Welcome to the October edition of ePathWay

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Keep checking in to our Facebook page. You can follow our CEO Dr Debra Graves (@DebraJGraves) or the College (@PathologyRCPA) on Twitter to keep up to date with pathology news.

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1371
The number of cases of plague recorded in Australia between 1900 and 1925, including 535 deaths.
The number of cases of plague recorded in New Zealand between 1900 and 1911.

Source: New Zealand Government Ministry of Health, Sydney Medical School (The University of Sydney), World Health Organization

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Professor Brett Delahunt

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Plague is still active after all these years

You probably thought the plague was dead and buried in the history books, but that’s not the case at all. A third plague pandemic started in 1894 and hasn’t ended yet. Unlike the first two pandemics, this one mostly sails under the radar because the outbreaks are usually isolated and small and the infection is now treatable. But a recent spike in the number of cases in the United States and Madagascar has put the plague under the spotlight again.

Before we address the current situation, let’s recap the previous two pandemics. The Justinian Plague arrived in 542 and ravaged the Eastern Roman Empire. The second pandemic, dubbed the Black Death, emerged in the 14th century. While experts may differ in their estimates, there is no doubt that these pandemics caused very high mortality and are likely to have had significant influence on socio-political development in affected populations.

The current plague wreaked most of its devastation in the pre-antibiotic era (up to 1941). It also reached the shores of Australia and New Zealand in the early 1900’s courtesy of infected rats hitching rides on sailing ships.

Dr Raymond Chan, Clinical Microbiologist at the Royal Prince Alfred Hospital, says the plague isn’t endemic to Australia and New Zealand, but it is endemic in many other countries, including the United States and Madagascar.

“The USA has had the plague for a long time and a few cases pop up every year, but this year’s outbreak is making people nervous because it is a small spike in numbers.”

So far this year, 11 cases of human plague have been reported and three people have died in the United States, compared to an average of seven cases reported each year. The situation is worse in Madagascar with 10 deaths in August this year. So what is the plague, and how is it spread?

“The plague is a bacterial disease caused by the bacterium Yersinia pestis which mostly affects rodents. It is usually transferred to humans when a flea bites an infected rodent and then bites a person, or if the person handles tissues or
secretions from an infected rodent,” explains Dr Chan.

He says a person can be inoculated in one country but not develop symptoms until they arrive back home a few days later. This is because people infected by the plague develop ‘flu-like’ symptoms only after an incubation period of three to seven days.

“If a person becomes ill after travelling abroad, a careful history of where they have been and what they have been doing is very important. For example, we always ask people if they have been in parks or handled animals. If we suspect they are infected with the bacterium that causes the plague, we will take blood or fluid from an infected site, such as a bubo, and culture it so we can confirm the diagnosis and start treatment,” explains Dr Chan.

A bubo is a swollen lymph node characteristic of the bubonic plague. The bubonic plague is the most common form of the disease, and is caused by the bite of an infected flea. There are two other types of plague as well.

Septicaemic plague occurs when the infection spreads through the bloodstream with or without forming a bubo. Pneumonic plague is caused by the infection spreading to the lungs from advanced bubonic plague or from inhaling infected secretions. This type is transmissible from person to person through infected droplets spread when a person coughs.

Modern disease surveillance methods, definitive diagnosis through pathology tests and effective treatment options mean the plague doesn’t wreak the same havoc on the world’s population as in times gone by. But it’s important to know the plague isn’t just a footnote in history. It’s an active disease still causing deaths and illness after all of these years.

**Facts about the current plague pandemic**

- Globally, between 1000 and 2000 cases of the plague are reported to the World Health Organization (WHO) every year.
- 38,310 cases and 2845 deaths were recorded in 25 countries between 1989 and 2003.
- The plague is endemic in many African countries, the former Soviet Union, the Americas and Asia.
- The 3 countries with the highest prevalence are Madagascar, the Democratic Republic of Congo and Peru.
- 14 cases and 10 deaths from the pneumonic plague have been reported in Madagascar in August this year. Another plague outbreak occurred in Madagascar between 2014 and 2015 (peaking in November 2014) when over 335 cases and 79 deaths were reported to the WHO.
New prostate cancer grading system offers an alternative to Gleason scores

The widely used Gleason grading for prostate cancer was introduced in 1966, and apart from some tweaks over the years, was still the main grading scale used – until now. A newly minted system based on the best available evidence is ready to go, and will be available to use internationally next year.

RCPA Fellow Brett Delahunt, Professor of Pathology and Molecular Medicine at the Wellington School of Medicine and Health Sciences (University of Otago) and Adjunct Professor of Biological Sciences at Victoria University (Wellington), was part of the six-person committee that developed the new grading system.

“The International Society of Urological Pathology (ISUP) held a consensus conference on Gleason grading in 2005 which updated it to more contemporary practice. Issues with this system were also addressed at that time. Subsequent and existing issues with Gleason grading were again addressed at another ISUP consensus conference in 2014 in Chicago,” explains Prof Delahunt.

“There was also a consensus recommendation and proposal to adopt a new grading system presented at this conference, and a six-person committee, which included myself and RCPA Honorary Fellow Professor John Srigley from Canada, was convened to develop it.”

The newly minted ISUP Grading System for Prostate Cancer subdivides prostate cancers histologically into five grades. Grade 1 is the least aggressive and Grade 5 the most aggressive. Prof Delahunt says this simpler system replaces the more complicated Gleason grading and score.

“The Gleason grading system has five grades as well, but the lowest score you can achieve is six out of 10 because of the need to add a primary and secondary score together based on the most abundant patterns. It is confusing and misleading for
Prof Delahunt says the new grading system has been accepted by the World Health Organization (WHO)/International Agency for Research on Cancer (IARC) Classification of Tumours and will be published internationally next year.

You can find more about the ISUP Grading System for Prostate Cancer here.
Coeliac disease has a growing list of mimics

Diagnosing coeliac disease is not so straightforward as you may think. The classic signs pathologists look for in a biopsy of the intestine - inflammation and flattening of the long, fingerlike projections that normally absorb nutrients and fluid, called villi- have other causes as well. The skill is in knowing how to differentiate genuine cases of coeliac disease from these mimics.

"Most cases that display the classic histological patterns typical of coeliac disease will be the real disease, but there is an increasing number of exceptions. In these cases, we go back to the clinician with our report and determine if the clinical symptoms fit the histological findings," explains Dr Ian Brown, histopathologist at Envoi Specialist Pathologists in Brisbane.

Conditions that cause the same intestinal damage as coeliac disease include tropical sprue (a malabsorption disease commonly found in the tropics), common variable immune deficiency (CVID), autoimmune diseases of the intestine, and intestinal disease caused by a particular class of drugs prescribed to treat high blood pressure.

Mimics are not the only challenge thrown at pathologists when diagnosing coeliac disease. Patients can also present with uncharacteristic symptoms such as osteoporosis at a young age, non-specific anaemia and a skin rash. This is where a blood test for particular antibodies can indicate this disease.

"This blood test is more reliable thanks to improving technology and frequency of testing, but it can occasionally return a false positive or negative result. This is why suspected cases of coeliac disease should always be confirmed by histology, but the blood test can point clinicians in the right direction," explains Dr Brown.

"In borderline cases we can also use tissue typing to assist with diagnosis. This is because coeliac disease is strongly associated with specific genes known as HLA-DQ2 and HLA-DQ8. If a person is tested and they have one of these HLA types, then we are more confident they have coeliac disease. If they don't have one of these HLA types then we can also be fairly confident they don't have coeliac disease."
Dr Brown says another way to ensure the diagnosis is correct is through follow up tests. If a person follows a gluten free diet and a subsequent biopsy shows the inflammation is subsiding or gone, and the villi are returning to their normal appearance, then it is further evidence of coeliac disease. If they follow this diet and the signs don’t change, then it probably isn’t coeliac disease but one of the mimics instead.

“There are checks and balances in place in terms of different tests to diagnose coeliac disease. If one of them isn’t definitive for coeliac disease then we look for further causes. We are certainly getting better at picking up more cases due to other causes, even though this list is growing.”

This growing list of mimics conjures up images of shadow boxing. It takes considerable clinical knowledge and testing capability to stay one step ahead of the impersonators, which is why diagnosing coeliac disease isn’t so clear-cut as it appears.

Coeliac disease is also covered in the [February 2013](http://epathway.rcpa.edu.au/three.html) and [June 2011](http://epathway.rcpa.edu.au/three.html) editions of ePathWay.
Long QT syndrome can lead to shocking outcomes if it’s not detected early

October is nationally recognised in Australia as Defibrillator Awareness Month when the Cardiac Arrest Survival Foundation encourages workplaces to host a Shoctober event. You may be wondering what cardiac arrest has to do with pathology. In the case of QT syndrome (LQTS) then pathology plays a vital role in identifying this familial condition through genetic testing, and in identifying it as the cause of death in people who succumb to it.

LQTS is a rare condition that affects the heart’s electrical system. People affected by it have a longer than normal distance between the Q and T waves on an electrocardiogram (ECG). This means the heart takes a longer than usual time to return to its normal resting state between heartbeats.

Many people with LQTS may not experience any symptoms, but when they do they are serious. Symptoms can include blackouts triggered by exercise (including swimming), seizures, and an erratically beating heart caused by a strong emotional response to triggers such as surprise from a loud noise, or feeling angry, leading to a cardiac arrhythmia. Sometimes the first sign of LQTS is cardiac arrest leading to death, and this is when pathologists often enter the picture.

“We can’t diagnose LQTS on autopsy, but if an autopsy is negative and the circumstances suggest sudden cardiac death then we start to look at it as an option, especially if the person is young. For example, if a young person was known to be a strong swimmer and they drown in a pool, then we would be suspicious that they may have died from a cardiac arrhythmic syndrome such as LQTS,” explains Dr Sarah Parsons, Forensic Pathologist at the Victorian Institute of Forensic Medicine.

If LQTS is suspected, or listed as the cause of death, then offering genetic testing and counselling to surviving close relatives is important. LQTS is inherited by autosomal dominant transmission. This means both males and females are equally affected, and each child of an affected parent has a 50% chance of inheriting the genetic abnormality.
About 10 to 15 percent of sudden deaths in young people are attributed to a cardiac arrhythmic syndrome such as LQTS. While the genetic abnormality does run in families, it can be a one-off mutation as well, but this is very rare. It's important to note also that if you have the mutation, it doesn't mean you will automatically develop LQTS,” says Dr Parsons.

The benefit of genetic testing is in identifying people with the abnormality, and subsequently diagnosing family members who have LQTS, enabling them to start treatment. Cardiac arrhythmic syndromes such as LQTS can also affect otherwise healthy infants (it can be a cause of SIDS), children, adolescents and adults. If it is diagnosed early then its effects, including sudden death, can be prevented, avoiding the shocking outcomes often associated with this genetic abnormality. There are medical treatments for LQTS, however some patients have their own implanted defibrillators to ‘shock’ their hearts back into normal rhythm if they go into cardiac arrest.

Dr Sarah Parsons was interviewed about sudden deaths in young athletes for the March 2014 edition of ePathWay.
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