NEW DIRECTIONS IN
COELIAC DISEASE TESTING

GLANDULAR FEVER
teenage troubles

Targeted therapies
REVOLUTIONISING CANCER TREATMENT
Welcome!
to our Bread, Baddies and Bugs issue of SNAPSHOT.

And it’s packed full of information on advances in testing.

First Daman Langguth, SNP’s expert on immune diseases, describes the new and deep understanding we now have of coeliac disease — a disorder that has been with us since the start of civilization when humans started growing and eating wheat. Along with the increase in knowledge have come better tests so now we can more easily diagnose coeliac disease and with effective treatment help these unlucky individuals who have it to lead normal lives.

Then something from our genetic experts, James Harraway and Shane Byrne, which is truly ‘cutting edge’ – tests for genetic changes in some cancers that can allow revolutionary new treatments to change some people’s lives.

And finally “Bugs are us” — from glandular fever to tuberculosis — introduced by our expert microbiologists, Meryta May, Jenny Robson and Margaret Allen.

There’s something in this edition for everyone — I hope you find it interesting and informative.

Happy reading!

Dr Michael Harrison

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Coeliac disease is a life-long autoimmune disorder triggered by eating gluten, a common protein found in wheat, as well as similar proteins in rye, barley and oats. The immune system attacks the lining of the small bowel, the tiny, hair-like projections called villi that cover it rather like the thick pile of a carpet. The villi become inflamed and flattened and the surface area that would normally absorb nutrients is reduced.

If left untreated, it can lead to serious medical problems including some cancers, so diagnosis and management are essential. There are no cures or medications and the only effective treatment is a life-long gluten-free diet. If glutens are avoided the bowel can repair itself. This can take up to 18 months.

Once it was thought to be a rare infant feeding problem, now we know that coeliac disease is much more common, it affects people of all ages and is genetically-determined.

In just the past few years our knowledge has advanced dramatically, new more sensitive tests have been designed and our ideas about diagnosis are changing.
Difficult to diagnose

The problem with diagnosing coeliac disease is that many people have no symptoms. It’s been estimated that as many as 75 per cent of Australian coeliacs don’t know they have it.

For others, symptoms are vague. They report persistent gut problems such as pain, bloating, constipation or diarrhoea. Some people have recurrent mouth ulcers, a distinctive itchy skin rash, tiredness or weight loss. And then to confuse matters even more, the majority of people who visit their doctor with gut symptoms usually find they have one of a range of other possible health problems such as irritable bowel syndrome, inflammatory bowel disease, diverticulitis, intestinal infections and non-coeliac wheat and grain intolerances.

Typically, someone is diagnosed with coeliac disease when they are having a check-up for something else. They have unexplained abnormal liver test results or blood tests that show vitamin deficiencies. Someone with early-onset osteoporosis is also a possible candidate.

Anyone who has a close biological relative with coeliac disease should be tested. Also, people with Down syndrome or Turner syndrome are at higher risk. Links have been made between coeliac disease and other autoimmune diseases such as rheumatoid arthritis, thyroid disease and systemic lupus as well as diabetes type 1. However, the evidence for this is not as strong as it once was. A possible link with infertility remains uncertain.

Why diagnosis is important

If left untreated coeliac disease can lead to serious health problems. As well as vitamin and nutrient deficiencies it increases the risk of some types of lymphoma, cancer of the small bowel and oesophageal cancer. Lymphoma of the small intestine is a rare type of cancer but may be 30 times more common in people with coeliac disease. No link has been established with colorectal cancer.
For centuries it was known that some infants were born with an inability to thrive; after birth they grew progressively weaker, had persistent diarrhoea and sometimes died. But it wasn’t until the 1940s, during World War 2, that the causes of the condition were discovered by accident and it was given a name — coeliac disease.

A Dutch paediatrician noticed that young children started to improve with wartime bread shortages. When bread was back on the table, their symptoms returned.

**What is an antibody?**
Also known as an immunoglobulin (Ig), an antibody, is a protein produced by the immune system to identify potentially harmful substances such as bacteria and viruses or for coeliac sufferers this is glutenin and gliadin so they can be destroyed. The antibody recognizes a particular component of the foreign target called an antigen and binds itself to it.

**In the majority of people with coeliac disease the immune system produces two types of antibodies, transglutaminase (IgA tTG) and IgG DGP also known as Anti-gliadin antibodies.**

To test for coeliac disease we perform three blood tests: Total IgA, IgA tTG and Anti-gliadin antibodies (IgG DGP).

**Total IgA**
This test detects the level of general IgA in the blood. Some people can have a general deficiency of IgA antibodies A (IgA). This is a separate condition and not exclusive to coeliac sufferers although they are 10 to 20 times more likely to have it than the general population.

**IgA tTG**
Measuring IgA tTG is considered the gold standard. This is because IgA tTG antibody is made in the small intestine and is more specific to coeliac disease. However, if someone has a general deficiency of IgA antibodies then it is possible that their IgA tTG antibody levels are also affected. That’s why we also test for Anti-gliadin antibodies.

**Anti-gliadin antibodies — IgG DGP (Deamidated gliadin peptide antibody)**
In recent years, testing for Anti-gliadin antibodies has been greatly improved thanks to the development of a synthesised form of the Anti-gliadin antibody called deamidated gliadin peptides (DGP). These are reflective of the gliadin antibodies produced in coeliac disease and test results are highly specific.

**Infants**
The IgA tTG test is less suitable for infants because IgA production does not develop properly until a later age. Tests for Anti-gliadin antibodies are used in conjunction with IgA tTG for babies.

For more information on your tests [www.labtestsonline.org.au](http://www.labtestsonline.org.au)
Tissue examination

If blood tests show raised levels of antibodies indicating coeliac disease, a diagnosis is usually confirmed by examining samples of bowel lining tissue under the microscope. This is performed by our histopathologists (pathologists who specialise in tissue).

First, several small samples (biopsies) of the small bowel are taken. This is a straightforward procedure usually performed by the gastroenterologist. Once in the lab, the samples are processed, placed on glass slides and then examined under a microscope to assess the level of damage to the villi. It is important that anyone having a diagnostic biopsy taken continues to eat gluten during this time.

Tissue damage grading

The changes to the small bowel from coeliac disease are graded by Marsh classification from 0 to 4, with 0 being normal and 4 being the most badly affected.

Gene testing

Gene testing may be considered for family members such as biological parents or children of people with coeliac disease to rule out genetic inheritance. Without the gene they cannot suffer from coeliac disease and need not adopt a gluten-free diet.

In people who are predisposed to coeliac disease, a negative result for HLA-DQ2 and HLA-DQ8 can effectively rule it out. For people with Down syndrome or Turner’s syndrome genetic testing can alleviate the need for life-long screening. However, it is unlikely to be of benefit to people with a family history of coeliac disease who are likely to have the genes whether or not they have the disease. Genetic testing is also useful in infants under two years old who are difficult to diagnose.
As an immunopathologist and a consultant physician, Dr Daman Langguth understands both sides of the coeliac equation – the mechanisms of the disease and the symptoms experienced by patients.

Dr Langguth specialises in auto-immune diseases, allergies, and immune deficiencies and at Sullivan Nicolaides Pathology it’s an important part of his job as Director of Immunology to advise on the latest research developments, new testing methods and changes to global health strategies.

“We’ve come a long way in our understanding of coeliac disease in just the last few years,” he says. “We now know that people with coeliac disease have a particular genetic make-up. We understand the role of tissue transglutaminase in the coeliac process and as a result, new highly-accurate serology tests have been designed to detect IgA tTG and IgG DGP antibodies.

“Because we now have far more accurate blood tests and because we can test for genetic susceptibility, our approach to diagnosing children is changing. Recently, one of the world’s coeliac disease authorities, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published new guidelines for doctors. These have been compiled by a group of 17 international experts.

“ESPGHAN states that children with coeliac symptoms and high antibody levels do not need a biopsy for diagnosis. Now that we can achieve more with laboratory tests we can avoid as much as possible putting children through this experience.”

New tests for coeliac disease have been designed that are more accurate than ever and this is leading to new ideas about diagnosis.
Targeted therapies

Revolutionising cancer treatment

Targeted therapies are something you can expect to hear more of in the future. These new drugs – the earliest have been around for less than 10 years – are transforming the way we treat cancer.

They are the culmination of a mass of global research into the way cancer develops and behaves at the molecular level. Different from anything that has gone before, they act on specific molecules in cancer cells and interrupt the cancer process. Tailored to the individual characteristics of the particular cancer type, they promise better recovery and survival rates.

A few of them are already in use, approved to treat specific forms of leukemia and breast cancer. The past few months have seen the Therapeutic Goods Administration (TGA) add targeted therapies to the Pharmaceutical Benefits Scheme (PBS) for some types of colorectal and lung cancer, with another to treat melanoma being considered for listing.

Targeting surface receptors and internal signallers

In developing targeted therapies scientists seek out potential protein molecules that play a key role in cancer cell growth and then design drugs to specifically block their activity. At the same time, testing technologies are designed to look for the specific gene mutations that control cancer cells by producing the protein molecules. These are called companion diagnostics. Someone with cancer must be tested to see if they have the gene mutations that indicate whether they will or will not benefit from the corresponding therapy treatment.

The two most common types of targeted therapies are monoclonal antibodies and small molecules.

**Monoclonal antibodies** work on the surface of the cell in various ways. In most targeted therapies they are used to bind to surface receptors, turning them to the ‘off’ position and blocking signalling to the cell interior.

Other ways of using monoclonal antibodies are being developed. Some turn on signals to encourage cancer cells to die, others stimulate the body’s own antibodies to trigger an immune response to destroy the cells. Yet others starve the cancer cells of nutrients and oxygen by preventing them from developing a blood supply and some act as a vehicle to deliver anti-cancer toxins or radiation to the surface of cancer cells.

**Small molecules**, as the name suggests, are small enough to penetrate the cancer cell’s surface and interact directly with the signalling molecules inside, preventing them from communicating with each other. There are many different molecules in the cell’s signalling systems and to be successful the drug must interact with the specific faulty one, like a key in a lock.

*LEADING THE WAY IN GENETIC DIAGNOSIS*

Here at Sullivan Nicolaides Pathology we are one of the leading private laboratories in genetic cancer diagnostics in Australia and we act as a referral site, undertaking genetic investigations for many other laboratories.

Genetic diagnosis is an area poised to play an immensely important role in medicine in the coming years and we are building on our considerable experience and expertise and using advanced technology to provide the most sophisticated testing. We are involved in clinical trials of new technologies and develop our own NATA-accredited tests. Last year, we were the Australian testing laboratory for the pilot of a new targeted therapy for lung cancer and among a group of diagnostic laboratories testing patients in a trial of melanoma treatment.
Dr James Harraway is one of only a handful of genetic pathologists in Australia, and the only one of his kind in diagnostic practice in Queensland. He joined the practice in 2009 after three years at Oxford University, where under a Nuffield Medical Fellowship he was researching the molecular mechanisms of Cockayne syndrome, a rare inherited disorder that leads to premature ageing. Dr Harraway is a Fellow of the Royal College of Pathology of Australasia in genetic pathology.

As Head of Molecular Pathology, Shane Byrne is one of Australia’s leading molecular infectious diseases scientists. He helped found the molecular laboratory in the mid-1990s, is the author or co-author of a number of scientific papers and regularly presents at conferences. He is a member of the Human Genetics Society of Australia, the Australian Society for Microbiology and the American Association for Molecular Pathology. Shane was selected as the Australian representative on an international panel and travels to Europe twice a year to provide his professional views on the development of next generation clinical molecular diagnostic platforms.

Targeted therapies have real advantages over conventional chemotherapy and radiotherapy – the mainstay of cancer treatment for past 50 years.

Chemotherapy works by destroying or damaging all rapidly dividing cells, a scatter gun approach that cannot avoid collateral damage to healthy cells. This can lead to severe side effects. While chemotherapy and radiotherapy will continue as the first-line of cancer treatment, expect to see more targeted therapies being introduced.
Nothing in our body stays the same — all cells have a life-span

Healthy cells are constantly changing. They are formed as stem cells and mature into different types of cells; eventually, they get the message that it’s time to go, so they replicate themselves and, having done so, they die.

Targeted therapies work by blocking the cell’s surface receptors or the faulty ‘switches’ inside

Cancer cells do not easily die off

They continue to grow chaotically and uncontrollably. This proliferation of cells also reduces the effectiveness of the normal cellular DNA repair mechanisms so more genetic mutations occur.

Mutant cancer genes subvert the normal signalling process

In cancer cells, mutated genes circumvent the body’s built-in cellular regulatory systems and install renegade protein molecules that are akin to faulty internal switches and ensure the cell keeps dividing and replicating, or else they block the normal signals telling it to die.

The messages are carried by ‘relay teams’ of signalling molecules

These protein molecules carry ‘on’/‘off’ messages, from one to the next, along ‘pathways’ into the cell. Signalling systems are complex and each relay team is dependent on several different types of signalling molecule.

They plug into receptors on the cells

Each growth factor has corresponding receptors on the surface of cells. They bind to the relevant protein receptors and this sets off a chain of chemical reactions, sending messages deep inside the cell.

Targeted therapies block the growth and spread of cancer by interfering with specific protein molecules involved in its development. Most targeted therapies work on receptors on the surface of cells or the signalling mechanisms within.

Genes are the personal blueprint we take from our parents

They are the coded instructions that govern absolutely everything our body does. Inside nearly every cell in our bodies there is a nucleus containing our own unique set of 23 pairs of chromosomes. Each of these chromosomes consists of a compact coil of an incredibly long molecule of deoxyribonucleic acid, better known as DNA, which is our very own hereditary blueprint. A gene is a section of DNA that is specifically coded to control a particular biological function.

First – when cancer develops...

Targeted Therapies — revolutionising cancer treatment
Genes tell the cell how to behave

They do this by making proteins. The gene sends out a message that triggers the creation of a protein molecule. Each cell has many genes and therefore can make many different proteins. These protein molecules operate in the cell doing specific jobs.

Cancer is the result of genetic damage or ‘mutation’

Even the slightest changes to DNA can result in serious consequences. Sometimes a DNA abnormality is the result of an inherited condition but it can also be caused by environmental factors. These genetic mutations that occur through daily life are called ‘somatic’.

Damage to genes can occur when the cell is going through its normal cycle of growth, division and replication. Something that makes a cell more susceptible to genetic damage is a carcinogen — for instance, ultraviolet light and skin cancer or the chemicals in cigarette smoke and lung cancer. Once a cell’s DNA is damaged it is copied when new cells are made, propagating the damage to more and more new cells. Cells with damaged DNA become less effective at correcting errors.

It is not easy for a healthy cell to turn into a cancer cell. Several different mutations have to take place. Most genetically-damaged cells die before they can cause cancer. They destroy themselves or else the body’s immune system gets rid of them.

There is not one but many gene mutations involved in cancer, and in any given cancer type, certain genes are more commonly mutated than others. Each type of cancer has its own signature set of mutations.

Growth factors trigger cell changes from outside

Cellular activities can be stimulated externally by proteins called growth factors that float around in the body. Some growth factors affect stem cells, triggering them to mature into a particular type of cell (differentiation). Others stimulate cells to grow, divide and multiply. Some initiate cell death (apoptosis).

Molecular Genetic Testing

It is only in the past two decades that genetic testing has emerged from the research lab to become part of everyday medical practice and this is almost entirely due to the Polymerase Chain Reaction (PCR). This Nobel Prize-winning technique that enables DNA to be studied has been hailed as one of the most important developments in the field of genetics since the discovery of DNA.

Genes are so small they cannot be seen — even under a microscope. In the PCR process, a segment of DNA is duplicated over and over again making millions of copies in a few hours — enough copies so that the sample can be examined in detail. PCR testing is highly sensitive and specific, and even low levels of genetic mutations can be investigated.

How we test

Targeted therapy genetic testing is usually performed on tumour samples that have already been diagnosed by the conventional method of observing cells through the microscope. This is carried out by a pathologist who specialises in investigating cancer.

If cell changes indicate the cancer is of a type that can be treated with a targeted therapy, the samples are sent to the genetics laboratory.

First, the tumour sample must be processed with a series of chemical washes so that pure DNA can be harvested. This has to be done in strictly-controlled laboratories so that the DNA is kept in complete isolation and cannot be contaminated, either by other samples, or by the DNA of the scientists doing the testing.

Next, the pure DNA is amplified in the PCR process. In order to look for the signature gene mutations of a specific cancer, only the segment of DNA containing those genes is amplified.

The genetic material is heated so the distinctive shape of the DNA double helix separates into two pieces of single-stranded DNA. Next, two short ‘primers’ bind to specific gene sequences along the strands. Then a special enzyme builds two new strands of DNA using the original strands as templates. Each of the new strands is used to create two new copies, and so on. The cycle of separating and synthesising new DNA is repeated as many as 30 or 40 times, resulting in millions of exact copies of the original DNA segment.

The amplified DNA is examined using fluorescent probes or DNA sequencers in order to highlight the target gene mutations. A camera captures the fluorescence and transmits the results to a screen where they can be studied and interpreted.

Most tests in our laboratory are conducted using real-time PCR. This is where the amplification and fluorescent detection processes are conducted simultaneously, making for a more rapid testing time.
New therapies

The first targeted therapies have been approved by the Therapeutic Goods Administration (TGA) for use on specific types of cancers where they have been shown to provide a benefit. Some newer drugs recently have been added to the Pharmaceutical Benefits Scheme (PBS) making them more affordable and easier to access.

HER2
Human Epidermal growth factor Receptor 2 (HER2) is a part of healthy cell growth but in some types of breast and ovarian cancer there is too much. Trastuzumab (Herceptin®) is a monoclonal antibody therapy used to treat this. It binds with HER2 protein molecules on the surface of cancer cells and prevents them from sending growth signals to the relay teams inside.

Testing to find out if a cancer is HER2 receptive involves assessing the numbers of HER2 gene copies in the tumour cells. Two types of technology are used — immunohistochemistry (ICH), which looks for the protein expressed by HER2, and In Situ Hybridisation (ISH), which counts the number of copies of the gene. Breast cancers with increased numbers of HER2 gene copies can be treated with Herceptin®. Testing for HER2 was added to the Medicare Benefits Schedule (MBS) in May 2012.

EGFR, KRAS and BRAF
Epidermal Growth Factor Receptors (EGFR) are found on the surface of many cells. Epidermal growth factor binds to these receptors that trigger signals to molecules in the cellular switching systems inside, instructing the cell to divide and reproduce itself.

EGFR, KRAS and BRAF are all part of the same set of signalling switches with KRAS and BRAF acting as downstream relay molecules in the EGFR pathway. Signalling through this pathway is important in many different types of cancer, and targeted therapies have been developed to exploit it. In quite a number of cancers, the EGFR pathway is ‘switched on’ more than in normal cells.

EGFR in non-small cell lung cancer
About 10 to 20 per cent of non-small cell lung cancers (NSCLC) have EGFR gene mutations that activate the EGFR signalling pathway. Someone with metastatic NSCLC, who has one of these mutations, can be treated with small-molecule EGFR inhibitors such as gefitinib (Iressa®). Testing for EGFR mutations was added to the MBS in May 2012.

Kras and colorectal cancer
KRAS genetic mutations keep the growth signal in colorectal cancer cells permanently ‘switched on’. More than 60 per cent of people with metastatic colorectal cancer (CRC) do not have KRAS gene mutations and therefore can benefit from treatment with anti-EGFR monoclonal antibodies such as cetuximab (Erbitux®). Testing for KRAS mutations was added to the MBS in May 2012.

Braf and melanoma
Between 30 and 40 per cent of people with melanomas have mutations in one specific part of the BRAF gene. Vemurafenib (Zelboraf®) is a small molecule inhibitor that targets the activated BRAF receptors. Vemurafenib manufacturer, Roche, has applied to have the drug funded through the PBS and to have the BRAF diagnostic test to be added to the Medical Benefits Schedule (MBS). A decision is expected later in 2012. In the meantime, Roche is funding BRAF testing for certain eligible patients.

Sullivan Nicolaides Pathology molecular genetics

- The national testing laboratory for the first commercial EGFR pilot project
- Participant in the BRAF clinical trials
- Developer of a NATA-accredited test for KRAS in conjunction with the Queensland Institute of Medical Research (QIMR)
- The first private laboratory in Queensland to be accredited for HER2 Chromogenic In Situ Hybridisation testing and Silver In Situ Hybridisation.
Glandular fever

TEENAGE TROUBLES

It’s the disease that can knock an active teenager sideways and cut a swath through a high school or university year, glandular fever, more formally known as infectious mononucleosis, is caused by one the most common of all human viruses but there’s nothing mundane about its impact.

The pathogen behind most glandular fever is the Epstein-Barr virus (EBV) and it is estimated that about 90 per cent of the adult population has been infected at some point in their lives – in other words, an antibody against EBV can be detected in their blood. Sometimes dubbed “the kissing disease” EBV is spread through saliva, but it doesn’t require contact that is quite so up-close and personal. It can be caught from drinking out of the same glass or sharing utensils. Because EBV can be symptomless, it is almost impossible to curb transmission.

Most people infected by EBV do not develop glandular fever. Normally, an infant inherits temporary immunity from its mother at birth. This wanes in a matter of months and in most countries around the world children become infected with EBV in the first years of life. At this age it causes only a few mild symptoms that often go unnoticed. However, in developed countries like Australia, with high standards of hygiene, fewer people are infected with EBV in their childhood and the virus often strikes in the teenage years. It triggers glandular fever in between a third and half of its victims.

The medical term for glandular fever is infectious mononucleosis. It is characterised by an increase of white blood cells that are mononuclear (have a single nucleus). Although it is most often caused by the Epstein-Barr virus, it can also be triggered by cytomegalovirus (CMV) and more rarely other infections such as toxoplasmosis, Q fever, hepatitis B or HIV.

Symptoms

It typically takes between four and six weeks from the time of infection for symptoms to appear. They can include a high temperature, sore throat, headache and swollen glands in the neck, armpits and groin. Some people also have swelling of the spleen or liver — in rare cases this causes jaundice. Perhaps most difficult of all, glandular fever can leave sufferers feeling deeply exhausted — a depressive lethargy that can go on for weeks or months on end. It’s not the virus itself that’s to blame but rather the body’s response.

EBV sends the body’s immune system into overdrive. Part of the problem is that by adulthood the immune system has become expert at fighting off infections and therefore more likely to respond aggressively. This may explain why teenagers and young adults are more often affected by symptoms.

After the initial acute infection, EBV stays in the body’s immune system for life, lying dormant in a few cells in the throat and blood. From time to time, it can reactivate, usually without any symptoms.

There is no need to isolate someone with glandular fever. The virus is not airborne and close personal contact is a prerequisite in spreading the infection. To help prevent this, simple measures such as not sharing drinks, food or utensils with an affected person and frequent hand washing are the best approach.
As a paediatrician and pathologist specialising in childhood infectious diseases Dr Meryta May belongs to an exclusive group of super specialists. There are perhaps only a couple of dozen of her kind in Australia and only a handful in Queensland.

Working with the microbiology department at Sullivan Nicolaides Pathology, Dr May devotes her days to investigating some of the planet’s trickiest and most elusive organisms, providing an expert diagnosis on everything from measles and mycoplasma to the more common whooping cough and ‘flu.

“Children are often more challenging to diagnose than adults as symptoms can be more non-specific,” she says. “Also, the younger they are and therefore the less able to communicate, the more close observation and listening carefully to the parents’ story become paramount.

“Children become sick and recover more quickly than adults. A sick-looking child needs to be taken seriously. Children are quickly back into usual activities. You don’t find them lingering in bed feeling sorry for themselves.”

How we test

A diagnosis of glandular fever is usually made based on someone’s physical symptoms and a range of pathology tests. There is no way of being sure which infection is causing the glandular fever symptoms just from someone’s appearance. Blood tests are needed to determine this, sometimes on more than one occasion.

Full Blood Count (FBC) looks for elevated white blood cells (WBCs), an increased number of B lymphocytes and the presence of atypical (infected) B lymphocytes.

Liver function tests (LFTs) are important even if there are no symptoms of hepatitis (jaundice). In acute EBV infection, liver enzyme levels are often mildly raised, providing a clue to the diagnosis.

ELISA serology test measures antibodies to two different EBV specific antigens, Viral Capsid Antigen-VCA IgG and IgM, and Epstein Barr Nuclear Antigen-EBNA IgG.
At Sullivan Nicolaides Pathology we use a test called the Diasorin LIAISON, a chemiluminescence immunoassay (CLIA) in which magnetic beads are coated with antigens then measured. This provides results much more quickly than previous tests.

**WHAT THE RESULTS TELL US**

Interpreting test results is complex and requires an in-depth understanding of the patterns of antibody production. Our microbiology pathologists must study the test results and make professional judgments that are based on a combination of factors. Often there is no ‘yes’ or ‘no’ answer and a range of options must be considered in the context of the patient’s physical symptoms and age. (For instance, a younger person is more likely to have EBV, an older person, cytomegalovirus.)

Detailed reports are prepared to help guide referring doctors and often phone conferences are needed between the pathologist and clinician to discuss the reasoning behind their findings.

**Other tests requested**

Diagnosis can be difficult when symptoms are more subtle. Sometimes, glandular fever can be confused with acute tonsillitis because the tonsils are coated and inflamed. Throat swab cultures are often tested to rule out bacterial tonsillitis. Nasopharyngeal secretions (NPS) are also tested for respiratory viruses to exclude ‘flu.

An early interest in childhood illnesses led Dr May to specialise in paediatrics. After a degree in medicine at the University of Queensland she worked at Brisbane’s Mater Children’s Hospital and the Royal Children’s Hospital before moving to Sydney and Australia’s foremost centre for paediatric medicine, the Children’s Hospital at Westmead.

“Pathology is integral to the diagnosis and management of infectious diseases and at Westmead we had two roles — clinician and pathologist,” she says. “Taking an additional qualification in pathology was the natural step.”

Returning to Brisbane in 2005, she took up dual roles as pathologist with Sullivan Nicolaides Pathology and as paediatric infectious diseases consultant at the Mater Children’s Hospital.

“Many medical disciplines require you to become expert in only one anatomical part of the body, she says. “Infections can affect any part of us, so in our speciality you have to remain familiar with all body systems.

“Infections have their own challenges. Despite technological improvements and increased scientific knowledge, we still have big gaps in our ability to test and provide accurate diagnoses for some diseases. This can be frustrating. Sometimes we still have to say: ‘It’s just a virus!’ What that does mean though is often we can exclude many serious and treatable causes of an infection; we just can’t pin down and name all the milder, self-limiting causes.

“Serological diagnosis is particularly challenging as it requires so much interpretation. Often without the full knowledge of the patient’s condition you are unable to provide a full interpretation. That’s why communication between GPs and other referring doctors and the laboratory is so important to achieve the best results.

“EBV is fascinating and its role in chronic diseases such as Chronic Fatigue Syndrome, Multiple Sclerosis and other illnesses is the subject of a great deal of research. While some sufferers of these conditions have evidence of EBV infection, it is so common in our community that it is hard to establish whether this has any significance or not. Study of the EBV virus has provided important clues about how our immune system fights infections, and some of this research has been used to help fight certain cancers.”

EBV is not a notifiable disease, and most infections pass unnoticed, so there is no way of tracking numbers of infections that occur in the community every year. It occurs all year round. It can be difficult for a doctor to diagnose if all the clinical features are not present at once.

“The most common misdiagnosis is strep throat or acute tonsillitis,” says Dr May, “This is a bacterial infection and requires antibiotics. It is often hard for the doctor to tell from examining the patient whether a throat infection is Strep or EBV. This is when laboratory testing can help. Some doctors will prescribe antibiotics while waiting for a result, and occasionally this can cause a rash to develop in EBV infection.

“It is important to distinguish EBV from other illnesses. Someone with glandular fever should avoid heavy exercise, especially contact sports, for several weeks as an enlarged spleen is more vulnerable to being ruptured. Also, if a woman is pregnant and showing glandular fever symptoms it is important to establish the cause. Cytomegalovirus, parvovirus or toxoplasmosis infection can all give glandular fever symptoms and can affect a developing baby in some cases.”
They are often known as the ‘disease detectives’, the pathologists and scientists in the microbiology lab spend their days investigating bacteria, viruses, mould and parasites to help piece together the puzzles of why someone is ill. It can be painstaking work and often the microbes they are looking for are evasive and chameleon-like.

The TB testing lab sits in a corner of the microbiology lab. Incubators stand in rows, visible through double glass doors. Safety systems are stringent because some of the bacteria in here are capable of causing serious illness and some are drug-resistant.

TB is a mycobacterium, a type of bacteria that can cause many illnesses from leprosy to ulcers. Although it usually affects the lungs, it can cause many illnesses from leprosy to ulcers. It is spread from human to human and in many parts of the world is on the increase with 8.8 million new cases and 1.7 million deaths reported each year.

With a thick waxy surface, mycobacteria take longer to culture in the lab than more commonly-seen bacteria. Staphylococcus (staph) and streptococcus (strep) can be grown from a patient’s specimen in an incubator in less than 48 hours but mycobacteria can take many days, weeks or even months to detect.

Dr Robson explains that testing often starts out as a search for one of the more common bacteria: “If someone has an infection and we have been unable to culture something like staph or strep from their sample we send it to Margaret for specialised processing including longer incubation times to see if it’s a mycobacterium. When the patient is showing obvious symptoms of TB and treatment needs to be started quickly we’ll send it for molecular tests where they can identify the genetic material of the mycobacteria. This can save quite a bit of time.”

Although the seriousness of TB means that it is an important focus for the lab, most of the workload revolves around non-tuberculous mycobacteria, also known as atypical mycobacteria (ATMs) or Mycobacteria Other Than Tuberculosis (MOTTs). Margaret, who came to Australia from Ireland in the 1980s, recalls that when she worked for St James Hospital in Dublin “about 99 per cent” of cases were TB. “That would apply in many countries,” she says. “Here, in Queensland, it’s the opposite and the majority of what we see is atypical mycobacteria.”

Dr Robson has tracked down and studied many different atypical mycobacteria. There are more than 125 species and they live in the environment including in the soil, water and air.

“There is no evidence they can be spread between humans,” she says. “Fishing, gardening, water spas, contaminated injections, pedicure foot baths and even drinking water supply systems can be the sources. Surgical procedures can put people at risk. People with immune problems or who have catheters in place for long periods are also more vulnerable. Many mycobacteria are resistant to disinfectant.”

Because they are uncommon, mycobacteria are not always the first thing a doctor thinks of when a patient has an infection. Says Margaret: “We’re often called in after other cultures are negative. When the infection persists, the patient can get very frustrated not knowing what they have. It’s an immensely satisfying part of the job to be able to give the patient an answer — to put a name to their infection.

“This job never gets boring. Mycobacteria are always surprising you. They turn up where they’re least expected, they are sneaky and they can cause havoc. Observing them so closely for so many years, it’s impossible not to have tremendous respect for them.”

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