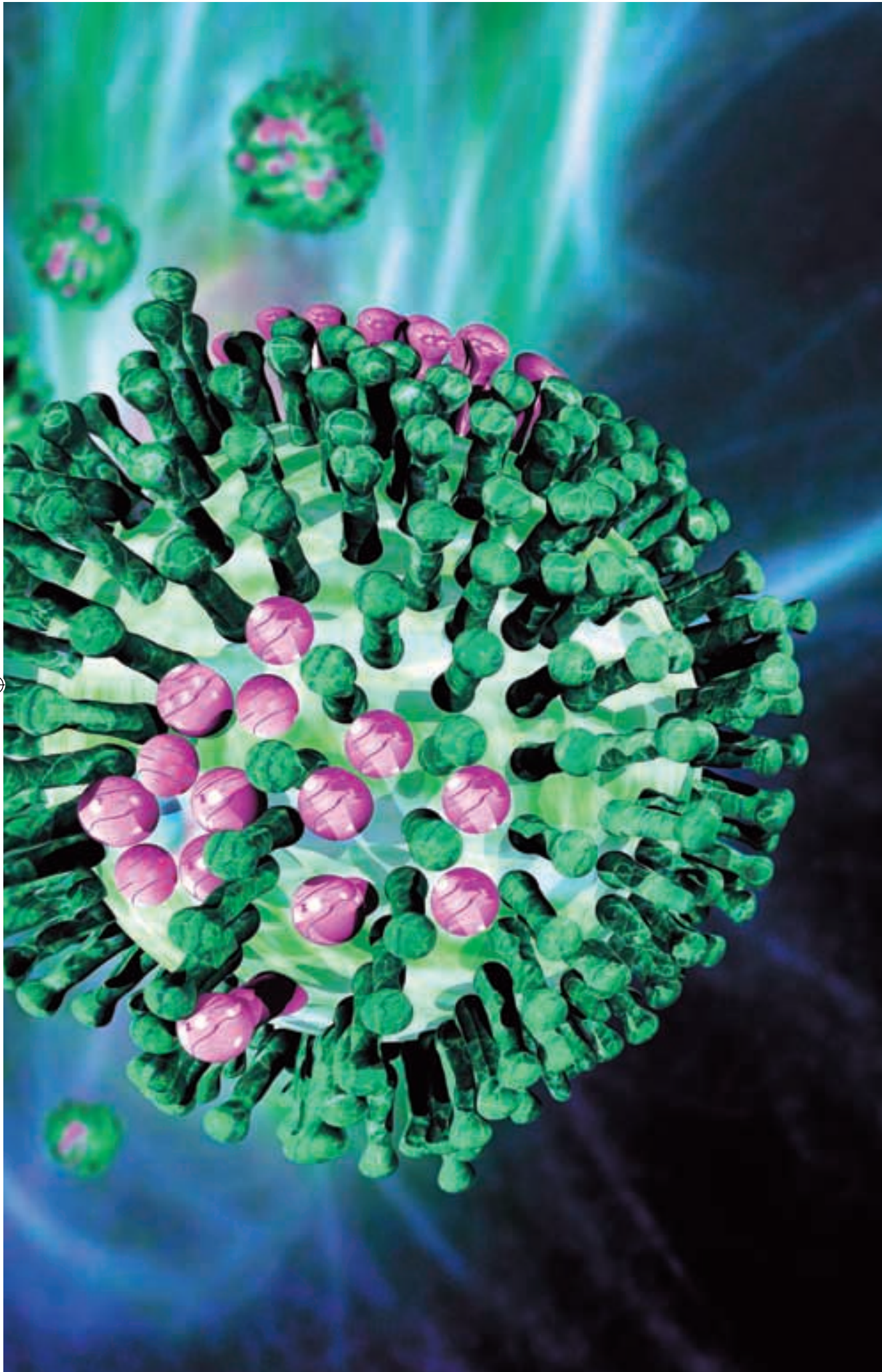
A detailed microscopic image of a virus particle, likely a flu virus, showing its characteristic spherical shape with a textured surface and a central core. The background is dark with blue and green light effects, suggesting a laboratory or scientific setting.

This is the virus that could claim millions of lives in a bird flu pandemic. If the worst happens, the world will rely on drugs developed by Australian researchers. *Mark Whittaker* details for the first time the extraordinary story of how a new class of drug was identified then developed against innumerable odds.

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All the volunteers had to do was lie back, point their noses to the ceiling and allow a nurse to drop in a dose of a virus that, on average, kills 36,000 Americans every year. Lured by the chance to help advance science and by free accommodation in a nice hotel, the Virginian students then had to wait a day before taking a puff on an inhaler, sucking in a lungful of an Australian-designed drug that promised to cure the illness – influenza.

At first, on that day in 1994, as the nurses took scrapings from the volunteers' throats and noses, and as they picked up a paltry number of discarded tissues to measure the volume of mucus, infectious disease specialist Dr Fred Hayden feared something had gone wrong with the experiment. Not enough of the volunteers were getting sick.

"Maybe it's a bad study," he thought. "Maybe we didn't screen them properly or gave them the wrong dose ... Or maybe the drug is working."

It seemed unlikely that the drug was succeeding. As with the common cold, it was almost a given that there was no cure for flu, certainly not one that hoped to stop all strains of the virus.

Then one of the volunteers, a male student, developed a raging fever. No-one knew it then, but he had been given a placebo.

Australian physicist Peter Colman from the CSIRO was there, and to see that poor kid get sick was one of the highlights of his scientific career. He was sure the drug was working on the other volunteers, and he even felt a bit sorry for one of his key collaborators, Dr Graeme Laver, who couldn't be present. The two of them had started this flu project back in 1978 but had fallen out in a spat that went to the heart of modern science.

Nevertheless, the two men earned considerable praise for their work. They went on to win Australia Prizes in 1996 and *The Sunday Times* of London named them as the 56th most powerful people in Britain in 1999 (ahead of the Pope, 81st, Posh and Becks, 91st). It looked like the first drug developed in Australia ever to get to market was going to be a blockbuster and they'd all be rich.

But then the little compound they invented dropped into obscurity, the victim of a Californian-designed rival drug, Tamiflu, that had piggybacked on half a century of Australian flu research and busted their patent. Tamiflu became the blockbuster: almost \$US1 billion (\$A1.3 billion) worth of it will be sold this year.

Indeed, such was its market dominance that the manufacturers of the Australian-designed Relenza pretty much threw in the towel, shutting down manufacturing centres and surrendering market share to Tamiflu and its Swiss manufacturer, Roche. Failure begat a \$430 million legal dispute between the Australian biotech that developed Relenza and the British company that manufactured it and was supposed to market it. And that was where it was expected to end, in the courts. But then bird flu started flying west towards Europe, reviving images of medieval pestilence.

Suddenly Relenza was in demand again, with the medical fraternity recognising that if it was going to defend the world against a new flu pandemic it would need as much help as it could get – that the two drugs, Tamiflu and Relenza, would be the only defence against a new flu strain during the initial months of a pandemic. In the time it may take for an effective vaccine to be

developed, unknown millions might die.

This then is the story of how a bunch of brilliant Australian scientists developed a wonder drug, missed the boat commercially, caught it again, and may yet be responsible for saving your life. Oh, and how they no longer talk to each other.

**A**USTRALIAN NOBEL PRIZE-WINNER Frank Macfarlane Burnet had the distinction of being in a British laboratory in 1933 when he heard a cry: “The ferrets are sneezing.” This signified that the stuff they’d given the ferrets – an animal highly susceptible to flu – was in fact flu, and meant that the human flu virus had been isolated for the first time.

The following year, Burnet returned to Melbourne’s Walter and Eliza Hall Institute of Medical Research. There he perfected ways of growing influenza in fertile chicken eggs, a technique still in use today in vaccine manufacture. He branched off into other viruses and then immunology, for which he won the Nobel Prize in 1960.

But back when the ferrets got the sniffles, a four-year-old Melbourne boy, Graeme Laver, was being indoctrinated into high culture. Laver’s grandfather was a professor of music who had a theory that if you took a child and exposed him to symphony concerts and all the rest, he’d become a prodigy. “I was so pissed off with the whole thing ... all I wanted to do was make mud pies,” recalls Laver. When his grandmother asked what he wanted to be, he said “a cook”. He just wanted to mix things together and see what happened. Cooking was a bit low-falutin for grandma, however, so his goal was modified to organic chemistry.

“It’s just cookery,” he says. “It’s all I ever wanted to do.”

Laver left school at 16 and went to work at the Walter and Eliza Hall Institute, where Burnet was director. It was 1946 and there was a genuine fear of another postwar flu outbreak like the one that killed between 20 and 50 million people in 1918-19 – more than had died in World War I. The discovery of antibiotics had meant that the risk of flu patients dying of secondary bacterial infections had decreased, but the primary killer was as untamed as ever.

Laver was a technician, a bottle washer, for a thickly German-accented scientist named Alfred Gottschalk. “He had a bald head which he used to scrub every day with a paper towel,” Laver recalls. “He was also totally obsessed with the work – totally obsessed.”

It had recently been theorised in the US that after the flu virus invaded human cells, turning each cell into a flu factory, the new virus used an unknown enzyme to cut itself free from the cell so it could go on to infect other cells. Gottschalk discovered what that enzyme was, a substance called neuraminidase. His discovery led to excited speculation that if a drug could inhibit neuraminidase,

it could control the disease. In those days, the universities and drug companies then took all the chemical compounds they could think of and threw them at neuraminidase in test tubes and animals. None of them worked.

Laver, meanwhile, had gone off to England to get a PhD in biochemistry and returned in 1958 to a job at the Australian National University in the new John Curtin School of Medical Research. He was given a lab and told to go off and do something with it. That’s the way science was back then. The 1957 Asian flu pandemic had been quite devastating and so flu was a natural subject to look at. He’s been looking at it ever since.

A flu vaccine had meanwhile been invented in the US – essentially dead

an equally bad but harmless vaccine.”

When the 1968 Hong Kong flu pandemic hit, the team discovered that the virus had the same neuraminidase as the 1957 Asian flu pandemic, but the hemagglutinin – the substance that binds the virus to the cell – didn’t match anything previously seen in humans. They found that it matched flu seen in horses and ducks. So it was quite clear to them what had happened – acquiring part of an animal flu made the new virus invisible to human immune systems.

They concluded that really lethal flus – perhaps all pandemic flus – were created when the virus crossed species. The scientific community didn’t believe them at first, but it’s accepted wisdom now.

It was known even back in the early

would poo all over the Americas on their annual migrations.

Webster, on his way to becoming the world’s foremost animal flu pandemic expert, then succeeded in proving the team’s theories about flu mutations by giving bird and pig flus to animals and creating whole new flu viruses. So between Webster and Laver, a significant part of the flu puzzle had been solved. They just hadn’t cured it.

**B**UT THAT QUEST TOOK A SIGNIFICANT turn one day in 1977. Laver was pottering away in his lab, making neuraminidase protein for chemistry work, when for no obvious reason some of it formed into a crystal. He knew this was significant, because a



“Only he can help you figure out why he chose not to stay,” says Colman (right) of fellow Relenza pioneer Laver (left).

virus which when given to people allowed their antibodies to recognise it. But the dead virus, consisting of fat and protein, was highly toxic.

The way Laver tells it, a few bright people, including his Kiwi student Robert Webster, just happened to start working on it with him – not working, more having a lark really, mixing mud pies. They put a little detergent into the vaccine to take out the fat and *voilà!* it was safe. “Now, every vaccine in the world is made that way,” says Laver. “Pretty important, except the flu vaccine has never been much good as far as I can see.”

Because the flu vaccine is always reacting to known strains, it cannot counter the periodic emergence of new varieties. “What we did was convert a relatively bad, highly toxic vaccine into

’70s that China was the world’s flu virus hotspot. In 1972, Laver was invited on a medical delegation behind the bamboo curtain, hot on the heels of Nixon and Whitlam. He delights in telling the story about how a spook from ASIS flew up from Melbourne to ask him to spy on China; how he failed as a spy and failed to find out anything about flu, too. They were allowed to bleed just one pig. When they asked to bleed more, their hosts told them that in China, all pigs were equal.

Laver and Webster, however, made major breakthroughs in discovering flu viruses in wild bird populations, helping to solve the puzzle of where flu viruses went between outbreaks. When Webster left Australia for the US, he found the wild duck populations of Canada just bubbling with flu viruses, which they

crystal’s highly ordered structure reveals a hell of a lot about the structure of the individual proteins.

Laver didn’t know what to do with his discovery, but he remembers an Australian immunologist, Alan Williams, visiting from Oxford, telling him: “Those crystals must not go out of Australia.”

That’s how a bright young molecular physicist from Adelaide, Peter Colman, then working in Germany, came into the project. Colman specialised in X-ray crystallography. He had been using crystals to work on the three-dimensional structure of human antibodies.

Colman started studying the crystals at the CSIRO in Melbourne. “We didn’t set out to discover a drug,” he says. “We were just doing it out of curiosity, really. To see how the virus changed from strain to strain.”

Imagine a woollen jumper scrunched into a ball. Colman and his computer collaborator, Jose Varghese, had to figure out how the garment was knitted, using

rough cross-section pictures from an X-ray. They had the pictures in the lab for at least two months in the middle of 1982, just staring at them, analysing them, until the eureka moment came. Suddenly the pictures all made sense to Colman. And what he found very curious was that, while the neuraminidase structure varied among flu strains, there was one little hole in it that was constant across all strains. It soon became clear that this pocket was crucial to the enzyme's action of cutting the virus free from human cells, and that if the pocket could be retarded, so could the virus.

They had found a target, but in 1982 the number of drugs that had been designed to fit a molecular target was exactly zero.

**A** COMPANY CALLED BIOTA WAS set up almost entirely based on this research. Colman was a director: "Even though there were no patents, just know-how, this was the mid-'80s when a lot of little companies were floating on ideas, some of which were mad and indeed a lot of people thought our idea a little mad, too."

There was also scientific resistance because a team in the US had tried a neuraminidase inhibitor in the early 1970s. It worked in the test tube but not in mice. Biota pushed on regardless and managed to raise \$3 million when it floated in 1985.

Laver would make the virus protein, crystallising some of it and sending some raw virus down to Melbourne on the plane in a little Esky. "For four or five years we got along very well," says Laver, "and then this split occurred when Peter liked to keep things secret and I liked to talk about them."

Laver resented the fact that Colman had used protein sequences that had been published by scientists overseas. "They hadn't kept them secret," he says. "Colman was using information which other people had got and deposited on data banks for him to get on and solve the structure."

When Colman asked Laver to stop supplying crystals to other flu researchers, Laver felt he could no longer work with him. And Colman thought that with Laver running off collaborating with whoever asked, he could no longer work with Laver. "I had agreed not to disclose," says Colman, "because CSIRO [his employer] had signed an agreement with Biota ... and it imposed reasonable conditions of confidentiality on us; and not only did ANU sign a parallel agreement, but ANU asked Graeme to sign every page of it himself. So you might argue the level of obligation was even higher on him. So to pretend that somehow I acted improperly or did things I shouldn't have done just gets the whole thing back to front."

Laver says he can't remember what he signed, but that his obligation to science was greater than any obligation

to the ANU. Colman says he can't figure Laver out: "The question is whether Graeme represents the old way or not. Only he can help you figure it out, why he chose not to stay with us. It couldn't have been about publication as he pretends ... Everything has been published in the fullness of time, in a timely way."

**W**HEN THE OLD TEAM SPLIT, organic chemist Mark von Itzstein joined to try to design the plug drug. A Queenslander who spoke four languages and represented his state at volleyball, he had been in Germany working on small molecule modelling, looking particularly at carbohydrates. He was 27 – young enough to say he could make an inhibitor, "no problem". Whether it would work in an animal to stop flu was another matter. The potential for a cure was dangling but there were no precedents and there was a long way to go.

He was just a few doors down from Colman on Melbourne's Royal Parade, Parkville – the most concentrated strip of biomedical brainpower in Australia. He was disappointed that the falling out between Colman and Laver broke the feeling of continuity right back to Burnet, who'd also worked nearby. And he felt he was the meat in the sandwich.

Von Itzstein started off with the crystal structure that Colman, Varghese and Laver had produced. But it was still a fuzzy picture, and the clunky computer programs of the day weren't giving the answers required, so von Itzstein's team had to start back at the beginning using old-fashioned chemistry. They spent a couple of years not even looking for the cure, just something to prove they were on the right track – "proof of principle".

In 1988, the team came up with a carbohydrate molecule that was pretty similar to the one the US team had used in the early '70s. But for some reason, theirs worked in mice and then, oddly, when the American compound was retested, it also worked in mice.

Von Itzstein likened his role to a conductor's and now the ensemble was showing some success it attracted more money and grew from a five-piece to an orchestra of 30. There were people designing drugs on computers, another group synthesising compounds and another testing them.

By 1989, Colman and Varghese had refined their picture of the structure to such an extent that when the chemists looked at their molecule and how it fitted into the hole, they could see one tiny pocket within the hole that wasn't filled up. Chemist Wen-Yang Wu got the job of designing a compound to bung it.

He developed two new substances and one of them was tested as being a million times more effective than the 1970s US compound. The compound was sent off to Biota's new partner, pharmaceutical giant Glaxo Wellcome in Britain, for testing in animals – first

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◁ mice, then ferrets, and indeed, the ferrets did not sneeze. From there, von Itzstein's orchestra got bigger as it ran through as many potential variations of the molecule as it could think of, trying to beat the patent-busters who would surely come. That was about to become a huge problem because the tests in Charlottesville, Virginia, showed that the drug worked in humans.

The drug, which became known as Relenza, has since been shown to reduce the duration and severity of flu symptoms provided it is taken within 48 hours of the onset of illness. And if you take it before you get the flu, you won't suffer symptoms at all. It was a monumental achievement for Australian science, yet remains curiously little known.

**W**HILE LAVER WAS OUT OF THE picture, he had kept busy. He'd had his crystals launched on the space shuttle. Then, after the *Challenger* disaster, he got his crystals onto the Mir space station, only to be accused by the Pentagon of aiding the Soviet germ warfare capability. Laver loves stirring possums, and the US military ranks as his biggest.

Once the flu drug had been shown to work, he provided neuraminidase crystals to the rush of scientists keen to get in on the act. Five competitors appeared immediately, three of which developed inhibitors. "All based on drugs we made here," says Laver. "They all plug the same hole but they have to be different, so they don't infringe each other's patents."

One of the competitors, Tamiflu, made it to market. Its developer, Gilead

Sciences in California, figured out a way to get it into the body via a tablet, whereas Relenza has to be taken via a puffer, making Tamiflu more marketable. Says Colman: "There's no doubt it was the publication of our stuff that set the hounds running, and those guys in San Francisco who discovered the other compound really did a good job, but it was done on the back of us. And that's something for us to feel proud about ... I mean, Tamiflu is as much our discovery as is [Relenza]."

Despite the huge head start Relenza had, it was delayed by the US Food and Drug Administration so that both drugs came on the market in 1999. They started out fairly level in sales, but by the end of 2000, Tamiflu was easily outselling Relenza's puffers. Last year, Relenza had just one per cent of the market.

Biota is now suing GlaxoSmithKline for up to \$430 million in a court case due to begin in Melbourne next year. Biota's chief executive Peter Molloy says GSK dumped Relenza and refused to promote it. "Fair enough at the time," he says. "It was a small drug for them. It didn't seem to have a lot of potential so they made a decision to kill it. They stopped all promotion, even though it was in breach of their agreement with us ... They had other fish to fry."

And then came bird flu. GSK sold just \$A7.1 million worth of Relenza last year while Tamiflu sales leapt 357 per cent to \$A603 million for just the first half of this year on the back of sales to stockpiles in 25 countries. Australia has a stockpile of four million Tamiflu packets.

Relenza, however, got a much-▷

## BIRD FLU: ARE WE AT RISK?

● The H5N1 strain of influenza has probably existed in the guts of wild fowl for hundreds or thousands of years. It doesn't make them sick. It was first detected in China in 1996, and is first known to have infected humans in 1997 in Hong Kong. In that outbreak, 18 people caught it and six of them died. All the territory's domestic poultry that hadn't already died were slaughtered.

Since then, it has killed more than 60 people. Half of all those who catch it die. But what has saved the world from a pandemic is that almost all the cases have been contracted directly from poultry. One exception was a mother in Thailand who held her infected daughter for five days as the young girl slowly died. Soon after, the mother became ill and also died.

By comparison, the 1918 flu (H1N1) pandemic killed only five per cent of those it infected, yet it killed between 20 and 50 million people



because it passed easily from person to person.

The great fear with H5N1 is that it will mutate or recombine with a human form of flu virus (perhaps in pigs, which also catch human flus) to become easily transmissible between humans.

For this reason, a bird flu vaccine currently in development may prove ineffective because it is designed for the present form of the virus and not that which may ultimately break out in a pandemic. MW



Rules of containment: Thai agricultural officials remove culled chickens for burial.

needed jab in the arm in August when the British medical journal *The Lancet* found that it was just as effective as Tamiflu but had fewer side-effects and was less prone to resistance. *The Lancet* recommended governments stockpile both drugs; Germany became the first to do so, putting in an order for 1.7 million courses of Relenza to back up its six million courses of Tamiflu. That single order was seven times larger than the drug's entire sales in 2004. Two weeks ago, health minister Tony Abbott said Australia would also begin stockpiling an unspecified amount of Relenza, and GlaxoSmithKline announced multi-million dollar plans to reopen a Melbourne production facility that had been shut down in 2000. Relenza was back on the map and so was Biota's share price.

**F**OR ALL THE DISAPPOINTMENTS associated with Relenza's success, its development has helped scatter an extraordinary amount of brainpower around the country. Biota is now concentrating on a long-lasting version of Relenza that will require just one puff a week. It is also working on a cure for the common cold, about to go into the first stages of clinical testing.

Mark von Itzstein is now head of the Institute for Glycomics on the Gold Coast, with a team of 55 people working on designing carbohydrates to plug all sorts of holes to cure cancers, golden staph and tuberculosis. Colman is at the Walter and Eliza Hall Institute in Melbourne, trying to get cancer cells "to behave using designed chemicals".

"People have gone their separate ways but everybody learnt a lot from the process and everybody would like to think we could do it again. I'm sure it will be done again. There will be other drugs discovered in Australia that get to market. Whether we're lucky enough to pull one off remains to be seen," he says.

The last eureka moment Graeme Laver had was back in 1999, when someone in an ANU corridor said to him, "I hear you're a millionaire."

"What?"

"Because of your Biota shares."

"I haven't got any Biota shares."

But that night he remembered he was included in a trust fund set up when Biota was started. He rang the stock exchange and found the trust was a major shareholder in Biota Holdings, which was then swinging about in the \$4.50 to \$5.50 range, so his fortunes were pretty good. Would he have acted differently through all this had he remembered he stood to be rich? "Good question. I don't think so. I can't tell you honestly," he says.

Biota shares, which peaked at \$9, were at 75c two months ago, but have since tripled. So Laver, 76, is not doing too badly, retired on his little farm north of Canberra. "Roche has sold \$1.7 billion of Tamiflu. How much do I get out of that?" he asks, laughing. "Not a cent. So I wrote to them and said, 'What about giving me some?' ... 'No, forget it.' ... God, they're mean buggers." Surely he realised that was going to be the case? "Of course I was stupid not to ask for royalties ... I'm not a businessman. It never occurred to me that I should do that."

Both von Itzstein and Colman had told me that as much as they liked the larrikin in Laver, they didn't understand what motivated him. I ask how he'd describe himself. "What I have done is not to set out to make any money, not to cure humanity's ills. What I've done is try to satisfy my curiosity in trying to discover new things, and having discovered something new, to publish it to tell everybody how clever I am." ☺

Staff writer Mark Whittaker's last story was "Fifteen minutes of infamy" (August 13-14) about the Big Brother phenomenon.



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