



# PathWay

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA



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Issue #027

## In This Issue

- The 'hygiene hypothesis' is more than a 'dirty' story
- Diagnosing vasculitis can be a tricky business
- Mass or molar? It's time to end the impasse to increase patient safety
- Star factor puts HPV induced head and neck cancer into the spotlight

## Interesting Facts

15-30%

The percentage of children affected by atopic dermatitis in industrialised countries

## Introduction

Winter is well and truly here although spring is just weeks away. Before you make plans for spring-cleaning you might like to read the article on the hygiene hypothesis and how we've cleaned ourselves into a corner (hypothetically speaking).

We've also looked at vasculitis\* and why it's such a tricky disease to diagnose, as well as the link between the human papilloma virus and head and neck cancer.

Our final article this month looks at why reporting concentrations of therapeutic drugs will become a safer proposition when the recommendations of an expert working party are adopted across Australia and New Zealand.

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Diary Note: \*The 2nd Brisbane Vasculitis Seminar for doctors is on Saturday August 31 at the Brisbane Airport Motel from 2-6pm. For more information contact Dr Claire Barrett at [jacksonbarrett@optusnet.com.au](mailto:jacksonbarrett@optusnet.com.au) or ph 07 3284 5035.

## The 'hygiene hypothesis' is more than a 'dirty' story

## More than 15%

The percentage of children in the United Kingdom, New Zealand and Australia who suffer from asthma

## More than 1000

The estimated number of species of bacteria that live in the human gut

Source: Okada H, Kuhn C, Feillet H and Bach J-F. The 'hygiene hypothesis for autoimmune and allergic diseases: an update. Clin Exp Immunol. 2010 April; 160 (1): 1-9.



At first glance the 'hygiene hypothesis' seems straightforward. Developed countries have a cleaner lifestyle and therefore infectious illnesses are less common. As a result, our immune system seems to have shifted away from fighting infections to developing more allergic tendencies. But this explanation, according to Associate Professor Mimi Tang, is too simplistic.

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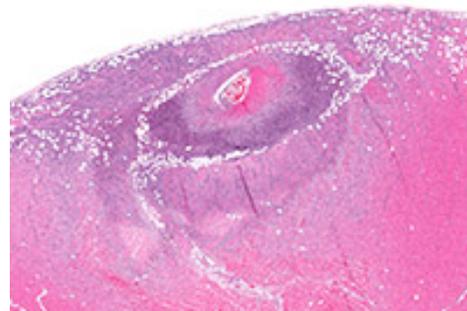


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## Diagnosing vasculitis can be a tricky business

Vasculitis is the name for a group of diseases that can affect any of the body's blood vessels – from the largest arteries to the tiniest veins. It has no specific risk factors, targets any age group and both sexes, and occurs when the body's immune system attacks its own blood vessels causing them to become inflamed and potentially close off. Vasculitis must also be diagnosed early to prevent damage to body organs.



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## Mass or molar? It's time to end the impasse to increase patient safety

Reporting concentrations of therapeutic drugs will become a safer proposition when the recommendations of an expert working party are adopted across Australia and New Zealand. Therapeutic drug concentrations are currently reported in either mass or molar units, depending on the policy of the laboratory, which introduces a risk point into the clinical interpretation of the pathology result.



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## Star factor puts HPV induced head and neck cancer into the spotlight

The case for human papillomavirus (HPV) as a cause of head and neck cancer has been building for decades, but it's barely made more than a small bleep on the public's radar - until now. Film star Michael Douglas was diagnosed with throat cancer caused by HPV a few years ago, and has recently shared the intimate details of how he contracted it making this issue international news.



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# ePathWay

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## Previous Editions



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### IN THIS ISSUE

- RCPA makes its position clear on when to test for vitamin D
- Structured reports for iron studies will provide a clearer picture
- Current coronavirus outbreak source is still a mystery

### Introduction

The inaugural Pathology Day (May 28) was a success with events held around the world. The winner of the iPad mini from the Royal College of Pathologists of Australasia (RCPA) for the best photos of their celebration in our part of the world is Dr Simone Van Es.

A compilation of Pathology Day events that have been advised to the College can be viewed at [Pathology Day winner](#).

Other Pathology Day events saw the RCPA and International Liaison of Pathology Presidents (ILPP) introduce a new statement surrounding international best practice in the diagnosis and management of cancer. RCPA Vice President Dr Michael Harrison

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## The 'hygiene hypothesis' is more than a 'dirty' story



At first glance the 'hygiene hypothesis' seems straightforward. Developed countries have a cleaner lifestyle and therefore infectious illnesses are less common. As a result, our immune system seems to have shifted away from fighting infections to developing more allergic tendencies. But this explanation, according to Associate Professor Mimi Tang, is too simplistic.

"We know that from the beginning of the last century there has been a decrease in infectious diseases, such as tuberculosis and hepatitis, and an inverse increase in immune-mediated disorders such as allergic diseases (e.g. asthma, eczema, allergic rhinitis, food allergy) and autoimmune diseases (e.g. multiple sclerosis and diabetes) in developed countries," explains A/Prof Tang, clinical allergist, immunologist and immunopathologist, Director of the Department of Allergy and Immunology at the Royal Children's Hospital in Melbourne.

"However we now understand that the real issue has been a reduced exposure to the natural variation and quantity of bacteria overall. In terms of the rising prevalence of these diseases, asthma came first, then eczema and allergic rhinitis<sup>[1]</sup> (hay fever) followed by food allergies."

The rapid rise in prevalence of immune-related disorders cannot be explained by genetic causes. They have happened too quickly which means they must be the result of changes in our environment. One possible environmental factor might be decreased exposure to certain pathogens.

However, A/Prof Tang says the hygiene hypothesis extends further than no longer being exposed to pathogens. It also encompasses the fact that we are no longer being exposed to a range of 'beneficial bugs' (good bacteria) that are important for the establishment of a healthy human microbiota<sup>[2]</sup>.

“Data is pointing to changes in human microbiota contributing to the modulation of immune disorders, but the evidence is not conclusive. We do know that children who develop allergies later in life have reduced diversity in terms of range and evenness of the intestinal microbiota in their early life,” she explains.

Researchers are still trying to understand what determines the establishment of a healthy and diverse intestinal microbiota. They know it is influenced by the maternal bacteria, type of feeding, diet and environmental bacteria a newborn is exposed to in the first days to weeks of life.

“The baby’s immune system may also play a role in determining how the microbiota evolves, so there appears to be a complex interplay between host immune status and early life microbial exposures.”

Microbiota colonise most parts of the body from the nose and skin to the mouth, but most densely colonise the gastrointestinal tract. These intestinal microbiota play a role in metabolic, nutritional, physiological and immunological processes and also help in the defence against pathogens. But it’s not a case of letting our children roll around in the dirt as a panacea.

“The dirt is different now and the microbiota in it is different,” explains A/Prof Tang. “We have progressively lost beneficial bugs in our environment due to stricter hygiene measures.”

This basically means our developed lifestyle has eliminated the natural variation and quantity of germs that our immune system needed to deliver more balanced responses to allergens. Research suggests that one way to rebalance the equation may be to replenish a healthy microbiota with probiotics. These are live microorganisms such as bacteria, yeasts and fungi which may improve digestion, help protect against disease and enhance immune function if taken in sufficient numbers.

Simply taking probiotics is not the only answer to this conundrum either. The underlying causes of the hygiene hypothesis are many and complex with the leading idea being that some infectious agents, particularly those that co-evolved with us, could provide protection against a number of immune-related disorders<sup>[3]</sup>. The theory underpinning the hygiene hypothesis is also evolving from the original observation of an inverse relationship between infectious diseases and immune-related disorders.

[1] Allergic rhinitis is covered in [ePathWay issue #007](#)

[2] The human body is home to a vast array of microbes collectively known as microbiota.

[3] Okada H, Kuhn C, Feillet H and Bach J-F. The 'hygiene hypothesis for autoimmune and allergic diseases: an update. Clin Exp Immunol. 2010 April; 160 (1): 1-9. (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2841828/>)

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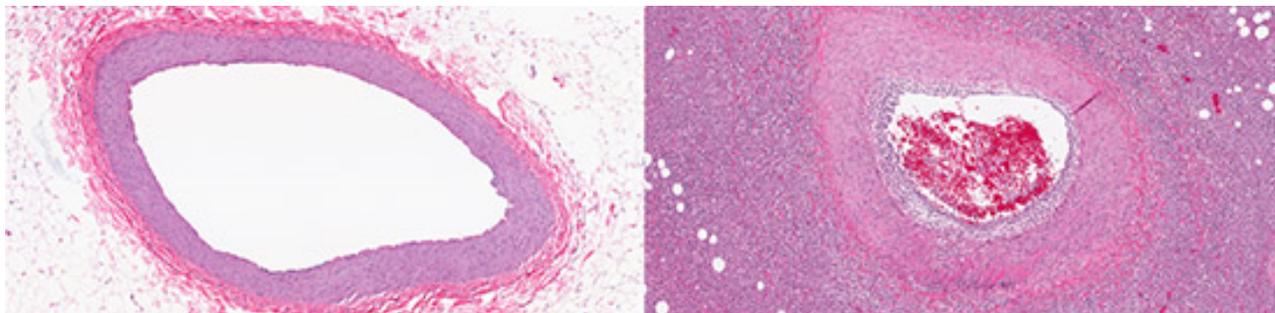
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## Diagnosing vasculitis can be a tricky business



Vasculitis is the name for a group of diseases that can affect any of the body's blood vessels – from the largest arteries to the tiniest veins. It has no specific risk factors, targets any age group and both sexes, and occurs when the body's immune system attacks its own blood vessels causing them to become inflamed and potentially close off. Vasculitis must also be diagnosed early to prevent damage to body organs.

Dr Daman Langguth, clinical immunologist and immunopathologist at Sullivan Nicolaides Pathology, says people with vasculitis often present with non-specific symptoms such as tiredness, fever, breathlessness or aching muscles. The diagnosis therefore rests on confirmatory pathology tests.

"Pathology is critical to the diagnosis, sub-typing and management of vasculitis. It involves many disciplines of pathology including histopathology, biochemistry, immunology and haematology," he says. "There is also the ANCA (antineutrophil cytoplasmic antibody) test which was discovered in Melbourne. This is a useful test for someone who may have autoimmune vasculitis."

While vasculitis occurs as part of a range of diseases, most types are classified according to the size of the blood vessels they affect such as large, medium and small vessel vasculitis. Within each of these classifications are many different diseases such as giant cell (temporal) arteritis.

"It's called giant cell arteritis because that's what pathologists see when they look at a biopsy of the blood vessel's tissue," explains Dr Langguth. "It affects the large arteries, usually in the head and neck, which become inflamed and can lead to complications such as clotting and blocked arteries."

Dr Langguth said if giant cell arteritis is not diagnosed correctly and treated, blindness can occur.

Another type of vasculitis, Takayasu's arteritis, is also known as 'pulseless disease'. This is because the body's blood vessels slowly close off and the body makes new blood vessels to compensate - but these don't work as well. Dr Langguth says this disease was first recognised in Japan and mostly affects people of south east Asian origin, especially young women.

While the size of the affected vessel is a determining factor, vasculitis can also be split into primary vasculitis, in which the disease attacks blood vessels first and foremost, and secondary vasculitis in which immune responses to viral and bacterial infections incidentally affect blood vessels. These infections may cause a rash, but most of the time they resolve themselves and don't need any formal diagnosis or treatment.

If some types of vasculitis resolve themselves, and others have dire consequences if they are not diagnosed and treated early, how do you differentiate between them? Well, it depends of the type of vasculitis, which organs are affected, how quickly the condition worsens and how severe it is. And of course pathology testing is critical. But when it's such a difficult disease to diagnose, continuing medical education is important.

"There is a seminar<sup>[\*]</sup> in Brisbane at the end of August to update doctors on the many presentations and current treatments for vasculitis which have significantly evolved on the past five years, including knowledge of the pathology of giant cell arteritis. The seminar will also look at equity of access to drug treatments," says Dr Langguth who is also a guest speaker at this event.

While this symposium is just for doctors, vasculitis should be on everyone's radar. The average adult body has about 100,000kms of blood vessels packed into it which leaves a lot of scope for this disease to manifest itself. And while smoking is a risk factor, Dr Langguth says most people who have vasculitis have no obvious risks. So, with no useful risk factors, non-specific symptoms and no overall target age or sex, diagnosis really does come down to confirmatory pathology tests.

[\*] The 2nd Brisbane Vasculitis Seminar for doctors is on Saturday August 31 at the Brisbane Airport Motel from 2-6pm. For more information contact Dr Claire Barrett at [jacksonbarrett@optusnet.com.au](mailto:jacksonbarrett@optusnet.com.au) or ph 07 3284 5035.

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## Mass or molar? It's time to end the impasse to increase patient safety



Reporting concentrations of therapeutic drugs will become a safer proposition when the recommendations of an expert working party are adopted across Australia and New Zealand. Therapeutic drug concentrations are currently reported in either mass or molar units, depending on the policy of the laboratory, which introduces a risk point into the clinical interpretation of the pathology result.

Professor Ray Morris, medical scientist at the University of Adelaide, says the problem is the existing “footy team’s” approach to this issue. One camp supports the use of molar units, the other supports mass units, and each camp believes right is on their side.

“Whilst this important issue fires up passion on both sides, both sides do have a common ground in terms of recognising that there is a problem and it needs to be fixed,” he explains.

The solution to this issue may be close. A working party established by the Royal College of Pathologists of Australasia (RCPA), the Australasian Association of Clinical Biochemists (AACB), the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) and the Royal Australasian College of Physicians has put forward a set of recommendations<sup>1</sup> to solve this impasse and improve patient safety.

“I was a member of the working party that unanimously agreed on the recommendations based on sound international opinions, including consensus guidelines published in UK. We also took into

account the fact that pharmaceutical companies produce medicines that are dosed in mass units as well as many other considerations. It therefore makes sense to report the concentrations of these medicines in mass units as well, as this allows convenient application of simple dosage adjustment tools," Prof Morris says.

"When we looked at all of the evidence we concluded that all therapeutic drug concentrations should be reported in mass units with a few exceptions where molar units should be used, such as vitamins, hormones, etc, that may also be given as doses. But, the end result will be that the same drug across Australia and New Zealand will always be reported in the same unit of measurement leaving little room for errors of interpretation."

Prof Morris outlined the following scenario to illustrate how this approach will improve patient safety. A patient with a history of epilepsy is admitted into an emergency department because he is experiencing seizures. He takes the anti-epileptic drug phenytoin. A blood sample is sent to the pathology laboratory to measure its concentration and the result reported back over the phone is 30 mg/L. What happens next is where there is the greatest risk for an error to occur.

The person writing the result down doesn't record the unit of measure or range, but just reports to the doctor that the result is "30". This number is high in mass units (target range 10-20 mg/L) but low in molar units (target range 40-80  $\mu\text{mol/L}$ ), and could lead to the patient's (already toxic) medication being increased further if the doctor misinterprets the result as a molar unit when the opposite action is needed.

"The recommendations have been made and published. The final step is universal adoption by laboratories and in journals, guidelines and websites. When all sources of information on reporting and interpreting a drug concentration are in the same units, the spectre of this avoidable source of medical error will be gone."

[1] Further information on this issue, including the working party recommendations, can be found at <https://www.mja.com.au/journal/2013/198/7/mass-or-molar-recommendations-reporting-concentrations-therapeutic-drugs>

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## Star factor puts HPV induced head and neck cancer into the spotlight



The case for human papillomavirus (HPV) as a cause of head and neck cancer has been building for decades, but it's barely made more than a small bleep on the public's radar - until now. Film star Michael Douglas was diagnosed with throat cancer caused by HPV a few years ago, and has recently shared the intimate details of how he contracted it making this issue international news.

HPV is a broad term for a group of viruses transmitted through close skin-to-skin (e.g. sexual) contact. Different types cause warts on the skin or genital region, cervical cancers and cancers of the anus, penis, vulva, vagina and head and neck. The head and neck region seems the odd one out of this group which is probably why it hadn't been on the general radar in terms of HPV infection.

"The main way HPV gets into the mouth is through oral sex," says Dr Jane Evans, histopathologist at LabPLUS in Auckland City Hospital. "We find that p16 is over expressed in these cancers and is a strong independent prognostic marker for oropharyngeal squamous cell carcinoma (OPSCC) induced by HPV infection."

So, what is p16? It's a protein that regulates the cell cycle. It is also strongly expressed in almost all cervical cancers as well as HPV-positive OPSCC. Dr Evans says this is good news if you are diagnosed with p16-related OPSCC because they are more responsive to treatment than cancers caused by other factors such as smoking and alcohol.

In fact, the main risk factors for head and neck cancer are still predominantly smoking and alcohol, so how do you know if it's caused by HPV? This is where pathology steps into the picture. Dr Evans says pathologists can examine a biopsy of a suspected lesion and test it for expressions of p16.

"We usually don't serotype a HPV-positive OPSCC cancer because the link between p16 and these types of cancer is very strong," says Dr Evans.

Michael Douglas may be the star of many films, but putting this sensitive issue into the spotlight may be his most important role to date. Drawing attention to what appear to be unusual causes of cancers can potentially save lives, which is why he is being applauded for sharing his real-life story with the world.

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