RESISTANCE IS FUTILE

An Australian family business is striving to create a super-antibiotic

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In April last year, a 49-year-old Pennsylvania woman turned up at a local clinic with what appeared to be a routine urinary tract infection. The following month, scientists at a US defence biomedical research facility announced the news doctors had been dreading.

The woman had been infected with a microbe immune to colistin, the "antibiotic of last resort". Colistin is considered the final defence against superbugs that have developed resistance to carbapenems, antibiotics used against rampant hospital infections.

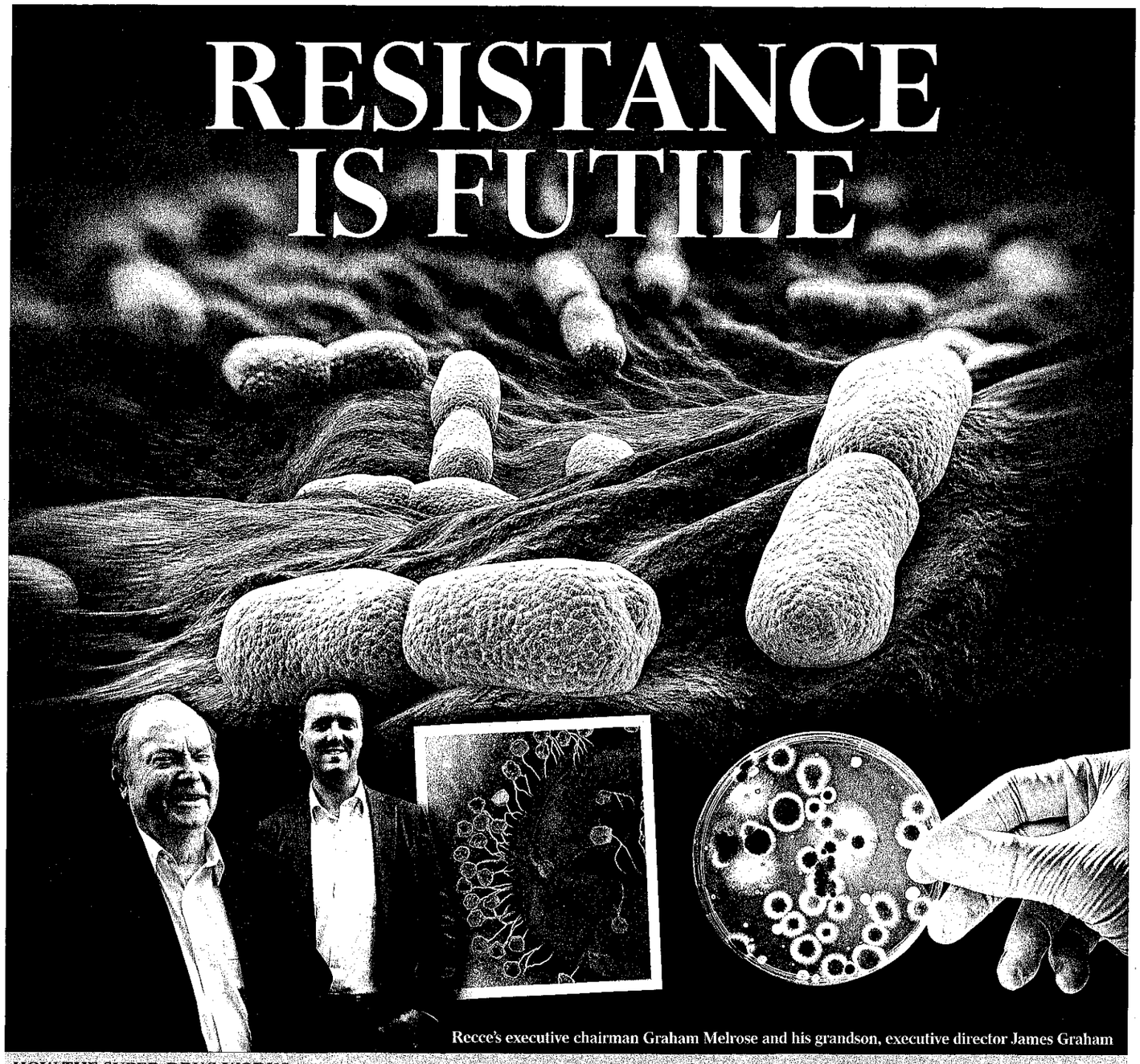
Carbapenem-resistant enterobacteriaceae, or CRE germs, have been dubbed the "nightmare bacteria", killing up to half of the patients they attack. Infections commonly picked up in hospitals spiral dangerously into untreatable pneumonia or bloodstream infections that do not respond to most drugs.

In such cases clinicians turn to colistin, an antibiotic that was discovered in the 1940s but soon fell out of favour. Doctors are reluctant to use it because it damages the kidneys, but the risks of CREs trump the undesirable side effects.

In February last year, Chinese scientists reported a colistin-resistance gene that can transfer from one type of bacteria to another — the first time resistance to the drug had emerged via horizontal gene transfer. The gene, MCR-1, was found in E. coli samples from animals, food and people in China and later Scandinavia. Now it was in the US.

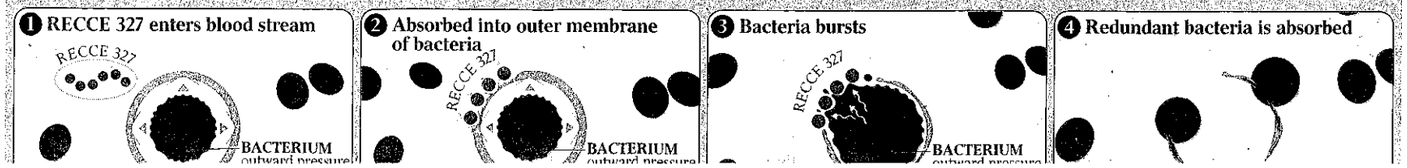
The Pennsylvania woman survived because her infection was treatable with other drugs. But once MCR-1 finds its way into a CRE bug, all bets could be off.

"It is the end of the road for antibiotics unless we act urgently," says Tom Frieden, director of the



Recce's executive chairman Graham Melrose and his grandson, executive director James Graham

HOW THE SUPER-DRUG WORKS



The power to kill should not be state-sanctioned

Legalising euthanasia for terminal illness can lead to 'scope creep'

ANGELA SHANAHAN

Last year I wrote about my brother who died of cancer. He suffered greatly and so did we who accompanied him into palliative care where he met his death. Later that year, another person in my life also died of cancer, but in very different circumstances.

Carolyn had a matter-of-fact attitude to her diagnosis. It was terminal, inoperable and she didn't want to prolong her suffering with chemotherapy. So she made the difficult decision to go into palliative care in a place she loved on the coast. With her doctor's support she maintained her right to refuse treatment except for pain, and she died with almost no pain, in the best circumstances anyone could wish for.

She was religious and her decision was not supported by all her friends. Many of them thought she should "fight it". I was one who did support her. Everyone has the right to refuse treatment. In a terminal situation we have the right to meet death on our own terms. Carolyn, bravely, did just that.

This being the case at present, one wonders why the Victorian parliament has decided there is any need to introduce the dangerous practice of assisted suicide, which will completely overturn present medical ethics. Personal autonomy is not a valid argument for this. Personal autonomy is well respected in Australian medical circles, but assisted dying in the medical system and across the broader culture. Third, there are "systemic failures in the safeguards".

In surveys in Belgium and The Netherlands, doctors acknowledge large numbers of unofficial unreported cases of euthanasia, most because doctors simply don't bother or don't want to report them.

Mulino's dissenting report makes clear that the majority report backed by Victorian Labor premier Daniel Andrews and Hennessy sidesteps the issue.

"It provides no attempt to explain either why persistent growth in cases is occurring or whether the risks with this trend can be managed," Mulino's report says.

His conclusion is that the case has not been made to legalise this practice. Nevertheless, euthanasia campaigners will continue to use the "terminal illness/unbearable pain" argument to justify a huge social change that has far more dangers than benefits, and that leads to the most horrific abuses.

If Victorian euthanasia activists are not interested in the mountain of evidence in Mulino's report, perhaps they should read some of the damning reports in the general media. There is the case of

> In all countries where assisted suicide is legalised, it has expanded to include non-terminal illnesses, psychological disorders and even

The warning struck home in September last year, when all 193 UN member states pledged to work together to tackle drug-resistant superbugs. This move could not have come soon enough for Sanjaya Senanayake, an infectious diseases physician with the Australian National University's medical school. Senanayake says that less than 80 years after antibiotics were introduced, resistance to the wonder drugs already claims 700,000 lives a year. Experts estimate that by 2050 that number will have skyrocketed to 10 million — more than the annual cancer toll — and will cost health systems $100 trillion.

The UN declaration commits states to addressing the triggers of burgeoning resistance: overprescription of antibiotics — with estimates that between one-quarter and one-half of antibiotic use is unnecessary — and widespread use in farm animals. Even more pressing is the need to develop new antibiotics, as the present stock loses its potency. "We grew up in the golden age of antibiotics," University of South Australia microbiologist Rietie Venter says. "A world without effective antimicrobials — where a simple scratch could cost you your life, and where most modern medical procedures would no longer be possible — is unthinkable. Yet the development of new antimicrobials is not pursued by pharmaceutical companies due to the low profit margins."

Now a modest Australian family business is taking up the challenge. Sydney biotech Recce, which relocated its head office from Perth last year, has developed a synthetic antibiotic that it claims can kill ordinary infection-causing bacteria and drug-resistant superbugs.

A US laboratory is testing Recce's antibiotic against mice infected with a CRE strain of E. coli. "If we come out positive, we are doing what nobody else in the world can do," Recce founder and executive chairman Graham Melrose says.

It is the latest of about 10 tests Recce has commissioned so far on its product, preparatory to an investigational new drug application to the US Food and Drug Administration, which would allow it to undertake phase one clinical trials in humans. The company says it has already notched impressive results in tests involving laboratory cultures of gonorrhoea and drug-resistant strains of E. coli and the superbug *Pseudomonas aeruginosa*.

Recce says tests also suggest the drug is effective against non-resistant *Streptococcus pyogenes* and *Clostridium difficile*, both of which can cause life-threatening infections. Another group of tests involved mice infected with methicillin-resistant *Staphylococcus aureus*, or MRSA, a rampant superbug that kills more than 18,000 people a year in the US.

In experiments at an independent US laboratory, 10 mice treated with the Recce antibiotic survived. This compared with nine of 10 rodents dosed with the current antibiotic oxacillin, and four of 10 that received no treatment.

Recce says the drug dissolves well in water-based solutions. Melrose says lack of solubility is the biggest problem encountered by candidate drugs in early stage tests. The company says other tests have demonstrated the product's safety, finding it is "non-genotoxic" — it does not cause cancer, in other words — and does not trigger other side effects in infected or uninfected mice.

It says the drug also appears to have a wide "therapeutic window", with patients able to tolerate doses four to eight times as high as what is required. "Twofold is considered good," says marketing and business development director James Graham, Melrose's grandson. "It's not inhibiting the healthy cells; it's not causing the animals to have any negative side effects," he says. "We've achieved a lot of great things between our listing (last January) and now."

Many antibiotics are modified from natural compounds found in living organisms such as yeast and bacteria. They have a shelf life of 20 years or so before resistance inevitably emerges, through a process of natural selection that has enabled microbes to survive and thrive for countless millennia.

But Recce's ambition is to provide more than just a stopgap antibiotic. It says its drug is immune to the natural emergence of resistance, partly because it is synthetic and therefore an unknown quantity to microbes. "The conventional antibiotic is found and bred from nature," Melrose says. "We decided to start from a theoretical basis. We worked out what we thought would be the best structure for an antibiotic, and then we made it in the laboratory."

He says natural antibiotics have a "lock and key" relationship with the microbes they target. "The germ and the antibiotic fit nicely together. But if the germ mutates, changes shape, the antibiotic will no longer fit.

"Our antibiotic kills the germ because the relationship is not specific. The germ can change its shape and it doesn't matter a damn. Our drug reacts with the same facility to a mutated germ."

Regulatory and microbiology executive Michele Dilizia, who is Melrose's daughter, says the drug has a "universal" mechanism of action. "It attacks proteins that are present in the cell walls of all bacteria," she says.

"Bacteria have high internal pressure. Once the cell wall is challenged by an antibiotic such as ours, it loses its integrity and the outward pressure will result in the bacterial cell bursting."

And the company is not only claiming resistance to bacteria's natural resistance ability. It says the drug has shown early indications that it kills viruses — something conventional antibiotics cannot do — and cancer cells.

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>
> RIETIE VENTER
> UNIVERSITY OF SOUTH AUSTRALIA

"We are like nothing that's ever been dreamt of," Melrose says.

He says he is aware of no other antibiotic that has demonstrated "prominent success" against both bacteria and viruses. "The third, anti-cancer, is dreamland."

These are big claims for a small Australian biotech, exposing it to a potential market that is already worth about $US170 billion ($235bn) and growing quickly.

The Australian market seemed to share the company's enthusiasm when it listed last January, seeking $5 million to help it meet pre-clinical regulatory requirements and fund the development of a production model of the drug. Listed at 20c, Recce shares opened on the Australian Securities Exchange at 30c and climbed to 52c before declining in value. Shares have settled back at between 15c and 20c, partly reflecting the "tightly held structure" of the company and investor jitters around any biotech offering.

Graham says this is ironic because the safety tests had not been conducted when the company listed. These results "enormously derisked" the company compared to last January, he says.

Investor nerves also could reflect Melrose's history. A former research director with healthcare giant Johnson & Johnson and head of applied organic chemistry at the University of NSW, he founded another biotech, Chemeq, after developing a synthetic veterinary pharmaceutical.

Like Recce, Chemeq was an early stockmarket darling but it collapsed in 2007 after Melrose's departure. Its woes were triggered by Australian Securities and Investments Commission proceedings over alleged breaches of disclosure requirements that ultimately led to a $500,000 fine for the company. No action was taken against Melrose.

Investors also could be jittery about the Recce drug's mechanism against viruses and cancer, which defies easy explanation. While bacteria have walls that can be breached, viruses are much smaller structures that can reproduce only in other creatures' cells. And cancer is the uncontrolled growth of mutated cells.

Recce has its own theories about its drug's mode of activity against these diverse pathogens and diseases. But it is not letting on, at least for a couple of years, for fear of spilling the beans to big pharma. "We will announce it when we have to," Melrose says.

If that sounds like a snake-oil merchant at work, the octogenarian says he is motivated by medicine rather than making a motza. "At my age I can only wear one shirt. I've got a damn nice car. What more can I want? It makes no difference whether I've got $1m or $100m in the bank, as far as I'm concerned."

Graham says Recce is pursuing a "short-term pain for long-term gain" strategy.

"Dr Melrose has walked this path many times," he says. "He is focused on presenting the technology to the FDA to get Recce to market as quickly as possible, not educating Recce's highly equipped and rich competitors."

Global regulators appear to be on Recce's side. The company says it has successfully secured patents covering 80 per cent of the global antibiotic market, including Australia, China, Europe, Japan and the US.

And in May it attracted another vote of confidence when Bernadette Murdoch — Australasian head of corporate affairs for pharmaceutical giant Glaxo Smith Kline — joined its board as an independent non-executive director. Murdoch says the move reflects her personal faith in the drug, rather than an official endorsement from GSK. She concedes that Recce's agenda is "very ambitious", and the pharmaceutical development process is long and challenging.

"There's a long way to go," she says. "(But) while it's still early days, their results so far speak for themselves. No new major antibiotics have been developed in the last 30 years. Any research into this space is incredibly important, given the serious global threat."

THE BUGS FIGHT BACK

1928 Scottish biologist Alexander Fleming's accidental discovery of penicillin launches the age of antibiotics.

1932 The first commercially available antibacterial, a sulfonamide, is developed at the Bayer Laboratories in Germany. Resistance to sulfonamides is first reported in the late 1930s.

1940 Five years before penicillin becomes widely available, scientists discover that certain bacteria produce an enzyme which can inactivate the drug.

1955 Despite many countries enforcing prescription access to penicillin, resistance to the drug is now widespread.

1955 First reports emerge that antibiotic resistance can transfer genetically between bacteria, via mobile pieces of DNA called plasmids.

1961 Within a year of scientists developing methicillin, in an effort to sidestep penicillin resistance, resistant bacterial strains emerge. "Methicillin-resistant Staphylococcus aureus" or MRSA attains superbug status after stronger strains emerge in the 1990s.

1976 Massachusetts researcher Stuart Levy reports that antibiotic resistant E. coli have spread from chickens to their human handlers. Antibiotics have been used in agriculture since 1948.

1980 Medical researchers introduce imipenem, the first member of the carbapenem class of antibiotics. In 1991 Japanese researchers report resistance to the drug is spreading via a plasmid.

1995 Multidrug-resistant tuberculosis is recognised as a major killer, forcing widespread revision of treatment guidelines.

2002 Up to 60 per cent of Staphylococcus aureus cases in hospitals are found to be resistant to methicillin. In 2005, MRSA reportedly kills more Americans than HIV, Parkinson's disease, emphysema and homicide combined.

2012 World Health Organisation chief Margaret Chan warns that rampant antimicrobial resistance is propelling the world into a "post-antibiotic" era.

2013 The US Food and Drug Administration implements a voluntary plan to phase out the use of certain antibiotics in animals.

2014 WHO's first report on global antibiotic resistance warns: "this serious threat is no longer a prediction for the future. It is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country."

2016 All 193 UN member states agree to work together to combat the proliferation of drug-resistant infections.

Daniel Mulino, the Victorian Labor Parliamentary Secretary for Finance who authored a comprehensive dissenting report on the state proposal, outlines the widespread abuse of euthanasia legislation in foreign jurisdictions. In those jurisdictions the practice was introduced as an end-of-life measure, in terminal cases, with safeguards and extrajudicial bodies overseeing the implementation of the law, as will be the case in Victoria according to state Health Minister Jill Hennessy.

Yet what happened? In all countries where assisted suicide is legalised, it has expanded in what is described as "scope creep", where the criteria for active killing grows to include non-terminal illnesses, psychological disorders, especially depression, and even the euthanasia of children.

And not only that; the number of people euthanised is increasing at an alarming rate.

In Belgium alone, the total growth in the 12 years from 2003 to 2015 rose from 235 reported cases to 2012, a compound annual growth rate of 19.6 per cent. In The Netherlands the numbers went from 2331 in 2008 to 5516 in 2015, a compound annual growth rate of 13.1 per cent. In Switzerland between 1998 and 2014 the numbers rose from 50 to 836. These numbers in Belgium and The Netherlands are from the official statistics.

Likewise in the US states of Oregon and Washington, the numbers off a smaller base grew by 13.2 per cent a year and 21.6 per cent, respectively.

In the Flanders region of Belgium, more than 6 per cent of all deaths are euthanasia. Rather than just a small minority of incurable cases, the number of granted requests was 76 per cent — which points to a basic shift in medical culture.

One reason often cited for this is an ageing population. But it is not quite that simple. Mulino gives three explanations.

First, there is "an expansion in the categories of people eligible to opt for assisted dying, either through formal legislative change" (as in Belgium and The Netherlands, where children and people suffering certain forms of depression and dementia can now be euthanised), or sometimes less transparently by gradual changes in the interpretation and application of existing provisions.

Second, Mulino points to a "normalisation" of euthanasia or Godelieva De Troyer, who was euthanised in Belgium for no reason other than depression. I interviewed her son, Tom Mortier, who has become an anti-euthanasia campaigner because of his mother's case. He told me he was originally indifferent to the legalisation of euthanasia until her death. The most infuriating aspect for Mortier was that the doctor called it an "act of love".

Says Mortier: "I loved my mother for over 30 years, and he never even bothered to tell me what he was planning to do!"

If the proponents of euthanasia do not want to believe the evidence of abuses presented by those who are against this practice, perhaps they will believe those who are actively in favour of it.

Wim Distelmans, former chairman of the Belgian regulation body, told *The New Yorker*: "We at the commission are confronted more and more with patients who are tired of dealing with the sum of small ailments — they are what we call tired of life."

Opponents of active euthanasia are often branded "religious zealots" or, the most spurious charge, anti-personal autonomy. As my friend Carolyn's death illustrates, there is plenty of scope for personal autonomy already in Australia without allowing doctors to have the power of death.

One last question we must ask is: where are the doctors? The Australian Medical Association has a moderate, sensible policy on end-of-life issues that hinges on the intent of doctors to eliminate pain, even if death is slightly hastened. It is the intention that counts.

Despite this, it is rare to hear from doctors in these arguments. Although I do not imagine most Australian doctors would back the open-ended Belgian legislation, it may be a good idea for them to be opposed more actively to the changes proposed in Victoria lest it lead them into areas in which they do not want to be involved, both because of creeping expansion in the practice of euthanasia and for their own personal autonomy.

The latest development in Belgium is proposed legislation to force doctors who are conscientiously opposed to euthanasia to refer for it. They can't do that here? Well, think again. Victoria has already introduced exactly the same legislation for abortion.