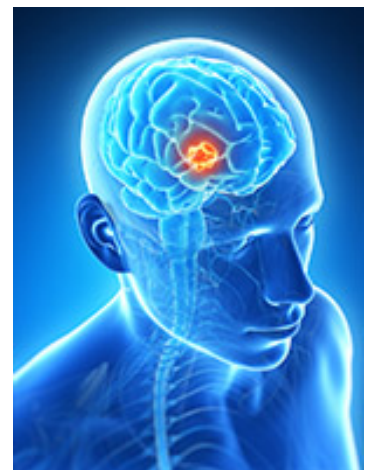
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Brain cancer needs some happy endings

When it comes to brain cancer, there are few '... and they lived happily ever after' endings. Dr Janice Brewer, histopathologist at Royal North Shore Hospital, says there has been no significant improvement in patient survival statistics for the past 30 years, despite better diagnostic and treatment regimes, due to lack of funds for robust research into the causes and potential cures for brain cancer.



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Philanthropists fund two fellowships to help find dementia cure

Two new fellowships worth almost \$2 million have been donated to the Queensland Brain Institute (QBI) to fund research aimed at better understanding learning and memory. Professor Jürgen Götz, Director of the Clem Jones Centre for Ageing Dementia Research (CJCADR) within the QBI, says the fellowships will focus on two forms of dementia - Alzheimer's disease^[1] and frontotemporal dementia.



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HbA1c helps pin down 'medical flibbertigibbet' but it has its moments

Our blood glucose levels fluctuate from minute-to-minute, hour-to-hour and day-to-day, depending on factors such as diet and exercise, making it a medical flibbertigibbet. A pathology test called an HbA1c^[1] can pin them down, but it's not perfect. The skill is in knowing when to question the result.



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ISSUE #030

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- RCPA Fellow's significant contribution to women's health recognised by RANZCOG
- Being medicine wise is important when you are dealing with Deadmen's bells
- Haemophilia Awareness Week promotes awareness and busts myths about

Introduction

Congratulations to Dr Annabelle Farnsworth who has received an Honorary Fellowship to the Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Our story on Dr Farnsworth highlights why this honour is well deserved.

We have also noted two important events – Haemophilia Awareness Week (13-19 October) and Be Medicinewise Week (14-20 October) – with articles on haemophilia and the importance of monitoring digoxin medicine levels.

Our final article gives a round up of botulism in the wake of the botulism scare that happened in New Zealand earlier this year (and we haven't left Botox out of the story!)

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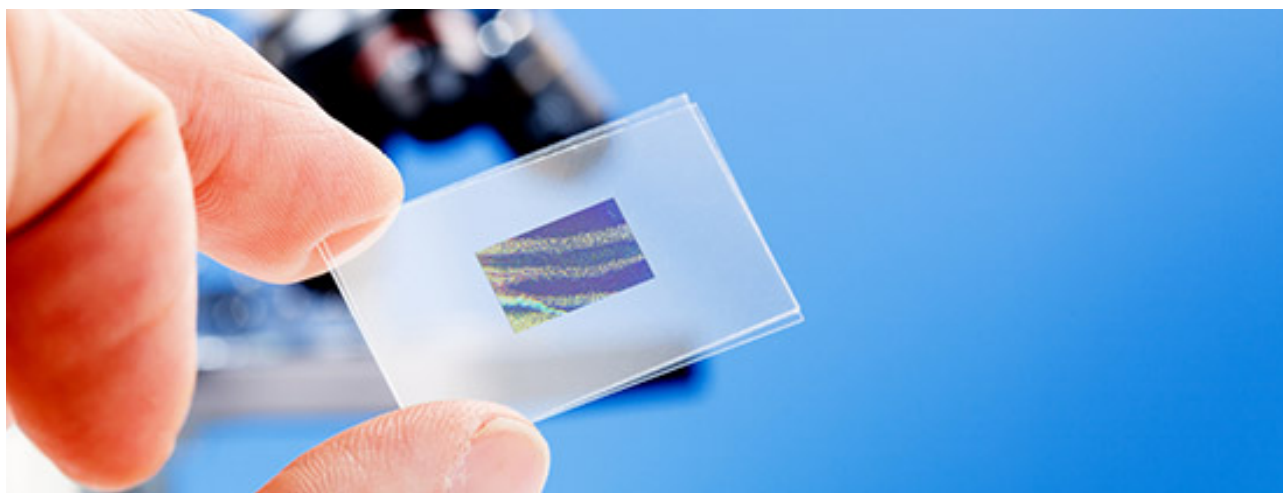
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Male 'Pap smears' help detect anal cancer earlier



This article has more than its fair share of uncomfortable words such as anal cancer, male 'Pap' smears, cervical cancer, human papilloma virus^[1] (HPV), anoscopy and human immunodeficiency virus^[2] (HIV). But if you join the dots between what these words represent, you'll find a picture of an uncommon form of cancer able to be detected early.

Anal cancer develops in the last 5cm of the bowel. Risk factors include certain types of anal wart virus infections, anal intercourse, smoking cigarettes, a history of an abnormal Pap smear^[3], increasing age (unless you are HIV positive) and HIV infection.

While both men and women can develop anal cancer, Dr Jeanine Bygott, clinical microbiologist at Sullivan Nicolaides Pathology in Brisbane, says the group most at risk is men who have sex with men (MSM) who are also HIV positive.

"Anal cancer incidence rates in this group vary up to 100 times that of low-risk heterosexuals," explains Dr Bygott. "There is a 74% prevalence rate of cancer causing or oncogenic-type HPV infection among HIV-positive MSM, and a rate of 37% among MSM who are not HIV positive. Persistent HPV infection can cause high-grade abnormalities in the anal epithelial cells which are believed to be the precursors of anal cancer."

Dr Bygott says anal cancer is analogous with cervical cancer in that 100% of cervical cancer and about 90% of anal cancer is caused by HPV infection.

“There are a number of different oncogenic types of HPV, but the two main causes of both cervical and anal cancers are HPV types 16 and 18. Both of these strains, as well as HPV types 6 and 11 which cause genital warts, are represented in the HPV vaccine.”

Dr Bygott says vaccination given prior to a person’s sexual debut is an important primary preventative measure for anal cancer. Secondary prevention involves detecting abnormal cells in a process best described as a ‘male Pap smear’.

“Doctors take a swab of the anus and this swab is sent to a pathology laboratory for analysis,” she says. “It’s the same process as a Pap smear for women in that pathologists are looking for abnormal cells and pre-cancerous changes in the anal smear on a slide.”

Dr Bygott says about 30% of MSM who are HIV-positive return high-grade pre-cancerous abnormalities due to HPV infection, but this doesn’t mean they will progress to anal cancer.

“Abnormal changes can regress over time. About 40 to 50% of women who have moderate abnormalities on their Pap smear regress and go on to have normal smears without any treatment. The problem is that we don’t know how many of the abnormal changes detected with anal smears will similarly regress over time because we don’t know enough about the natural history of anal HPV infection.”

Dr Bygott says if an abnormality is found in an anal smear, the person is usually referred for a high-resolution anoscopy (HRA) where a specialist doctor looks inside the anus with a high-powered microscope. The female equivalent is a colposcopy which looks at the cervix in the same way.

If high-grade abnormalities are found in women then extensive areas of the cervix are normally removed and the cervix rapidly regenerates. If anal cancer is found then you can’t remove the anus, and this presents a conundrum of what happens next. Treatment can be toxic causing pain and narrowing of the anus (anal stenosis), and the lesions often recur.

“There is also the issue that only about one to two percent of women with abnormal Pap smear changes go on to have a colposcopy. In contrast, about 30% of high-risk men would progress to a HRA. This strategy would potentially lead to overtreatment of very large numbers of MSM because only a small proportion will actually develop anal cancer. Trials are currently underway looking at the validity of screening for anal cancer,” explains Dr Bygott.

While the benefits and risks of screening are investigated, primary and secondary preventative measures remain available for anal cancer. And even though it is an uncomfortable topic, when you join all the relevant words and their meanings together, the overall picture is brighter than it seems for early detection of anal cancer.

[1] HPV and cervical cancer is covered in [ePathWay Issue 002](#) and [ePathWay Issue 027](#)

[2] HIV is covered in [ePathWay Issue 005](#)

[3] Pap smears is covered in [ePathWay Issue 008](#)

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Brain cancer needs some happy endings



When it comes to brain cancer, there are few ‘... and they lived happily ever after’ endings. Dr Janice Brewer, histopathologist at Royal North Shore Hospital, says there has been no significant improvement in patient survival statistics for the past 30 years, despite better diagnostic and treatment regimes, due to lack of funds for robust research into the causes and potential cures for brain cancer.

“Most brain cancers are very aggressive in nature and there is no known cause or cure,” she says. “Many people think that using mobile phones is linked to brain cancer, but this link has not been proven. Some cases are related to radiation from treatment for other brain cancers, but there are no identifiable risk factors and no absolute causes known for the vast majority of cases.”

Dr Brewer says brain cancer survival is measured in months, or a few years at the most. This situation may not change anytime soon, because brain cancer doesn’t have the same ‘community’ profile as many other cancers making lobbying for research funds difficult. Research is needed because:

- Brain cancer is the leading cause of cancer death in children.

- It strikes adults and children alike, with the incidence highest in adults in the prime of their life.
- It has no clearly identified risk factors and no screening procedures are in place.
- It includes high-grade glioma which is the most common and most aggressive brain cancer.
- One person is diagnosed with brain cancer every six hours and one person dies from brain cancer every eight hours in Australia^[1].

Brain cancer usually goes undetected until symptoms occur when the cancer may be quite advanced. Dr Brewer says symptoms might include an epileptic fit in someone who does not usually have them, or a stroke in an elderly person due to a bleed into the brain from the cancer. There might also be localised signs such as numbness in an arm or changes in vision.

“Once the presence of a brain lesion is confirmed, the surgeon may take a biopsy or try and remove it completely, and send the brain tissue to a pathologist,” says Dr Brewer. “Pathologists advise the surgeon and treating physician if it is cancer or something that mimics cancer, such as an abscess. If it is cancer then we inform them of the type and grade, and if it is a primary or secondary cancer.”

Dr Brewer says pathologists can tell the difference between a primary cancer (one arising from brain cells) and a secondary cancer (one which has spread, or metastasised, from somewhere else) based on its appearance.

“Cancers mimic the tissue from which they originated. So, if it is a cancer that originated in the bowel that has metastasised to the brain, then the cancer tissue will look like bowel tissue that is located in the brain. But the cells look more bizarre and disorganised compared to normal bowel tissue.”

Dr Brewer says pathologists also run a panel of genetic and molecular tests to check for genetic alterations. All of this information informs the patient’s medical team about the best treatment options, including their predicted response.

Treatment is available in the form of surgery, chemotherapy and radiotherapy in varying combinations, although Dr Brewer says brain cancers have a terrible toll because testing and treatment is very expensive. This places an enormous financial burden on families, especially if the person who has the cancer is unable to continue working due to side effects such as altered mental function. And if that’s not bad enough, almost everyone who has brain cancer eventually dies from it. This is because the cancer cannot be completely eradicated and usually recurs, dashing any hopes of a ‘happily ever after’ ending.

[1] Taken from http://www.cureforlife.org.au/brain_cancer_facts_and_statistics/

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Two new fellowships worth almost \$2 million have been donated to the Queensland Brain Institute (QBI) to fund research aimed at better understanding learning and memory. Professor Jürgen Götz, Director of the Clem Jones Centre for Ageing Dementia Research (CJCADR) within the QBI, says the fellowships will focus on two forms of dementia - Alzheimer's disease ^[1] and frontotemporal dementia.

"The \$1.4 million QLD Freemasons Senior Research Fellowship in Learning and Memory ^[2] will fund an outstanding researcher over a period of about five years to complement our ongoing studies and work on aspects of dementia in a broader sense," explains Prof Götz. "The \$500,000 Peter Hilton Research Fellowship in Ageing Dementia ^[3] will support an outstanding early career researcher for five years to look at key proteins implicated in brain function."

While dementia research is dotted with breakthroughs, the bigger picture of a definitive cause and a cure remain elusive. Dementia is a progressive brain disorder that affects a person's ability to function normally. Around 280,000 Australians currently live with the illness, and this may rise to almost one million by 2050 and cost around \$83 billion without a significant breakthrough.

“The CJCADR aims to find the pathological mechanisms and changes to the brain, determine the role of proteins implicated in the neurodegenerative process in a physiological and pathological context, and to develop therapies and biomarkers^[4],” explains Prof Götz.

He says research currently seesaws between examining animal and synthetic models that mimic the human experience of dementia and actual human brain tissue.

“We source brain tissue from brain banks in Australia and from overseas which is examined in our own histology laboratory located at the QBI,” says Prof Götz. “We also collaborate with neuropathologists and neuroanatomists in Brisbane, Sydney, Germany, and Switzerland.”

Prof Götz says we all know what the end stage of dementia looks like, so his centre’s research is retracing the steps that led to that end stage, and examining every anomaly along the way.

Finding these anomalies is a herculean task. A healthy human brain contains about 100 billion neurons, and each of these is connected to 1000 other neurons. The neurons in a person with dementia switch off and die, but it’s a lot of connections to examine and rewind. No wonder images of needles and haystacks come to mind.

“We have had some success. For example, we have found a protein that is normally located in the nucleus of a cell forming aggregates in the cytoplasm of people with dementia. This protein is important for brain function by regulating gene expression. Perhaps the researchers who are offered the fellowships will understand how proteins and genes associated with dementia impact on neuronal functions and ultimately impair learning and memory.”

A breakthrough for this devastating illness is needed soon. For example, Alzheimer’s disease is the third leading cause of death in Australia after heart disease and stroke, and one in four people over 85 suffer from it. Thanks to philanthropic generosity, these two fellowships will help move us closer to that elusive breakthrough that may eventually lead to a cure.

[1] Alzheimer’s disease is also covered in [ePathWay Issue #012](#)

[2] Jointly funded by the charitable arm of the Freemasons Queensland, the Board of Benevolence of Aged Masons, Widows and Orphans’ Fund, and UQef which is a private fund established by Wotif.com founders Andrew Brice and Graham Wood

[3] Funded by Robyn Hilton in memory of her late husband Peter Hilton

[4] A biomarker is a protein measured in blood, and its concentration reflects the severity or presence of some disease state.

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HbA1c helps pin down 'medical flibbertigibbet' but it has its moments



Our blood glucose levels fluctuate from minute-to-minute, hour-to-hour and day-to-day, depending on factors such as diet and exercise, making it a medical flibbertigibbet. A pathology test called an HbA1c^[1] can pin them down, but it's not perfect. The skill is in knowing when to question the result.

"There is a rapidly growing awareness that the HbA1c test has some issues in terms of providing an accurate result if the patient has certain conditions," explains Dr Graham Jones, chemical pathologist at SydPath in Sydney.

Before we move on to these conditions, it's important to understand what the HbA1c test measures. Red blood cells contain a molecule called haemoglobin (Hb). Glucose sticks to Hb to make a glycated^[2] Hb molecule called HbA1c. The more glucose there is in the blood, the more HbA1c will be in the blood.

When a blood sample is collected it contains red blood cells from one day to four months old, with an average age of about eight weeks. The amount of HbA1c produced depends on the average blood glucose level over that period of time. Problems can therefore occur when a person has a condition that affects their red blood cells or Hb.

“If a person has a condition where red blood cells don’t live as long as they should then you can get a falsely low HbA1c result,” says Dr Jones. “Examples include chronic kidney disease, severe liver disease, haemolytic anaemia, some forms of thalassaemia and certain drugs which can lead to haemolysis (breaking the red blood cell open).”

Dr Jones says recent bleeding prompting new red blood cells to form can also lead to a falsely low HbA1c result. This is because the new cells have been exposed to glucose molecules for a shorter period of time.

“Iron and B12 deficiency can lead to a falsely elevated HbA1c result, although the result goes down when these conditions are treated. Recent blood transfusions also make the HbA1c test result invalid because it is essentially measuring another person’s blood components, as well as the effect of storing the blood.”

Haemoglobinopathies or haemoglobin disorders can also affect an HbA1c test result. These disorders encompass all genetic diseases associated with haemoglobin, can present in many different ways and range from completely asymptomatic, through very mild (such as mild hypochromic anaemia) to severe, lifelong, transfusion-dependent anaemia affecting many organs. About seven percent of the world’s population are carriers of haemoglobin disorders making them a major world health problem.

“Most haemoglobin disorders shouldn’t cause problems in modern test methods, although some of the less common abnormalities which cause shorter red blood cell survival can be an issue,” says Dr Jones. “There are over 600 haemoglobin disorders and most are very rare. Patients may not know they have one of these disorders and it may not be picked up in the HbA1c test method, which in some cases means they can lead to a false result.”

Dr Jones says the cautionary tale with HbA1c tests is that if a patient’s regular blood glucose measures don’t match the HbA1c result, then conditions that affect the test result should be considered.

“For example, if a diabetic person’s finger prick tests are consistently high, but their HbA1c result is normal, then there is a disconnect. You therefore have to investigate which test result is wrong, and to also know when to question a HbA1c test result in terms of conditions present which can render the result invalid,” cautions Dr Jones.

While the HbA1c is still regarded as one of the best ways to check whether diabetes^[3] is under control, it does have its moments. It is therefore important to remember that an HbA1c result is not the same as a blood glucose level. The skill is in knowing when to question the result and look for conditions that affect a person’s red blood cells and Hb levels.

[1] The HbA1c test is also covered in [ePathWay Issue #018](#)

[2] The proces of adding sugar units to proteins

[3] Monitoring diabetic health is also covered in [ePathWay Issue #002](#)

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