



Emmanuel College

THE UNIVERSITY OF QUEENSLAND

Cancer Prevention in the 21st Century

By

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Emmanuel College
The University of Queensland
Enriching lives since 1911

Emmanuel College is Australia's ninth, and with St John's College, The University of Queensland's first residential college to gain affiliation. It was founded by the Presbyterian Church of Queensland in 1911 with the first students taking up residence in Wickham Terrace in 1912. As the Presbyterian Church moved towards partnership with other religious denominations during the 1970s, Emmanuel College also came under the auspices of the Uniting Church. Upon its inauguration, Emmanuel College was an all male residence but this changed in 1975 when women were admitted as collegians. Now, the College numbers around 340 students with half our population being female.

Further change was experienced by the College when it moved in 1955 from its original site in Wickham Terrace to its present location on the main university campus in St Lucia.

Since 1911, Emmanuel has stood for excellence in all round education and has had seven Rhodes Scholars during its history. Its graduates have gone on to make a major contribution to Australia in many areas, including as doctors, scientists, teachers, engineers, lawyers and judges, politicians, ambassadors and diplomats, and church leaders.

THE AUTHOR

Professor Ian Frazer

Ian was born in Glasgow, Scotland. He was educated at Robert Gordons College, Aberdeen and at the University of Edinburgh, as a renal physician, specialising in immunology. He emigrated to Melbourne in 1980 to research viral immunology at the Walter and Eliza Hall Institute of Medical Research, and moved to Queensland in 1985 where he currently heads The University of Queensland's Diamantina Institute for Cancer, Immunology and Metabolic Medicine at the Princess Alexandra Hospital.

His current research interests include immunoregulation, and immunotherapeutic vaccines for papillomavirus associated cancers. Professor Frazer holds research funding from several Australian and US funding bodies. He is a director of a biotechnology start up company, Coridon, with an interest in optimising and targeting polynucleotide vaccine protein expression. He chairs the medical and scientific advisory committee of the Queensland Cancer Fund, and advises the WHO and the Bill and Melissa Gates Foundation on papillomavirus vaccines. He won the 2005 CSIRO Eureka Prize for Leadership in Science and was the Australian of the Year in 2006.

In 2005 Professor Frazer and his research groups undertook a clinical study of a vaccine against human papillomavirus, which was 100 per cent effective in preventing common cervical cancers caused by the virus. The drug is named Gardasil and has been approved by the US Food and Drug Administration and for use in the European Union. Ian Frazer personally administered the first publicly available injection of the vaccine in Australia in August 2006. He is also involved in a large clinical trial taking place in Australia and China of a therapeutic vaccine against genital warts.

In 2006 he was awarded the Cancer Research Institute's William B Coley Award for Distinguished Research in Basic and Tumor Immunology along with Harald zur Hausen. This year Ian has received the International Life Award (Sezione Ricerca Scientifica) in Rome in January, the Florey Medal for biomedical research in Sydney in March, the Clunies Ross Award in Melbourne in April and most recently the 2007 Novartis Prize for Clinical Immunology in Rio in August.

He is married to Caroline and is passionate about skiing, a hobby developed growing up in Scotland.

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Cancer Prevention in the 21st Century

Thank you for the opportunity to address you this evening. It's a measure of the way my life works these days that this is the fifth public lecture I've given in Australia in the last week, and I've only been in the country four days. While it's been a great honour being Australian of the Year, and it's a satisfying feeling when total strangers come up and greet you in the street, it's perhaps less satisfying when they introduce themselves as your wife and children, whom you just haven't seen for about 18 months. So it's considerate of you to invite my wife Caroline to the function this evening – she may not get to speak to me but at least she can see that I'm still alive and well!

It's natural that we all wish to live long healthy lives, untroubled by the concerns that faced Mozart when at the age of 35 and realising that his health was not good he wrote:

“I know well that my hour is near, that I am at the point of death. I shall die without having known any of the delights my talents would have brought me and yet life is so full of beauty. Alas, one cannot alter one's own destiny, and I must be resigned....”

We don't accept 'destiny' these days. Indeed we have, over the last century, done very well in using knowledge developed through research, and the resources that have come with industrialisation, to considerably alter our own destiny. In Australia, we live on average 25 years longer now than we did 100 years ago – this gain in longevity is largely due to control of infectious disease through the public health measures of provision of clean water and adequate nutrition, and two major benefits of medical research, antibiotics and vaccines. Indeed, it's hard for our children to imagine how things were in the pre-vaccine, pre-antibiotic era when epidemics of serious infectious disease claimed the lives of one in three children.

If the 20th century was the era in which we learned to control infectious disease, (note, control, not eradicate, though we have managed to eradicate smallpox and should probably succeed in eradicating polio within the next 20 years), then the challenge for the 21st century is likely to be cancer. Cancer is already the commonest cause of death in Australia, and it is estimated that within the next 25 years it will be the commonest cause of death in both the developed and the developing world. This is not to minimise the risks of cardiovascular disease, diseases of over-nutrition, and mental illness, all of which contribute huge burdens to health care in the industrialised world. However, cancer stands out in people's mind as something to fear: the image is of a slow, painful and certain death.

Let me stress at the outset that this image is now in large measure inappropriate – in the developed world, 60 per cent of patients with cancer are now cured of their disease, a significant improvement on the 10-20 per cent cure rates common 50 years ago. However, in a theme I will return to later in my talk, we must note and accept the

challenge provided by the huge discrepancy in health and life expectancy that has grown up between the developing and the developed world, largely due to the unavailability in the developing world of all the benefits of research that we now can take for granted in Australia. It's a mark of a socially just society that quality health care should be available to all on an equitable basis, and without regard for the ability of those in need to pay at the point of use. Our challenge is to help achieve this through affordable interventions.

Prevention is said to be better than cure, and that is certainly true for cancer.

Before I talk further about the benefits of investing in health research and the impact of such research on prevention and cure of cancer, I think it's important to stress that a large part of the responsibility for our good health lies with ourselves – significantly, we know in large measure what we should do, though we're perhaps not as good at receiving the wisdom as we should be. A significant part of the chronic disease that affects us can be attributable at least in part to our own choice of lifestyle. Depending on how the sums are done, between 25 per cent and 50 per cent of cancers come about as a result of lifestyle choices.

Cancer is, put simply, due to genetic damage to our cells. Cells with damaged genes usually die, but unfortunately they can also acquire the ability to grow indefinitely, spread where they shouldn't go, and eventually to kill their host. Most of the things we know about that increase our risk of cancer are genotoxins – agents that can damage our genes.

The four significant measures we can take to reduce our risk of cancer are well known.

- 1) We need to stop smoking – smoking contributes to nearly 40 per cent of avoidable cancer deaths in Australia. Tobacco is a legal poison, and is a \$6.2 billion dollar Australian industry promoting legal poisoning. While only 18 per cent of Australians smoke, a much better figure than 20 years ago, we can do better. For example Canada manages 13 per cent.
- 2) We need to stay out of the sun to reduce our risk of skin cancer. Queensland is the melanoma capital of the world and one in 16 of us will develop this lethal skin cancer in our lifetime. Non melanoma skin cancer is so common in Queensland that we don't keep statistics. We just assume that everyone will get at least one in their lifetime. The '*Slip Slop Slap*' program has been very effective at reducing sun exposure in our children, but we have a way to go with teenagers, as anyone who visits a beach will realise. Why, for example, do we still allow commercial solariums to promote 'healthy tanning' in our country?
- 3) We need to drink less alcohol. The International Agency for Cancer Control rates alcohol a category one carcinogen. Alcohol consumption contributes to the risk of head, neck and stomach cancers. These are particularly unpleasant, and hard to treat. While it appears that moderate alcohol consumption on

average prolongs life, the carcinogenic effect of alcohol is there at all dose levels. The definition of appropriate drinking is hard to provide – probably the old adage of ‘less than your doctor’ is the right way to go!

- 4) We need to watch our weight. While dietary advice on cancer prevention is confusing and often self contradictory – coffee either causes or prevents cancer depending on whom you read – there is no doubt that overweight increases your risk of several cancers. For example, bowel cancer is the commonest cancer in Australian males and is 10 per cent more common in those overweight.

If these measures are what we ourselves can do to help reduce our risk of cancer, what can scientific research offer?

One part of what research can provide is an understanding of the self determined causes of cancer, cancer epidemiology if you like, and also of the best way to educate people to avoid them. Another research focus is to look for better treatments, an important issue which I’ll not have time to address tonight. However, perhaps the most important information that research can contribute to cancer control is a clear understanding of the environmental causes of cancer, because these should be preventable. Environmental causes include environmental pollution, and they also include infectious agents. It may come as a surprise that almost 25 per cent of cancer deaths can be attributed to infection. Most of the rest of what I have to say tonight will focus on this issue, which has occupied a large part of my research career.

There are several viruses, one bacterium, and several parasites that we know contribute to our risk of cancer. As a general rule, the cancers are a rare complication of the infections, and as a general rule at least some of each cancer type associated with infection is not caused by the infection. Thus, stomach cancer is associated with infection with a bacterium called *Helicobacter*, discovered by Australians Barry Marshall and Robin Warren to be the cause of stomach ulcers, a discovery for which they were awarded the Nobel Prize for Medicine in 2004.

Most stomach cancer in south east Asia and Japan is caused by this infection, but in other countries it’s a rare contributor to the disease. The viruses most commonly associated with cancer are Hepatitis B and C viruses (responsible for two/three of all liver cancer and about five per cent of the total cancer burden worldwide), Epstein Barr Virus (the glandular fever virus) which is responsible for tumours of the lymph glands, as well as a nose and throat cancer in China and a form of leukaemia in Africa, altogether about 2 per cent of the global cancer burden and papillomaviruses, about which I will talk in more detail.

Papillomaviruses are responsible for cervical cancer, and more than 99 per cent of cervical cancer can be attributed to infection with one of these viruses. They’re also responsible for other cancers of the genital skin (vulva, vagina, penis and anus) in men and women, and for some throat and oesophageal cancers, and some skin cancers. In total about five per cent of all cancer world wide is caused by infection with these

viruses. They come in many varieties. Some produce warts (and never cancer). A subset of about ten papillomaviruses, not associated with warts, is termed high risk because they cause persistent infection of the genital tract and increase the risk of cervical cancer. The two commonest of these high risk types are types 16 and 18. In the late 1970s, Professor Harald zur Hausen drew the link between these viruses and cervical cancer as a result of studies on the virus and on cancer tissues, where the virus persists, and indeed is necessary to keep the cancer as a cancer.

Cervical cancer is one of the commonest causes of cancer death among women worldwide, killing over 250,000 women each year, predominantly younger women in the developing world. Cancer occurs in about two per cent of women infected with a high risk human papillomavirus. Acute infection with this virus is acquired during sexual intercourse and is exceedingly common, as the virus persists for up to two years after infection and the person infected, who is unaware that they have the infection, can infect others throughout that time.

In some persisting infection, the papillomavirus damages the genetic information of the cells it infects, and in so doing immortalises the cell. These immortal cells become gradually more abnormal with each cellular division and after a period of on average 15 to 20 years (it can be as short as two years) a cancer ensues.

In 1991 my colleague, the late Dr Jian Zhou, and I came up with a technology that has enabled development of vaccines to help prevent cervical cancer. After 16 years, \$1 billion of expenditure, the efforts of 2000 scientists, and with the help of 60,000 volunteers in clinical trials the technology has been translated by two pharmaceutical companies into vaccines of proven efficacy in the prevention of cervical cancer, now being used worldwide. These prophylactic vaccines are designed to produce virus neutralising antibody.

Trials have demonstrated that the vaccines are very safe, and provide long lasting immunity against infection with the HPV genotypes that they incorporate. They are shown to protect 100 per cent against the premalignant conditions caused by infection with the two cancer causing virus strains protected against by the vaccine. If given to girls before the onset of sexual intercourse, these vaccines could reduce the global burden of cervical cancer by over 70 per cent. Vaccination will not replace screening programs, where these are available, but in Australia should reduce the need for operations to treat cervical pre-cancer by about 20,000 per year.

The vaccines are, unfortunately, not therapeutic for existing infection with the virus – hence the need to give them early, and it's also better to give them early because the immune system is at its best when you're young. However, while universal immunisation may be better given at age 12, older women not yet infected with the virus may benefit from vaccination at any age if they are likely to become at risk of infection. We know the vaccines protect for at least five years, and suspect that they will likely give lifelong protection following three immunisations. We don't yet know

whether they will prevent disease in men, though we expect that they will, and that they will also reduce the risk that men are infectious for their partners.

So how did I get into the area of papillomavirus research, and how was the vaccine developed?

I was born in Glasgow, and educated in Scotland, where science was deemed an important part of education. I was naturally curious as a child, and enjoyed the practical aspects of science at school. I went to the University in Edinburgh to study medicine and specialised in immunology following a chance encounter with a couple of influential immunologists.

When I had completed my basic clinical training I emigrated to Australia in 1981 to complete my clinical training in immunology at the Walter and Eliza Hall Institute. There I became particularly interested in the immunology of chronic viral infection and in the consequences of a damaged immune system for persistence of infection. With colleagues Ian Mackay and Gabrielle Medley I made the observation that genital warts and anal pre-cancer associated with chronic papillomavirus infection was more common in patients with a damaged immune system, and when I moved to Brisbane in 1985 I brought with me an interest in papillomaviruses and in their relation to cancer.

We couldn't grow the papillomavirus in the laboratory so I set out to build an infectious papillomavirus in the laboratory to allow me to study the immune response to the virus. To help with this task I went to visit Professor Margaret Stanley and Professor Martin Evans in Cambridge – experts in the field of making transgenic cells and of cervical cancer. There I met Dr Jian Zhou, a medical doctor and virologist from China who was, like me, interested in papillomaviruses. He and I collaborated in Cambridge, and he came back with me to Brisbane to continue work on building an infectious papillomavirus, a task we eventually completed in 1993.

However, along the way we had to build the shell of the virus, and, somewhat to our surprise, when we got the recipe right the building blocks of the shell of the virus assembled themselves into a complete virus shell. This was a 'eureka moment' - a bit like buying a Lego kit, and finding that the bricks had self assembled into a model of the Sydney Opera House without any input from the builder. These virus shells, or virus like particles, look so like the real virus that the body's defences think they're seeing the real virus, and produce a response to protect the body against the infection which is remembered after vaccination, and allows protection against the real infection in the future.

Jian passed away unexpectedly in China in 1999 – his contribution to the field of virology and to cervical cancer vaccine development during the years he was working cannot be understated. He is sorely missed.

The cervical cancer vaccines are now in 2007 a reality, made available in Australia by the government at the tax payers' expense for all young women, to help protect them

against cervical cancer. The challenge now of course is to get the vaccines to prevent cervical cancer and there are two, used throughout the world, and especially in the poorer regions of the developing world where the rate of cervical cancer is high and the vaccine at commercial cost is not affordable.

This challenge is part of a larger one, which is to ensure that the many benefits of medical research which have become available over the last 25 years are made available in the emerging nations of the globe, to ensure that health inequity is not added to the list of inequitable distribution of resources that might serve to increase global tension. The Gates Foundation and World Bank have together assisted in getting vaccines to the children of the developing world. Our challenge is to develop mechanisms for universal and equitable deployment of all of the positive outcomes of medical research.

It's a great honour being Australian of the Year and it's also been great fun, at least so far. I have however used my position (some would say exploited my position ruthlessly) to press for better resources for medical research and for consideration of the equity issues for vaccine deployment.

I must say that my kids are rather jealous of my title, - no, not the 'Australian of the Year' one - they're after the one the Weekend Australian gave me - 'God's Gift to Women'. I'm not sure if my wife Caroline is so thrilled about that one, though fortunately most of the invitations I've received have related to the official AOY title rather than the GGTW one Of course the journalists do have a habit of bringing you down to earth. In Australia, the headline for the *Cosmopolitan* article about me and the vaccine was 'The Little Prick That May Save Your Life' and in Scotland my position of Australian of the Year was celebrated in the *Perthshire Advertiser* with the headline 'Perthshire Woman's Husband Honoured in Australia!'



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