THIRTY-FIVE YEARS AGO, when Professor Ian Frazer was a young medical student in Scotland, doctors regularly decided not to tell patients they had cancer. Hiding the bitter truth was widely thought to be kinder. After all, there was often little that doctors could do to treat the disease, says Frazer, the 2006 Australian of the Year who helped develop a vaccine against cervical cancer. “It was considered better for them not to know.”

Cancer treatment has changed radically since then. In the 1970s, when Frazer was in training, doctors might have hoped to cure 15–20 per cent of cancer patients by deploying the limited arsenal of surgical and radiation tools they had at their disposal. Now, a transformation in cancer treatment means today’s oncologists might expect to cure more than half of the cancer patients they treat.

“Now we have effective therapies that attack the fundamental problem in a whole range of common cancers, plus we have effective screening programs against some that we didn’t have before,” says Frazer, now the CEO and Director of Research at the Translational Research Institute in Brisbane. “If you did a ‘then and now’ analysis of cancer over the last 50 years it would be a very impressive shift.”

Australian researchers have played a significant part in those successes, from the
most fundamental laboratory research to the development of effective public health campaigns. In spite of all these improvements, however, cancer remains the most common cause of death in Australia. Roughly half of us can expect to develop cancer by the time we are 80 and many common malignancies, such as pancreatic and ovarian cancers, are often deadly.

**KNOW THINE ENEMY**

David Bowtell, a cancer geneticist at Melbourne’s Peter MacCallum Cancer Centre (Peter Mac), is optimistic science will make further strides against cancer in coming decades. He says that’s because scientists have learned a lesson famously taught by a Chinese general in the sixth century BC.

“When I talk about cancer, I like to quote Sun Tzu. He said that if you know your enemies and know yourself, you need not fear a hundred battles,” says Bowtell.

Bowtell explains that cancers develop in much the same way that computers crash. Where a bug in your laptop’s operating system might cause it to fail, with cancer the errors in your ‘operating system’ are mutations in the DNA of a cell. These lead to cells growing and dividing in an uncontrolled way (see: What is Cancer?).

Over the past 20 years, scientists have developed DNA sequencing technology, allowing them to read the cancer’s code and see how it’s corrupted. This technology shows clearly that, even within the same tissue, a multitude of different mutations can lead to cancer.

Understanding the specific mutations that arise in an individual’s cancer has already allowed scientists to design drugs targeting diseases such as breast cancer, some leukaemias and melanoma.

“We are already undergoing a paradigm shift away from traditional therapy in cancer to targeted therapy based on the mutations in an individual’s cancer,” says medical oncologist Ian Olver, chief executive of Cancer Council Australia.

Traditional chemotherapy and radiotherapy was based on a one-size-fits-all approach, causing severe side effects. Those traditional treatments target all rapidly dividing cells. So they kill healthy cells, such as hair follicle and gastrointestinal cells, as well as the cancerous cells. These side effects are why some cancer patients lose hair and experience nausea.

**REVEALING THE DETAILS**

The more scientists learn about the changes that drive individual cancers, the greater the number of treatment advances that will emerge, claims University of Queensland’s Sean Grimmond.

In the near future, scientists will be able to decode the entire genetic blueprint of an individual’s normal cells cost-effectively, then compare it to the complete series of errors in a tumour. “This is really a new tool for us to battle cancer,” he says.

Australian researchers are participating in some of the large international projects that will make this a reality. Both Grimmond’s group at the Queensland Centre for Medical Genomics and Bowtell’s group at Peter Mac are taking part in the International Cancer Genome Consortium project, which is building an atlas to understand the major events that cause the 50 most common cancer types worldwide.

Australia’s contribution on this project is to investigate pancreatic and ovarian cancers. So far, Bowtell’s group has sequenced about 80 patients with ovarian cancer, looking for mutations associated with drug resistance. The Queensland group has analysed cancers from about 400 pancreatic cancer patients. According to Grimmond, their pilot work has more than doubled survival rates by helping doctors to decide on the most effective treatment for patients.

Beyond understanding changes in the genetic sequence underpinning cancer, researchers are also looking at other changes and modifications made to DNA, notes Susan Clark from Sydney’s Garvan Institute.
“It’s very clear that understanding the changes to the DNA code is not enough to understand how parts of the code are turned on and off in cancer cells,” she says.

Scientists refer to the additional information that determines which genes are switched on and off as ‘epigenetic’ changes. Some of these changes are made in response to the environment, whereas other epigenetic ‘marks’ are made during early embryo development, shortly after the egg is fertilised. These include chemical modifications to the DNA, which alter how the DNA is packaged into each cell and how genes are switched on and off. Epigenetic marks in cancer cells can be substantially altered, leading to many changes in gene activity, Clark says.

Of course, this extra information will pose new challenges for doctors trying to interpret it to treat their patients.

“I think we’re going to see a big emphasis on this kind of medicine across a whole lot of cancers, and that will really require a big change in the way we think about health care,” says Grimmond.

**FUTURE THERAPIES**

In 2012, Australian scientists reported in the journal *Lancet Oncology* that some melanoma patients with advanced disease received a dramatic benefit when treated with a drug designed for use in people whose cancers had a specific mutation. The drug was able to shrink tumours that had spread to the brain, which is a common problem in melanoma, and added months to the lives of many patients.

“The findings are among the most important in the history of drug treatment for melanoma,” claims study co-author Georgina Long from Melanoma Institute Australia.

The study powerfully illustrates the promise of future therapies. Yet it also highlights a major challenge: relapse. While many patients saw a major benefit, for most the response was limited to a few months. The cancer became resistant to the therapy. The drug was no longer effective.

“I think where the personalised medicine story is falling down at the moment, and where Australia has a grand challenge, is in treating patients who we aren’t able to cure up-front and whose cancer comes back,” says Bowtell.

In fact, future cancer treatment may involve managing cancer rather than curing it, adds Grimmond. Technology that allows scientists to study the sequence of a person’s entire genetic make-up – their genome – might become a tool for routinely reviewing and fighting cancers as they change.

**RISK RECKONING**

Scientists know the genes some people inherit put them at increased risk of developing cancer. Perhaps the most infamous of these cancer predisposition genes are *BRCA1* and *BRCA2*, which can cause a small fraction of breast and ovarian cancers. In 2013, actress Angelina Jolie raised awareness of these genes when she announced that she’d had a double-mastectomy to reduce her breast cancer risk, after finding that she carried a high-risk version of the gene *BRCA1*.

Scientists such as Georgia Chenevix-Trench from the Queensland Institute of Medical Research are identifying other genetic variants that can increase vulnerability to cancer. She says: “That’s something we’ve been focusing on hard for the past five or 10 years, particularly for breast and ovarian cancer.”

The researchers have found close to 80 genetic variants that increase breast cancer risk and 20 for ovarian cancer. Although each individual variant only confers a very small increased
cancer risk, in combination they may increase an individual’s risk to the level of a BRCA1 or BRCA2 mutation.

Of course, even people who do not inherit cancer-risk mutations can develop cancer. Environment and lifestyle substantially increase the risk of developing multiple types of cancer. Such factors can combine with internal genetic mutations to disrupt the normal checks and balances on the growth and development of cells, leading to cancer. Smoking, sun exposure and asbestos exposure are known culprits.

Scientists know that one-third of all cancers are preventable with existing knowledge, says Frazer. Reducing smoking and alcohol consumption, avoiding obesity, staying out of the sun and ensuring people take part in screening programs and receive vaccines against hepatitis B and papillomavirus will protect millions from cancer.

If science can deliver those messages, along with new genomic treatments and better assessments of inherited risk, then cancer treatment will be unrecognisable to the doctors he trained with all those years ago, says Frazer.

Can those challenges be met? Frazer is “very optimistic”.

FURTHER READING

Cancer Council Australia is Australia’s peak national non-government cancer control organisation, advising the Australian Government and other bodies on practices and policies to help prevent, detect and treat cancer.

The International Cancer Genome Project – based at the Wellcome Trust Sanger Institute – aims to identify sequence variants/mutations critical in the development of human cancers.

The World Health Organization Cancer Programme’s mission is to promote national cancer control policies, plans and programmes, integrated to non-communicable diseases and other related problems.
Medical researchers are tackling the underlying causes and frightening symptoms of dementia, writes Stephen Macfarlane

The words ‘dementia’ and ‘Alzheimer’s’ are often used interchangeably. This is incorrect. Dementia is not a diagnosis in itself. Rather, it is a term used to describe any condition that leads to a progressive cognitive decline. It is estimated that dementia affects some 280,000 Australians. By 2030, this number is projected to double.

More than 100 causes of dementia are known, the most common being Alzheimer’s disease, which accounts for between 60-70 per cent of all cases. Increasing age is the single biggest risk factor for Alzheimer’s disease, and with modern medicine steadily increasing its capacity to extend the lifespan through the improved management of chronic disease, more people are surviving longer and to a very old age.
For those of us lucky enough to survive into our nineties, we will have a 50-50 chance of suffering Alzheimer’s at that point.

Treatments for Alzheimer’s disease are in their infancy. So-called cholinesterase inhibitors are the current mainstay of treatment. These drugs help damaged and dying brain cells – neurons – function better, producing a short-lived improvement in memory and cognition. They fail to modify the outcome of the disease in any way, however, and their benefit generally abates within two years of treatment.

There is a singular urgency, therefore, to develop treatments that target the pathology of the disease to produce a true disease-modifying effect rather than purely symptomatic benefits.

Two key pathologies are present in the brains of Alzheimer’s disease sufferers. The first is the presence of abnormal Tau protein within affected neurons. When Tau is normally configured it allows transport of nutrients and brain chemicals called neurotransmitters along neuronal extensions. It provides the ‘backbone’ of these cellular transport channels. When Tau becomes involved in a chemical reaction known as hyperphosphorylation – regulated by a large molecule known as the GSK enzyme – it loses its structural rigidity and collapses in upon itself, forming a characteristic ‘tangle’. The formation of a tangle, per se, is not causative for Alzheimer’s disease, but represents the end stage of a chain of pathological processes involving Tau.

A protein called amyloid is the second disease-defining pathology in Alzheimer’s. In its usual physiological form amyloid is ubiquitous in animal species. We all have the protein circulating within our systems, but when an abnormality occurs in its production, resulting in a molecule slightly longer than usual, amyloid can become involved in a series of chemical reactions that damage neurons.

Abnormal forms of amyloid attract various metals that are present as trace elements within our bodies. When these metals react with oxygen in the bloodstream they produce toxic products, known as free radicals, that damage cells and disrupt cell functions, leading to neuronal death.

While researchers differ over which of these two pathologies kickstarts Alzheimer’s disease, they are following both lines of inquiry.

There are a number of medications known to target the abnormal phosphorylation of Tau. Lithium, for example, has been used for 60 years in psychiatry and is known to inhibit the action of GSK at low doses. High-dose selenium supplements may also help reverse

The challenge is to identify and treat people with the pathology before they develop symptoms of cognitive impairment.

JOHN’S STORY

‘John’ was 63 when he lost his job as a senior manager in a multinational corporation. His colleagues thought he had lost his edge, or perhaps was drinking too much. His wife suspected that something was wrong, but was aware of his stress at work, and attributed any changes to that.

Six months later, John was diagnosed with Alzheimer’s disease.

He began taking a cholinesterase inhibitor and shortly thereafter enrolled in a clinical trial of an antibody engineered to target the amyloid protein. He remains on the study drug and continues to be independent in many of his personal, domestic and community activities. After three years on medication he has declined at a rate some 30 per cent less than might have been expected in the absence of the study drug.

John is arguably one of the lucky ones, having been in a particular subgroup of patients who have been shown to benefit from this intervention. More research is needed to clarify the reasons for varying response rates in different patient groups within clinical trials.
Tau pathology by decreasing the amount of insoluble protein present. Melbourne company Velacor Therapeutics is at the forefront of this latter approach.

Illustrating the contributions from branches of science as diverse as immunology, biochemistry and genetics, several therapeutic approaches to the presence of abnormal amyloid are in the pipeline. They include various immunisation strategies, medications that inhibit the formation of amyloid by blocking the enzymes that lead to its production and others that promote dissolution of plaques by disrupting their toxic interaction with metals. Such a compound is PBT2, developed by Melbourne-based Prana Biotechnology, which has been in clinical trials for more than a decade now and is slowly progressing towards commercialisation.

While medications that target the pathology of Alzheimer’s have been in clinical trials for more than a decade, these trials have generally had disappointing results. A number of studies have demonstrated that some drugs produce dramatic changes in measurable levels of markers of the disease in blood, but very few trials have demonstrated cognitive, or other clinical, benefits. In those that have, such benefits are largely confined to specific patient subgroups and to improvements on specific subscales of broader cognitive measures; their clinical significance is doubtful.

These disappointing results might best be explained by the stage at which people seek medical assistance, worried they might have Alzheimer’s disease. While the oft-repeated claim that we only use 10 per cent of our brain power is an overstatement, it is certainly true that our brains hold more neurons than they need to work effectively. We have, consequently, a vast ‘cognitive reserve’.

By the time somebody notices symptoms of memory loss, the capacity of our brains to compensate for the damage inflicted by Alzheimer’s has, by definition, already been exceeded. A large amount of damage has already been inflicted and it may be unreasonable to expect improvement or even stabilisation of the disease, even at the point where difficulties first become apparent.

It’s well known that amyloid pathology is present in the brains of those who subsequently develop Alzheimer’s for at least 10-15 years before the earliest symptoms of the disease appear. But

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>INTERNATIONAL PREVALENCE (%)</th>
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<tbody>
<tr>
<td>60–64</td>
<td>1.3</td>
</tr>
<tr>
<td>65–69</td>
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<td>75–79</td>
<td>6.5</td>
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<td>80–84</td>
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<td>85–89</td>
<td>20.1</td>
</tr>
<tr>
<td>90+</td>
<td>41.5</td>
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</tbody>
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Table 1: The percentage of people within the specified age group who suffer from dementia.
neurons continue dying throughout that time. So now the challenge is to identify and treat people with the pathology before they develop symptoms of cognitive impairment.

Alzheimer’s cannot yet be prevented. Still, the development of radioactive tracer compounds that bind to amyloid and are detectable by brain scanners has opened the door to the possibility that asymptomatic individuals who harbour the pathology might be identified, leading the way to preventive treatments. These scans are being used in large-scale local research efforts, such as the Australian Imaging, Biomarker and Lifestyle Study, to help track the progress of both healthy volunteers and people with various stages of cognitive impairment in an effort to learn more about the progression and development of Alzheimer’s pathology.

Prevention, in medicine, is always easier to achieve than cure. For those concerned about developing dementia in later life, there are a number of simple and powerful interventions that can help lower an individual’s chances of developing the illness. The risk factors for Alzheimer’s disease are now well known by clinicians, and are identical to those for cardiovascular disease and stroke. It is epidemiological research, rather than efforts focused within the laboratory, that has led to the clear elucidation of these risk factors over the past three decades.

Although old age and a family history are unmodifiable risk factors, other known contributors, such as high blood pressure, cholesterol, smoking and diabetes, can be reduced or controlled by lifestyle changes and medical intervention. It is the control of these variables on a national scale that gives modern medicine the greatest opportunity to impact the prevalence of dementia in the 21st century.

**FURTHER READING**

Alzheimer’s Australia is the peak body providing support and advocacy for the more than 321,000 Australians living with dementia.


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**MANY KINDS OF DEMENTIA**

While Alzheimer’s is the most common form of dementia in Australia, other causes are also frequently diagnosed.

**Vascular dementia** accounts for 10-15 per cent of all dementia cases. Its onset is often relatively sudden and there can be periods of stability punctuating ongoing decline. A history of vascular disease is often present in other organs and evidence of multiple small strokes or of blood-vessel disease in the brain is often discovered during brain scans.

**Lewy Body dementia** – 10-15 per cent of all cases – is closely related to the dementia that can accompany Parkinson’s disease. In its early stages, it is frequently misdiagnosed as Parkinson’s, as patients tend to develop the motor slowing, shuffling gait and rigidity that characterise the better-known neurological condition. Other common symptoms include visual hallucinations, fluctuations in cognition, daytime sleepiness, vivid dreams, problems in the regulation of the autonomic nervous system – often experienced as urinary incontinence or falls – and extreme sensitivity to antipsychotic medications often used to treat hallucinations.

**Frontotemporal dementia** accounts for 5 per cent of cases and tends to strike younger people. For those in their fifties it is probably more common than Alzheimer’s disease. Telltale symptoms include either behavioural and/or personality changes or early language difficulties, usually problems finding the correct words or a difficulty recognising objects for what they are.

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**ASSOCIATE PROFESSOR STEPHEN MACFARLANE** is the director of Caulfield Aged Psychiatry Service in Melbourne, and associate professor of Aged Psychiatry at Monash University.
IT’S NOT ALL IN THE MIND

“Our mind is racing. It’s making connections between people, places, events, figuring out things you’ve never understood before.

“There is no such thing as a coincidence,” says Matt (surname withheld). “Your mind is working things over and over.”

Matt has schizophrenia and is describing his first psychotic episode. His brain made false connection after false connection. His heightened awareness focused on things that were not real.

“I just started to think everything I saw and heard was about me… I was terrified,” he says.

Schizophrenia is a life-changing condition. Australians diagnosed with it die, on average, 25 years early. It is part of a spectrum of symptoms and experiences we call “mental illness”, an enormously broad term that will apply to one in five Australians each year.
Understanding, treating, and preventing mental illness is one of the most complex and difficult tasks facing scientists. The research depth and breadth needed – from understanding the tiniest molecules to the broadest measures of population health – is enormous.

But research into mental illness holds the promise of spectacular gains: not only curing emotional pain but understanding how the most social organ in the body – the brain – is affected by the world around it.

Just what is a ‘normal’ behaviour is defined by culture. Our expectations of behaviour change over time and differ between societies. And as scientists look deeper into mental illness they are questioning the established ‘objective’ boundaries of disease.

For Matt, the difference between healthy and unhealthy is obvious. But sorting illness from normal emotional and personality differences is frustratingly difficult at times.

This tension between treating illness and ‘medicalising’ normal life came to a head in May 2013 with the launch of the fifth volume of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-V), which influences diagnosis, and shapes research, law and policy.

US psychiatrist Paul Chodoff summed up the difficulties in a 2005 letter to Psychiatric News proposing a new diagnosis: “the human condition”. It would cover everything from distractibility, unhappiness, body image dissatisfaction and upset when things go wrong. The diagnosis “would facilitate insurance reimbursement… and encourage the quest for a drug to cure the disorder of being human,” he wrote. Many critics of modern psychiatry argue Chodoff’s joke wasn’t far off the truth.

Among them is Allen Frances, architect of the fourth edition of the manual. “We were definitely modest, conservative and non-ambitious in our approach to DSM-IV,” he says. “Yet we had three epidemics on our watch – autism, attention deficit-hyperactivity disorder (ADHD) and child bipolar disorder.”

When his taskforce reduced the number of symptoms for ADHD they thought it might increase by 15 per cent. Instead, diagnosis increased by 200 per cent.

In Canada, a 2012 study of nearly a million primary school children showed how subjective diagnosis can be. It found boys were 30 per cent more likely to be diagnosed with ADHD – and 41 per cent more likely to be medicated – if they were simply the youngest in their school year.

Critics fear the new manual will create a new generation of epidemics.

So controversial is it that, on the eve of its release, key treatment and research bodies have called for it to be abandoned. But they’re split

**FUTURE DRUGS**

Medications for mental illness are known for their side effects and limited efficacy for some symptoms. Antipsychotics, for instance, increase the risk of weight gain, diabetes and elevated triglycerides and cholesterol.

But researchers like Karen Gregory hope future drugs – some already in early trials – will seek out new targets, with fewer side effects.

A National Health and Medical Research Council (NHMRC) Overseas Biomedical Postdoctoral Research Fellow, Gregory says traditional antipsychotics target dopamine, which is involved in motor control, motivation, arousal, and reward.

“However, these therapeutics don’t treat all the symptoms associated with schizophrenia,” she says. “One of the key challenges is… how to target negative and cognitive symptoms, which are correlated with long-term patient outcomes.”

Two promising neurotransmitters being targeted are glutamate, which has reduced signalling in schizophrenia, and acetylcholine, which modifies areas of the brain believed to have reduced functioning when someone has the condition.

Dr Gregory says new drugs targeting these transmitters could be available within 8-10 years.
on whether the focus should shift to developing new, better, solely medical models of mental illness, or broader models that take into account both individual experience and measures of population health.

The US National Institute of Mental Health, the world’s largest mental health research body, made waves by saying it would abandon the DSM in favour of a new biomedical model, which, it states, will “transform diagnosis by incorporating genetics, imaging, cognitive science”.

It’s an ambitious project. As yet, “no scientific studies to date have shown that a brain scan by itself can be used for diagnosing a mental illness or to learn about a person’s risk for disease,” the Institute says.

Sydney psychiatrist Tad Tietze quotes Samuel Beckett to describe the Institute’s announcement. “Try again. Fail again. Fail better.” He says such an approach will always be too narrow because it fails to pick up the underlying social causes of mental illness.

The British Psychological Society says attempts to pin down mental illness objectively on symptom lists, brain dysfunction or chemical imbalances are not evidence-based and are doing more harm than good.

“Patients can spend years rotating in and out of hospital without anyone sitting down and trying to help them make sense of their distress in terms that are personally meaningful to them,” says Lucy Johnstone, a psychologist and member of the Division of Clinical Psychology with the society.

But what if these big picture social factors could be revealed under the microscope?

In his University of Newcastle lab, geneticist and molecular biologist Murray Cairns is working to discover what goes wrong in the brains of people like Matt. Cairns’ work on microRNA has found these tiny molecules – which enable complex patterns of gene expression, or action – could be the key to understanding schizophrenia.

He says massive global genetic studies are pinpointing hundreds of genes potentially linked to the disorder. Cairns is not bound by the DSM. Instead, he seeks to understand gene
expression in different subtypes of schizophrenia such as those with psychotic symptoms or cognitive impairment.

“In most people, schizophrenia is probably caused by a large number of (gene) variants that are actually common in the population,” he says. The question is why some people with the variants develop the disorder while others don’t.

MicroRNA could be the answer, says Cairns. It enables brains to change, responding to environments and experiences by forming new connections, turning genes on and off in the process.

Cairns thinks it’s unlikely single microRNA molecules or genes will be identified that cause illness. Instead, he is looking at complex pathways, or combinations of changes, that may lead to similar types of symptoms.

“Everything boils down to molecules,” Cairns says. “Healthy or unhealthy, every second there are changes going on. Every thought we have changes the chemistry in our brains and that chemistry is defined by both environmental inputs and genetic inputs.”

Early-life poverty, stress, inflammation, maternal infection and circadian rhythm disruptions are among the many issues identified as potentially pushing people down a path towards illness.

And scientists are now discovering genetic risk factors thought to be linked to one condition are actually linked to multiple mental illnesses, with genetic changes initially investigated for schizophrenia now linked to conditions such as autism, ADHD and bipolar disorder.

In his 2010 book Crazy Like Us, Ethan Watters shows how socially and historically defined frameworks for expressing psychic pain can also influence illness progression.

He visits Zanzibar to explore the puzzling phenomenon that people with schizophrenia in developing countries seem to fare better than those in western countries – a reversal of the usual split of health outcomes between rich and poor.

There, Watters discovers that researchers have found that religious, fatalistic and non-individualist beliefs allow a more accepting attitude towards schizophrenia, decreasing emotional intensity between families. Lower levels of “high expressed emotion” are known to be protective against relapse.

Belief in commonly occurring spirit possession also helps explain psychosis. “The point was not that these practices were effective in combating the biological causes of schizophrenia,” he writes. “Rather, they were simple examples of the sick person [being kept] within the social group.”

President-elect of the Royal Australian and New Zealand College of Psychiatrists, Mal Hopwood, says the complicated story behind mental illness leaves the public feeling confused and perhaps bemused.

But in the end, “to consider either biological or social factors exclusively would really be missing the point,” he says.

That’s a complex web to untangle. The scientific examination of the spectrum of mental disorders – a spectrum as diverse as each individual who suffers from them – requires input from scientific disciplines as varied as anthropology and genetics. The lives and happiness of Matt and millions of others are at stake.

AMY CORDEROY is a journalist and the health editor of the Sydney Morning Herald.

FURTHER READING
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Watters, E. 2010, Crazy Like Us, Free Press, New York City.
Tad Tietze’s blog, Left Flank, http://left-flank.org/.
THE HISTORY OF humanity is replete with examples of disease scourges that have devastated human populations – infections such as Spanish flu, bubonic plague, smallpox, and tuberculosis. In the 14th century, bubonic plague – an infection of the lymphatic system resulting from the bite of an infected flea – killed an estimated 25 million people, or 30–60 per cent of the European population, while the 1918–20 outbreak of Spanish flu killed more people than all the military deaths in World War I.

Some of the old threats have now disappeared: for example, certain poliovirus strains have all but been eradicated and the smallpox virus was eradicated in the 1970s in a process overseen by one of the greats of Australian science, Professor Frank Fenner of Australian National University. However, the World Health Organization (WHO) still reports 1000 to 3000 cases of bubonic plague every year globally and new viruses with pandemic potential have appeared in recent decades, such as HIV, Hepatitis C, and new influenza subtypes. Some new pathogens, such as Severe Acute Respiratory Syndrome (SARS) and the newly described Middle East Respiratory Syndrome Coronavirus (MERS–CoV) are significant, but fortunately outbreaks so far have been localised rather than becoming true global pandemics.

Of all the diseases that affect humans, it is the influenza virus that is most associated with pandemics, and it is the influenza virus that this essay is focused on.

INFLUENZA PANDEMICS THROUGH HISTORY
Although influenza pandemics have been described throughout history, differentiating influenza from other infectious diseases was difficult in the past. From 12th century Europe there were convincing descriptions of possible influenza pandemics, but determining whether
these epidemics were truly global was impossible for many centuries (See: Epidemic or pandemic).

Perhaps the first modern description of an influenza pandemic occurred in 1889-1891: a pandemic that arose in Russia in the spring of 1889 and spread globally. This outbreak reached Australia and New Zealand in March 1890. In this pandemic, the secondary bacterial infections that cause pneumonia, and may complicate influenza, were first recognised. It was also observed that pandemic diseases may come in waves, sometimes becoming more severe with each surge.

The next great pandemic, often called Spanish flu, is the event to which all others have been compared. At least 50 million people died, and some 25 per cent of the world’s population at the time was infected. Indigenous peoples, previously unexposed to the influenza virus, were the most severely affected, with up to 90 per cent of infected people dying compared with one per cent of those in urban communities. This is likely because urban dwellers had a higher degree of pre-existing immunity to similar flu viruses that protected against the worst ravages of Spanish flu.

The origin of Spanish flu is still uncertain. It possibly started in China and then moved,
through immigration, to the United States. The influence of World War I was strong in the distribution of this pandemic; it spread through the Western Front in Europe, and then quickly scattered around the world as soldiers returned home after the war. It took around 10 months for the virus to reach Australia, most likely due to the length of time it took for ships to reach here, and the strong quarantine measures initially imposed on arriving ships.

Once the virus arrived in Australia and the Pacific, the impact was significant; particularly in some of the remote Pacific islands where mortality rates as high as 25 per cent were reported. Clinical descriptions at the time included the sudden onset of what would now be diagnosed as acute viral pneumonitis (inflammation of the lungs), with rapid progression and death. Secondary bacterial infections such as pneumonia were also common, and may well have been the major cause of death.

An important feature of the 1918-20 pandemic was that deaths occurred mainly in young adults, in contrast to what is usually observed in the very young and elderly during the annual winter influenza epidemics.

**SUBSEQUENT FLU PANDEMICS**

There were further pandemics during 1957–58, 1968–70, 1977–81 and 2009, caused by different influenza A subtypes. Normally the new pandemic subtype displaces previous circulating influenza subtypes; however, sometimes subtypes can co-circulate, which happened in 1977–81 (A/H1 with the previously circulating A/H3) and 2009 (a reassortant A/H1N1 with the older A/H3N2) (See: *Reassortant influenza viruses*).

The 2009 influenza A/H1N1 pandemic spread quickly – in contrast to earlier pandemics, air travel was very important in its rapid global movement. As with Spanish flu, younger adults were most frequently affected. Very elderly individuals, alive in 1918 or the decade following, were less affected as they had A/H1N1 immunological memory through antibodies formed during childhood exposure to the Spanish flu subtype.

**INFLUENZA ISOLATION AND IDENTIFICATION**

Although influenza pandemics have been described throughout history, differentiating influenza from other infectious diseases was difficult in the past.
The influenza virus was first isolated from pigs and then grown in laboratories using chicken eggs, and then later using new methods of growing viruses in laboratory cell cultures. These methods were enhanced by Sir Macfarlane Burnet and others in Australia, and are still used today in specialised virology laboratories.

The isolation of the influenza virus from a human occurred two years later in 1933 and accompanying epidemiologic, laboratory and public health investigations now allow the accurate assessment of influenza pandemics. Today, we are able to grow and culture the influenza virus in the laboratory and use molecular biology techniques to determine which virus subtype is responsible for the infection.

In the 1980s, Peter Colman’s protein crystallography group at the CSIRO in Melbourne discovered the crystal structure of the influenza neuraminidase protein, found on the surface of the virus, which is critical for the influenza virus lifecycle (See: What is influenza?). This discovery fast-tracked the development of the now widely used neuraminidase-inhibitor drugs, such as Relenza and Tamiflu.

Advances in science also now allow us to determine the mechanisms by which these viruses attach to receptors in birds, pigs or humans; their sensitivity to antiviral drugs; their likelihood of responding to vaccination; and to understand their spread in the community, including closed communities such as university colleges, schools, and aged care facilities.

**PREVENTING FUTURE PANDEMICS**

Science has helped us come a long way since Spanish flu. As a result of work by the CSIRO and others, antiviral agents were available for the A/H1N1 pandemic in 2009, although their value was not always easy to determine. An influenza A/H1N1 vaccine was available soon after the first wave, meaning that where it was routinely available, the subsequent waves – and there have been at least three – were probably diminished. Unlike many other countries, Australia has influenza vaccine manufacturing capacity.

Advances in medical technology – such as the antibiotics used to treat secondary infections following infection with the flu virus, and

**REASSORTANT INFLUENZA VIRUSES**

For a new influenza subtype to cause a pandemic, it must not only move into humans from its animal source, but must also be readily transmissible from person to person. Reassortant influenza viruses occur when influenza genes from different animal sources mix to become a novel subtype. For example, the 2009 pandemic virus contains genes from influenza viruses from humans, birds and pigs from both North America and Asia, resulting in a novel virus that then spread worldwide.
intensive care medicine – probably contributed to a significantly reduced death rate in 2009 compared with 1918-20. By the same token, immune suppression in the general population – due to therapy for other illnesses, diabetes and respiratory disease, transplantation and other immune-suppressive diseases and newer problems such as obesity – are likely to have contributed to the mortality and morbidity attributable to the influenza outbreak.

Other influenza viruses continue to pose concerns for future pandemics. The avian A/H5N1 virus has been circulating in poultry throughout various countries in South East and Central Asia, and the Middle East and Africa, for some years. Although human infections are associated with a very high mortality, significant person-to-person transmission has not occurred. Thus, although the potential remains, a pandemic has yet to develop.

Similarly, the emergence of A/H7N9 influenza in China in the last 12 months has raised concerns about worldwide spread. Fortunately, this has not happened and cases remain essentially limited to China. However, these examples show that although new influenza viruses continue to emerge, we cannot predict the likelihood of them causing a pandemic.

New scientific technologies have allowed an understanding of how these viruses
cause disease: for example, the ability to detect the 1918–20 virus in old clinical specimens using molecular techniques, and the ability to ‘recreate’ these viruses in the laboratory. Despite careful attention to biosecurity, this has raised ethical concerns on how such research should be undertaken; work is currently being done to address these concerns.

Rapid and sensitive laboratory tests to detect new viruses are a focus of research and development in Australia, especially at the WHO National Influenza Centres in Sydney (ICPMR at Westmead Hospital), Melbourne (VIDRL) and Perth (PathWest). The WHO Collaborating Centre for Influenza Research and Surveillance in Melbourne is one of five collaborating centres worldwide, and has a particular role in determining the annual influenza vaccine components.

THE FUTURE OF PANDEMICS

The ease, volume and rapidity of air travel, the increasing world population, diminishing vaccination rates, changes in animal husbandry (especially of birds and pigs) and the increasing frequency of mass gatherings (sporting, cultural and other such events) all contribute to rapid spread of new viruses. These features now guide approaches to public health management and preparedness for viral infections. Surveillance, both in the clinic with infected patients and in the laboratory with virus strains, underpins pandemic responses, at state, national and international levels.

The contribution of scientific advances to allow rapid identification and isolation of influenza virus strains together with these advanced surveillance techniques means that we are more prepared than we have ever been to deal with the pandemic threats of the future.

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FURTHER READING


WHO Collaborating Centre for Influenza Research and Surveillance (Melbourne) – part of the WHO Global Influenza Surveillance and Response System established in 1947 to monitor the frequent changes in influenza viruses.


Research on sets of individuals, whether in the community or laboratory, only partly explains the causes of disease, writes Tony McMichael.
The Stream of media stories about the seemingly ever-increasing numbers of Australians who are overweight or, frankly, obese continues relentlessly. Meanwhile, other media reports tell us excitedly about every newly discovered gene in laboratory rats that affects weight gain, about obesity that runs in families – “it must be genetic” – or about overweight people being more likely to be sugar and fat addicts.

So you might conclude from this that the overall problem is due to individuals’ abnormalities of genes, metabolism or behaviour. Well, that conclusion is largely wrong.

The mistake is to have looked only within the population and noticed some distinctive things about the most overweight people. The health research arena offers us many such individual-level observations: individuals who have a stroke from a burst blood vessel in the brain often have very high blood pressure; individuals who smoke are much more likely to have lung cancer; individuals experiencing heart attack typically have personal histories of eating a lot of fatty foods. These are important initial findings, but they fail to consider the larger-framed and more interesting question about trends in the health profile of the whole population.

The Population Perspective

A different perspective emerges, however, when these health problems are viewed on a larger canvas, at population level. Focusing first on stroke, national statistics show that the average blood pressure in the adult Australian population drifted upwards during the 1920s to 1940s and then in the late 1950s began to come down.

When I studied medicine in the 1960s the ‘normal’ blood pressure for a person was said to be 100 + Age. So a 60-year-old was expected, on average, to have a top (systolic) pressure of 160. That systolic blood pressure of 160 in 60-year-olds, then considered ‘normal’, would today be deemed significant hypertension, needing drug therapy. Meanwhile, the annual rate of death from stroke in Australia followed a similar up-then-down time-trend.

That time-trend raised an important question. Why did average blood pressure in the Australian population—at-large rise during the first half of last century and then fall over the final four decades? Further research indicated that the rise was related to the increase over time in the amount of available food per person in Australia, gradual increases in average body weight, and in the intake of salt (including as a food preservative in the pre-refrigeration era). The subsequent post-1950s downturn was largely attributable to the advent of new blood pressure-lowering drugs and a decreased reliance on salted foods.

Similar population-level explanations exist for the other examples. As the Australian diet became less fat-laden during the latter 20th century, partly influenced by the introduction of Mediterranean dietary habits and partly due to increases in public understanding, rates of heart attack decreased (clinical interventions, too, were becoming more effective). The adding of fluoride to reticulated drinking water (except for Queensland!) was followed by a reduction in childhood dental decay.

That larger-canvas perspective is the essence, the challenge, of population health. On that view, the population itself, as a living super-organism, has its own ecology – its own way of living, working, eating, relaxing and socially interacting. Changes in human ecology over time make big differences to patterns of poor health, diseases and premature death. So, our society will continue to miss the key point in much public discussion and policy-making if the primary focus on individual-level factors persists, buoyed by the prevailing philosophy of neoliberalism and individual responsibility. Good population health research provides guidelines for society as to what should be modified in our shared way of living; it addresses ‘Big Policy’ options.
A larger-canvas perspective is the essence, the challenge, of population health. On that view, the population itself, as a living super-organism, has its own ecology...

en masse. There must, then, be some change in the physical and social environment in which the population is living, a change in human ecology.

The basic problem is that, over the past 4-5 decades, the entire population has undergone a shift in average personal daily ‘energy budget’ – the ratio of energy intake (from food) compared to the amount of energy expended (mobility, working, recreation, and household activities). Hence, the population-level domain offers the best opportunity for substantial and enduring solutions – unless we use mass medication (analogous to fluoride in drinking water) to suppress appetites, or prohibit people from sitting down for more than four hours per day!

This population health perspective on overweight-obesity leads us into more creative, community-wide and far-reaching solutions. These include improving urban and suburban design to facilitate walking and cycling; upgrades in urban transport to reduce reliance on cars (good for urban air quality too); better recreational facilities and more green space for physical activity; and changes in work habits so that we spend less time glued to desks and computer screens without moving more than a few finger muscles for 2-3 hours at a time.

OTHER IMPORTANT ROLES AND INSIGHTS FROM THE POPULATION APPROACH

The population health perspective has other important roles. Two examples are illustrative. First, this perspective prompts comparison of health risks, experiences and needs of sub-populations: suburbs of lower and higher socio-economic position, males and females, different age-groups, ethnic groups and urban versus rural. And that provides an evidence base for much social policy.

SEEKING EXPLANATIONS FOR THE RISE OF OVERWEIGHT AND OBESITY

Now, returning to the overweight-obesity topic, undoubtedly some individuals are at higher risk than others. Populations always comprise a range of individuals with minor, genetically-determined, differences in their metabolism, including how food energy is either stored or burnt. Indeed, that’s generally true for most diseases.

When a population lives in a way that generally fits natural human biological needs, then those minor differences rarely matter. But when the population’s rate of some particular health disorder rises over several decades, that means something more general is amiss.

The recent rapid rise in overweight-obesity can’t be due to good or bad genes; their frequency within the population is essentially unchanging. It can’t be because the proportion of aberrant personalities and behaviours has increased; those are fairly culture-bound and don’t change
Multiple sclerosis (MS) is an autoimmune disease in which the body’s immune system inadvertently attacks and destroys the insulating protein lining of the central nervous system, the myelin. In the ongoing Australian ‘Ausimmune’ study of risk factors for MS, the rate of occurrence of the preclinical MS condition (the ‘first demyelinating event’) ranges from 2.1 per 100,000 people per year in Brisbane to 8.7 per 100,000 in Tasmania. A fourfold increase as you travel south. There is no evidence of greater genetic susceptibility in the Tasmania population compared to Brisbane, which suggests that the observed difference in rates is due to some locally pervasive environmental factor. This population-level observation, similar latitude gradients in Europe and several other countries, suggests that the lower the local population’s level of sun (solar ultraviolet) exposure, the higher the MS risk.

Ultraviolet radiation is known to affect the body’s immune system. One pathway may involve vitamin D, largely produced within the skin by sunlight exposure. Average vitamin D levels are higher in Brisbane than Tasmania – indeed actual vitamin D deficiency is more common in Tasmania. Overall, we’re finding that both lower levels of sun exposure and lower vitamin D levels are linked to an increased risk of having a first demyelinating event.

Genetic studies have shown that variants of several genes affect the body’s response to vitamin D, and some may affect MS susceptibility more directly. So, individual genetic make-up may influence which individuals are most likely to develop MS. We and others have also considered epigenetic influences, whereby the lifelong activity of certain genes is, in effect, switched on or off in very early life by contact with exogenous factors, particularly dietary components. Some dietary molecular fragments can attach permanently to a particular gene during foetal life and switch the gene on or off.

Epigenetic phenomena contribute to a variety of disease processes. This, interestingly, is a case of nature via nurture.

Second, it helps us understand and control the spread of infectious diseases. Occasional cases of measles occur anyway, but when an epidemic breaks out it indicates that the population’s ‘herd immunity’ has been lost. That is, an insufficient proportion of oncoming youngsters have been vaccinated, such that the measles virus can now maintain active circulation within the population.

A further role is that observations at population level can provide clues leading to more detailed studies. Our Environment and Health research group at the Australian National University’s (ANU) National Centre for Population Health and Epidemiology working with a network of collaborators, has discovered one such clue by comparing regional rates of the autoimmune disease multiple sclerosis (MS) especially in reference to latitude and sun exposure. (See: Influences on the occurrence of Multiple Sclerosis at population, individual and molecular levels: the fun of piecing together a jigsaw puzzle).

THE KEY MESSAGE: UNDERCURRENTS CAN PROVIDE GREATER INSIGHTS THAN SURFACE RIPPLES

To reiterate, the key message here is that understanding rising rates of diseases in populations often requires attention to the underlying ‘upstream’ population-level influences. If a whole population eats a high-fat diet, then the annual rate of heart attack will be higher for that population than in others. Yet if, for example, every individual within that population eats very similar amounts of fat, but 30 per cent of them smoke and 70 per cent do not, then individual-level studies will mistakenly indicate that smoking, not dietary fat, is the main cause of heart attacks. Policy priorities may then be misdirected.
Similarly, to reduce MS rates we have learnt that a population should maintain a sufficient but not excessive exposure to sunlight, and avoid vitamin D insufficiency. As both work and recreation are tending to move indoors in modern Australia, average personal levels of sun exposure within the population are declining. At the individual level, there are some opportunities for family counselling based on genetic testing, although the role of genes in MS appears modest.

So the lesson is clear. Bifocal lenses should be used when examining the causes of disease, considering influences at both population and individual levels. Population health research often provides the best basis for the long-term lessening of various diseases in the population. With overweight and obesity, the real challenge, and long-term pay-off, is at the whole-community, or population, level – getting our planning of living environments and facilities and our way of daily life back in kilter with natural human biological needs, including restoring an input-output energy balance.

And that is where the challenge, the satisfaction and the fun of thinking in population health, resides – in thinking more broadly, and integrating one’s ideas and strategies with those of interesting colleagues from other disciplines and sectors.

FURTHER INFORMATION


The remarkable development of the Australian wheat industry clearly illustrates the role science plays in securing our daily bread, writes Snow Barlow.

AGRICULTURE BEGAN with the domestication of wheat and barley in ancient Mesopotamia (part of the Middle East based on modern Iraq and Syria) more than 10,000 years ago. The food stability provided by these temperate cereal grains that could be stored over winter, enabled the development of ‘settled’ societies and allowed people free time for intellectual pursuits, culminating in the science we know now. It is on the modern version of this science that our civilisation will now depend in our efforts to ensure the world can feed the nine billion people projected by 2050.

In 1798, English scholar Thomas Robert Malthus predicted that populations would soon outpace food production: “The great law of necessity which prevents population from increasing in any country beyond the food which it can either produce or acquire, is a law so open to our view … that we cannot for a moment doubt it.”

Despite these dire predictions, over the past 150 years food production has generally kept pace with the seven-fold human population growth, from about one billion to today’s seven billion plus. Science has played a pivotal role in increasing crop yields by up to tenfold over those of our ancient ancestors. Today, wheat, rice and maize (corn) supply more than 60 per cent of the globe’s carbohydrate demand, essentially humanity’s daily fuel.
The rise of Australia's wheat industry to one of the major global wheat exporters – with the United States and France – illustrates the role science plays in securing our daily bread. Globally, wheat accounts for one-third of total cereal production, or 700 million tonnes per year. It is grown across a broad range of temperate environments, including the drier edges of the world’s great cropping areas.

The Australian wheat belt is a good example, stretching some 4000 km around the drier edges of the cropping zone, from Emerald in central Queensland to Geraldton in central Western Australia. In this region, 38,000 wheat farmers produce 38 million tonnes per year valued at AUS $8.5 billion – 5 per cent of world wheat production and 14 per cent of world wheat trade.

**CONSERVATION AGRICULTURE**

Conservation agriculture is a farming system developed in recent decades to conserve rainfall in soils, resulting in significant wheat yield increases. Moisture loss from soil has been reduced by replacing traditional mechanical cultivation of land – to control thirsty weeds during the summer – by chemical weed control that requires minimal tillage or soil disturbance. Additionally, the wheat stubble that remains after harvesting is left in place instead of being removed by burning or cultivation, again conserving water in the soil. Weeds are controlled by herbicides and crops are directly planted into the previous year’s stubble.

Global Positioning Systems (GPS) have been an essential part of the development of these new farming systems. GPS allows farmers to sow seeds at an accuracy of 20 mm, directly between adjoining stubble growths from the
previous year, to protect further the emerging crop from the weather (see Figure 1: Australian wheat yields from 1860 to 2012). Because of this technology farmers don’t drive around and around their paddocks. They drive up and down, reducing ‘overlap’ and using 5-10 per cent less time and fuel. This precise and repeatable positioning allows the farmers to set up ‘tram tracks’ for farm machinery in their paddocks, thereby minimising the compacted area. Reduced soil compaction can provide a further 5-10 per cent increase in yields.

Scientific advances in plant disease control have also contributed to increasing wheat yields. Wheat fields are complex biological systems where disease organisms, particularly those causing root diseases, can multiply if the same crop type is grown each year. As these disease organisms are usually specific to each crop, the build-up of disease organisms and resulting yield decreases can be averted by growing a different crop type – a so-called ‘break crop’ such as canola or chickpeas – as part of a crop rotation that can increase the yield of the subsequent wheat crop by as much as 20 per cent.

**DEVELOPING NEW WHEAT VARIETIES**

To reduce further the problem of getting the crop sown before winter, crop physiologists are seeking to exploit genetic variation in ‘coleoptile’ length. The coleoptile is the strong tube that emerges from a germinating wheat seed and grows towards the soil surface while protecting the soft first leaf within it. Current wheat varieties have coleoptiles some 50 mm long, effectively limiting their sowing depth.
to 50 mm. However, varieties do exist with coleoptiles as long as 150 mm (see picture, p59). Using wheat varieties with this length would allow seed to be sown into the subsoil where moisture from summer rains is available, enabling crop establishment at the correct time and likely resulting in increased yields.

Land plants, including crops, use water as a means of transporting nutrients from the soil to their leaves where photosynthesis occurs. During photosynthesis, as plants open the small holes (stomata) in their leaves to absorb carbon dioxide (CO$_2$) from the atmosphere, the water within the leaf evaporates and is lost from the leaf to the surrounding air (see: A brief guide to photosynthesis).

For every molecule of CO$_2$ absorbed by the leaf in photosynthesis between 100 and 1000 molecules of water are lost to the atmosphere through evaporation. This is why plants need so much water.

In the 1970s, CSIRO agricultural scientist John Passioura reasoned that Australian wheat yields are limited by the quantity of water available to the crop as the wheat grain grows to maturity and by the crop’s efficient use of water. The challenge was how to measure plant water-use efficiency in a practical way.

At about that time, Graham Farquhar of the Australian National University and his American colleagues discovered that atmospheric CO$_2$ incorporating two isotopes or types of carbon, C$_{13}$/C$_{12}$, diffuses into the plant leaf at different rates because of the differing atomic weights of the carbon isotopes. These different rates are reflected in the composition of the plant. Farquhar and colleagues then showed that the ratio of C$_{13}$/C$_{12}$ could be used in a practical way to measure the water-use efficiency of the plant as the ratio is a measure of the rate of CO$_2$ absorption through the leaf stomata.

Farquhar teamed up with Passioura’s colleague, CSIRO wheat-breeder Richard Richards, to demonstrate that the C$_{13}$/C$_{12}$ ratio of different varieties of wheat could be used to measure their water-use efficiency. Richards has used this technique to identify and breed a new generation of more water-efficient wheat for the Australian environment.

A Brief Guide to Photosynthesis

Photosynthesis is the basis for nearly all life on Earth as it captures energy from the sun’s rays (light), combines it with CO$_2$ to produce carbohydrates – the primary energy source. In the process, oxygen is released which provides the oxygen we breathe from the atmosphere.

\[
\text{Carbon Dioxide (CO}_2\text{) + Water (H}_2\text{O)} \xrightarrow{\text{Light energy}} \text{Sugar (C}_6\text{H}_12\text{O}_6\text{) + Oxygen (O}_2\text{)}
\]
**DRY SOWING**

Australia’s highly variable rainfall is becoming even more variable in the wheat belt due to climate change. This can be challenging for farmers who have traditionally relied on autumn rains to sow their crops before winter. Often summer rains have resulted in good moisture in the subsoil, but the surface soils where the seeds are sown are dry. Enterprising farmers have adapted to this variability and now sow their seeds into the dry surface soils, so-called ‘dry sowing’, so that they are ready to germinate when the rains come. This practice combined with the new long-coleoptile varieties described previously provides Australian farmers with a way to adapt to the changing rainfall patterns resulting from climate change.

**CONCLUSION**

The additive effects of these scientific advances on potential wheat yields is clearly shown in the graph on page 54, illustrating why Australian wheat yields have increased by 50 per cent in the past 25 years. These figures give strong encouragement that the continued application of science to Australia’s most important food crop will lead to further yield increases into the future. As the global population increases beyond nine billion, applying good science to our food systems is the only way they will all receive their daily bread.

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**FURTHER READING**


Prime Minister’s Science, Engineering and Innovation Council 2010, ‘Australia and food security in a changing world’, PMSEIC, Canberra.
