



PathWay

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA



Issue #032

DECEMBER 2013/JANUARY 2014 | Published by RCPA

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- Solid evidence should be the catalyst for change when it comes to heart disease
- Study finds sunscreen protects our superhero gene
- Natural disasters reach further than the eye can see
- Genetic revolution may turn hopes and Christmas wishes into reality

Interesting Facts

About
1.4
million

The number of Australians affected by heart disease.

Introduction

The holiday season is here and Christmas is just days away. Before you tuck into Christmas dinner, check out our article on the facts about heart disease, dietary fats and cholesterol.

You might also slather sunscreen on with extra vigour these holidays after reading our article about how it protects our superhero gene.

We also look at how medical services – including pathology – are rebuilt after natural disasters in the wake of typhoon Haiyan. And for some families, increased genetic capability will deliver a much-awaited diagnosis for their child's neurodevelopmental disorder. Our article explains how.

We also have a new-look College website. Check it out at www.rcpa.edu.au.

And finally, thank you to the ePathWay editorial team – including our four wonderful pathologists – who guide this eMagazine's editorial content throughout the year.

Merry Christmas from the ePathWay team. We'll be back with more articles in February. Don't forget to check in to our Facebook page - www.facebook.com/TheRoyalCollegeOfPathologistsOfAustralasia - over the holidays to keep in touch with the pathology community, and follow our CEO Dr Debra Graves (@DebraJGraves) or the College (@PathologyRCPA) on Twitter.

Solid evidence should be the catalyst for change when it comes to heart disease

59

The number of Australians who die each day from heart disease. This equates to about one person every 24 minutes.

1 in 4

The number of adult Australians who have three or more risk factors for heart disease.

Source: National Heart Foundation of Australia

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- 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

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.

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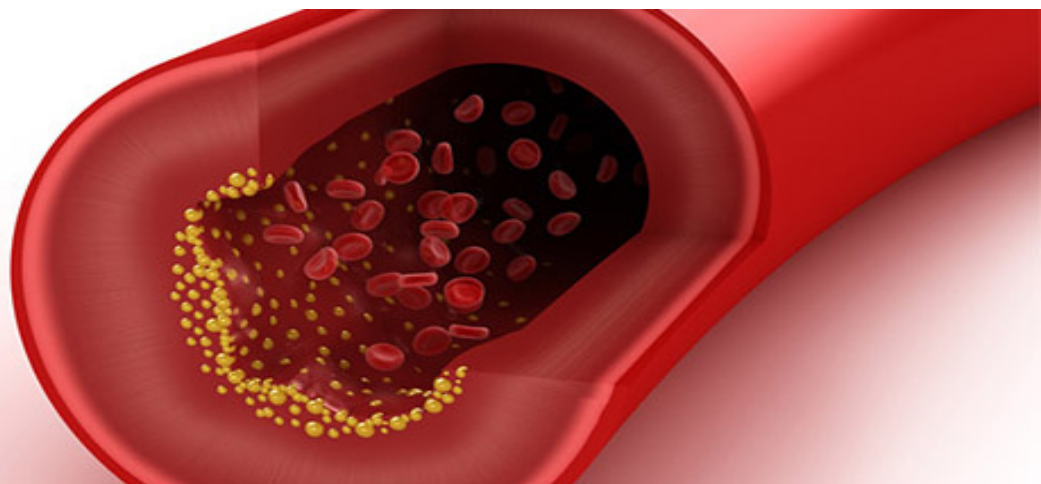
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Solid evidence should be the catalyst for change when it comes to heart disease



The debate about the relationship between saturated fat, cholesterol^[1] and heart disease raised by two Catalyst programs^[2] ruffled a few feathers. Open debates about health and causes of disease are important, but it's equally important not to lose sight of known facts. Associate Professor David Sullivan^[3], who was interviewed by the program's presenter, has shared these facts about dietary fats, cholesterol and heart disease.

"To provide accurate advice on public health in the areas of diet and therapy, you need to understand the pathology of atherosclerosis (a build up of plaque in the arteries) in terms of managing morbidity (illness) and mortality (deaths)," explains A/Prof Sullivan, chemical pathologist at Sydney South West Pathology and physician at the Royal Prince Alfred Hospital.

"Atherosclerosis is a multifaceted process and the inflammatory process is only a part of the picture. For example, we know that decreasing lipoproteins leads to favourable changes in terms of providing protection against plaques forming on artery walls."

Plaque is made up of cholesterol and cells derived from the blood as well as connective tissue produced by the artery wall. Lipoproteins carry cholesterol – which can't dissolve in the blood - throughout the bloodstream where it is delivered to cells. If there is too much bad cholesterol (low-density lipoprotein) then it penetrates the artery wall where it undergoes a chemical change called oxidation, and becomes a source of inflammation. This leads to a pimple-like collection of debris under the thin lining of the artery wall which makes the atherosclerotic plaque 'vulnerable'. These vulnerable plaques may rupture resulting in blockage of the vessel leading to a heart attack or stroke.

“Cholesterol levels are only a part of the picture when it comes to heart disease. For example, there has been a shift in the pattern of risk factors over the past 20-40 years in response to changing diets and the types of fats consumed. We also know that about 50 percent of all heart attacks are due to disturbances in a person’s blood lipid (fat) profile,” explains A/Prof Sullivan.

“We also have increased obesity levels and a corresponding increase in blood triglyceride levels. We now know that triglycerides suck cholesterol out of LDL particles in obese people. This means their damaging cholesterol levels appear to be lower or even normal, when the number of damaging particles has actually increased.”

Triglycerides are fuel in the form of insoluble fats transported with cholesterol in some lipoproteins. They can be elevated due to obesity or being overweight, physical inactivity, cigarette smoking^[4], excessive alcohol intake and a high carbohydrate diet. Most of these risk factors can be modified through healthy lifestyle choices.

The variables that don’t change are a person’s age, gender and family history. A/Prof Sullivan says that these, and all other risk factors, as well as a person’s overall blood lipid profile, including cholesterol levels and fractions^[5], should be taken into account before they are prescribed cholesterol-lowering treatment known as statins.

“There is very strong evidence that the cholesterol lowering effect of statins provides protection against heart disease,” he says. “Several statin trials were conducted by academic institutions and not drug companies, including in Australia, and there is overwhelming evidence for their benefit and safety in patients with and without prior heart disease. Perhaps the targeting of statin therapy could be improved, but they are valuable for patients with a high absolute risk of heart disease.”

Statins are only one part of the heart health picture, as are saturated fats and cholesterol. It’s a complex area of interwoven physiological causes and effects. So, while the ruffled feathers are settling from the current debate, you can access reliable advice on heart health through the Heart Foundation at <http://www.heartfoundation.org.au/Pages/default.aspx>.

[1] Cholesterol is covered in [ePathWay Issue 006](#) and [ePathWay Issue 024](#)

[2] Catalyst aired two programs: Heart of the Matter Part 1: Dietary Villains on 31 October 2013, and Heart of the Matter Part 2 - Cholesterol Drug War on 1 November 2013

[3] Further commentary by A/Prof Sullivan can be found at <http://www.abc.net.au/catalyst/heartofthematter/default.htm>

[4] Smoking is covered in [ePathWay Issue 029](#)

[5] The ratios between 'good' cholesterol (high-density lipoprotein), 'bad' cholesterol and triglycerides

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Study finds sunscreen protects our superhero gene



Applying sunscreen this summer might have more meaning since researchers^[1] found it also shields our 'superhero' gene that protects us from developing skin cancer^[2]. When our skin's cells are damaged by ultraviolet (UV) light, the p53 gene repairs the damage and prevents skin cancers occurring. But even superheroes need protection so they can do their job properly.

"The p53 gene is the guardian of the genome and is present in every cell in our body," explains Professor Richard Scolyer, skin pathologist at the Royal Prince Alfred Hospital (RPAH) and Melanoma Institute Australia. "Its role is to repair damaged genes that can mutate and lead to cancer, including mutations that lead to skin cancer."

Researchers from the Queensland University of Technology (QUT) in Brisbane discovered the link between sunscreen and the superhero gene when they assessed the impact of sunscreen on human skin at the molecular level. They found no evidence of UV-induced skin damage³ when SPF30+ sunscreen was properly applied to the exposed area, including no DNA changes to the skin and no impact on the p53 gene.

"The p53 gene can be damaged by UV light, and the more damage that happens to it, the less effective it will be to help repair and prevent skin cancers," says Prof Scolyer.

“This means if a mutated cell divides, there might be nothing to fix it if the p53 is also damaged. The mutated p53 gene might not cause skin cancer, but it can lead to cancer developing if other genes are damaged and it can't recognise there is a problem and repair them.”

Prof Scolyer says this research provides further evidence that sunscreen helps to prevent skin cancer.

“It also reinforces the complete sunsmart message including using physical barriers such as protective clothing and hats when you are in the sun, seeking shade, using sunglasses and applying broad spectrum 30+ or greater sunscreen.”

[1] <http://onlinelibrary.wiley.com/doi/10.1111/pcmr.12157/full>

[2] [Skin cancer is covered in ePathWay Issue 009](#)

[3] [Sunburn is covered in ePathWay Issue 010](#)

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Peter McMinn, clinical microbiologist and Bosch Professor of Infectious Diseases at the University of Sydney, has been up close and personal with the aftermath of natural disasters before. He helped rebuild Aceh's pathology capability after the 2004 tsunami, and knows first hand about the medical and social issues that arise from natural disasters.

"About 60 to 70 percent of the pathology laboratory staff were killed in the Aceh tsunami, and those who survived were often too traumatised to work. A number of international and bilateral organisations sent medical teams to Aceh to take over in the short term and build capacity again," he says.

While the dead and injured are the visible toll of natural disasters, countless others suffer in different ways. Cancer patients' biopsy results can be blown away with the pathology laboratory. Diabetic patients can't access insulin, blood sugar level monitoring equipment or enough food to stabilise their blood sugar levels. Women with high-risk pregnancies may need to give birth without adequate medical support or even a clean sheltered place to labour. People with chronic illnesses are cut off

from pathology laboratories, test results and medicines. And people with compromised immune systems run the gauntlet of a highly infectious environment.

“People who have a chronic illness certainly suffer because medical records are lost and there is an interrupted drug supply,” explains Prof McMinn. “There is certainly a mortality associated with these situations, and it’s important that people with a chronic illness, or their families, identify themselves as soon as possible to international medical teams.”

The Global Outbreak Alert and Response Network (GOARN), run by the World Health Organization, coordinates a number of international medical teams - including pathologists.

“Pathologists are integral to post natural disaster medical care, especially for diagnosing and monitoring infectious diseases,” explains Prof McMinn. “I led a team of pathologists into Aceh, and I have received an inquiry from GOARN about my availability for the Philippines.”

Prof McMinn says the first priority for an international pathology team will be to determine what spaces can be used as a laboratory, and where the closest functioning health centre is located. These resources are needed for the important work that follows.

“Pathologists monitor diarrhoeal diseases such as cholera which thrive when water and sanitation systems break down. Wounds exposed to contaminated water can become infected with water-based organisms which must be identified so the correct treatment can be given. Infectious diseases such as measles can also spread quickly due to overcrowding in relief shelters or camps, and these must be monitored, diagnosed and treated.”

Prof McMinn says many children are immunised against diseases such as measles in these situations to try and contain the spread of disease. Other diseases and infections must be identified and treated as quickly as possible. For example, tetanus and pneumonia from inhaling dirty water were prominent after the Aceh tsunami.

Medical assistance doesn’t end when the debris is cleared, the wounded are treated and the dead are buried. Prof McMinn stayed in Aceh for two years to help rebuild their pathology capacity. This means medical assistance to the Philippines will continue long after the situation has dropped out of the international news feeds.

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Some Christmas wish lists might include jewellery, season tickets to the theatre or perhaps a few bottles of fine wine. Others might include a definitive diagnosis for their child's neurodevelopmental disorder. Thanks to advances in genetic technology and capability, this sort of wish has finally advanced from hope to reality.

Dr Damien Bruno, laboratory geneticist at the Victorian Clinical Genetics Services and a Fellow of the Faculty of Science at the Royal College of Pathologists of Australasia (RCPA), says you can't understate how valuable a diagnosis is to families.

"Many people have been on a diagnostic odyssey to try and find a name for their child's genetic disorder," he says.

Dr Bruno says neurodevelopmental disorders is an umbrella term for a range of conditions including the autism spectrum, developmental delay and intellectual disability. Diagnostic capability traditionally focused on large chromosome disorders such as trisomy 21 (Down syndrome), but better technology has enabled geneticists to delve further into the genetic causes of these conditions.

"Up until recently, diagnosing conventional chromosome abnormalities involved looking down a light microscope," he explains. "Advances in genomics technology, and specifically the availability of DNA microarrays^[1], enables us to detect much smaller changes in DNA which lead to genetic abnormalities.

We weren't able to detect these changes with traditional light microscopy.”

These smaller changes - some so small that they involve single genes - are known as copy-number variants. Pathogenic copy number variants have been associated with a myriad of genomic disorders or syndromes. An example is DiGeorge syndrome (also known as 22q11.2 deletion syndrome) which results in the poor development of several body systems. Schizophrenia has also been linked to a range of copy-number variants.

The success of the current raft of genetic capability and technology, such as microarrays, means about 12 to 15% more cases have a definitive diagnosis for their neurodevelopmental disorder - but scientists have only just begun. Dr Bruno says there is now an increased demand for prenatal diagnosis when a copy-number variant of known or suspected clinical significance is detected in a family. Parents as a group also want wider and more comprehensive pre-natal genetic screening tests.

“Parents who are confronted with an abnormal fetal ultrasound scan, or who have a concern based on family history, are choosing to have prenatal microarray tests,” says Dr Bruno. “Interpretation of the clinical significance of many copy number variants in the prenatal situation is not straight forward due to variable phenotype^[2] amongst affected patients described in the literature. Each person's phenotype may be expressed differently and sit on a spectrum of severity.”

While most genetic testing for neurodevelopmental disorders occurs in early childhood, Dr Bruno says there are legacy cases where people are seeking a diagnosis as an adult because this technology was not available to them during their childhood.

While the closure and relief associated with a definitive diagnosis is very important, the elephant in the room going forward is the clinical and ethical aspects of increased genetic testing capability. However, Dr Bruno says these dilemmas are the same as those traditionally faced when screening for large chromosome disorders (such as Down syndrome), but there will simply be more cases where they apply.

Dr Bruno says the other issue going forward is the lack of good information available on the predictive value of the copy-number variants in terms of how they will be expressed. But this bridge will probably be crossed in due course because genetics is a rapidly evolving work in progress. In the meantime, let's hope more people can cross a definitive diagnosis for their child's neurodevelopmental disorder off future Christmas lists because that wish was finally achieved.

[1] A DNA microarray is a collection of microscopic DNA spots attached to a solid surface.

[2] Observable characteristics of a person which result from the expression their genes as well as the influence of environmental factors, and the interactions between the two.

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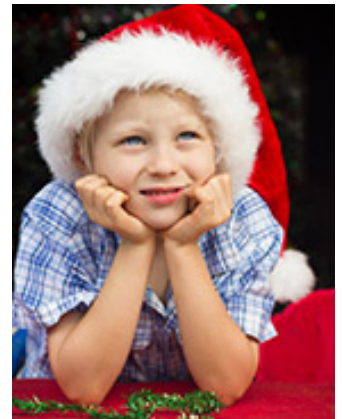
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