TRANSCRIPT OF PROCEEDINGS

THE MEDICO-LEGAL SOCIETY OF VICTORIA

"GLOBAL STRATEGIES FOR CANCER REDUCTION IN THE 21ST CENTURY"

PRESENTED BY: Professor Ian Frazer

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The Chairman of the meeting was Dr. M. Hurley

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"Global Strategies for Cancer Reduction
In the 21st Century"

PROFESSOR FRAZER: Good evening. What I'd like to do - and it's perhaps not the appropriate subject to have just before you have dinner - is to address you a little bit on the topic of cancer. I do that in part as President of the Cancer Council of Australia which is one of the non-government bodies that's responsible for promoting cancer control within Australia and it's a topic which is close to my heart because I think that we all recognise that cancer is a disease that we would prefer to avoid if we can.

Cancer, indeed, has now become the commonest cause of death in Australia. We live on average 25 years longer now than we did 100 years ago and that's largely due to the control of infectious diseases, twin inventions of antibiotics and vaccines. The benefits of medical research done by our forefathers have basically given us that extra 25 years of life.

But in the 21st Century cancer is the major challenge facing us as a society and, interestingly, according to the UICC, which is the international body of cancer organisations, within the next 25 to 50 years cancer will become the commonest cause of death, not only in Australia but in every other developed and developing country in the world. So, we face a challenge and a challenge which will basically solved through research.

But what I would like to do for you this evening is talk just a little bit about what we as individuals can do to help control cancer and then what research is doing to help control

the epidemic of cancer that we will otherwise face.

I'll start in China because that's, indeed, where this picture was taken. And this is me visiting some colleagues in China who are very interested in the same cancer that I'm interested in. I'm interested particularly in cervical cancer, which is a cancer caused by infection with a virus of which I'll talk more later. But the reason that I was visiting my colleagues in Western China - and this is in Xinjiang Province which is about four hours west by plane from Shanghai and, indeed, is nearer to Moscow than it is to Shanghai - was because in that particular province cancer is a major public health problem and cervical cancer is the commonest cause of death amongst women.

Interestingly, another cancer, oesophageal cancer the commonest cause of death amongst men in that province is almost certainly due also to infection with this human papilloma virus with which I have a particular interest. So, that these colleagues here, including the state president, were particularly keen to talk with me about whet they might do in China to try and control the epidemic of these cancers that they now face.

So, how do we go about this business of trying to control cancer? The same approach applies to every clinical problem that we face. We recognise first of all that there is a problem and by observation decide that we need to do something about it and that leads us to do basic research to understand the nature of the problem itself and, indeed, there are many people working on cancer worldwide, as I'm sure you're aware.

We then have to decide who is at risk and try and develop

treatment strategies to try and reduce that risk so that that process is called transational research, in other words getting the basic stuff that's done in the lab out into the clinic and the public where it's needed. There is a critical further step that follows that and without that step nothing very much happens and that is education, to distribute that knowledge back into the working environment for the medical profession and also back to the general public so that they can take appropriate action.

What we've actually achieved over the last 50 years in cancer control is actually a very good outcome. When I was a medical student approximately 15 per cent of cancers were regarded as curable and at the start of the 21st Century we now recognise in Australia that between 50 and 60 per cent of cancers are completely curable. In other words, cancer is no longer the death sentence it once was thought to be. We do very much better now with cancer than we used to and that's good news, clearly, we've developed a whole range of new treatments which result in longer life for all patients with cancer and a better outcome for the majority, we can at least cure half.

I need to tell you a little about what cancer is before I tell you about what you can do to help prevent yourself developing it. Cancer is fundamentally a disorder of the growth of your cells and that, in turn, is due to genetic damage to those cells. The genetic damage is not to all of you but just to the cells which, in due course, are destined to become cancers and the damage can be caused by a whole range of different things about which I'll talk in a moment.

But the bottom line is that if the cell acquires the right

sort of genetic damage it will survive and grow out of control. Most genetic damage simply kills the cell and the cell is replaced by another cell but it's damaged results in a cell which can grow out of control, that would be what we would recognise as a cancer. Of course, the damage has to be passed on from cell to cell and cancer is a whole clone of cells growing up from one parent, if you like. It's not a single disease because every different part of your body can develop a cancer and the cancers are all different one from another, both in terms of the cause of the cancer and in terms of how it behaves.

This picture here is a picture of a very common cancer in Australia - melanoma - and it's a very good example of a cancer to put up because Queensland, particularly, is the melanoma capital of the world, we have a higher rate of melanomas amongst our population than any other country in the world. One in every 16 of us in Queensland is destined to develop this very serious cancer in their lifetime and that’s really almost as common as breast cancer in women, which is universally the commonest cause of cancer in women. So, this is a very significant public health problem.

But perhaps, more importantly, we can also point out that this is a cancer that is absolutely preventable because we recognise it as almost entirely due to sun exposure and therefore the cure for that particular cancer lies not so much with the medical profession as with ourselves.

So, what is all this cancer biology about? If you start off with a picture of skin and, if you like, this cartoon is a cartoon of the cells of your skin behaving themselves in a nice

neat row along the surface of your skin. If there's damage to one of those cells, to the genes within it, then that cell may change in its properties. It's not a cancer cell just because the genes have changed, it just behaves differently and that cell will divide and grow and the cell will change genes, it will then become part of your skin.

Further changes can occur and the cells may acquire new properties, so they may grow up as a heap, a wart if you like. Not a cancer but just behaving differently and further changes may occur which make the growth in the cell more obviously different. None of this is cancer but it's the steps towards cancer and all these steps have to occur before a cancer can develop. It's estimated that you need changes in at least nine genes in each cell of the right sort before that cell will become a cancer.

So that the changed cells may eventually come to the stage where they're not controlled by the things that make our skin normally misbehave itself and only grow when it needs to repair itself and if these cells acquire new properties sufficiently abnormal then we can recognise this as either cancer in situ or eventually cancer that invades and goes somewhere that it shouldn't. And the primary property of a cancer is that the cells survive and go places they shouldn't go: they spread and that’s why the cancer causes problems for our health.

So, basically, all this process is about damage to genes and it's trying to prevent the damage to genes is the solution to preventing cancer. Most of our cells can actually repair damage to genes or if they can't repair the damage the cells simply die. So that in fact you have to be unlucky in the set

of gene changes that you acquire before a cancer occurs. Some people are more prone to cancer because their ability to repair that damage is less than normal and these people are recognised as cancer prone and they can inherent that trait and then you see cancer-prone families.

At the start of the 21st Century, what can we do about cancer prevention? The surprise is that we can do a great deal. We recognise that there are a number of risk factors for that genetic damage which we can avoid ourselves. We recognise that 25 per cent of all cancers worldwide are caused as a result of infections and I'll come back to that topic because that's the one that particularly interests me. We also recognise that 25 per cent of it is due to what we do to ourselves and I'll come back to that as well because you need to be guided as to what we know at the moment about what should be done to avoid it.

About 25 per cent of all cancers are recognised to be due to things in the environment that are not entirely in our controls as individuals but, collectively, we can do something about. A classic example of that would be asbestos exposure. And only ten per cent of our predisposition to cancer is due to the genes that we inherent from our parents. In other words, cancer is mostly what we find in the environment and much less than you would expect what you've actually inherited.

The important point, of course, is that the top three in that list there - the top three reasons for cancer development are, in practice or in theory at least, within our control and if we manage to control each of those then we could reduce by 75 per cent the rate of cancer that we see worldwide. That, if you like, is our challenge for the 21st Century.

So, preventing cancer. What can we do? As I say, what are those things on the list that we do to ourselves that we need to avoid? Well, the tendency of course is to be prescriptive and say "thou shalt not" - these are the things you must not do but we sometimes get the messages rather confusing. If you read the newspapers you will in the same newspaper on the same day find one article that tells you that, for example, coffee and caffeine will increase your risk of a particular cancer and further on in the same newspaper by a different or sometimes even by the same journalist there will be an article that says that caffeine can reduce your risk of another cancer. So, it is clear that the messages have to be consistent if we're going to get people to change their behaviour.

This will bring back some memories perhaps for some of you who were in Russia as part of the Medico-Legal Society's trip there a couple of years ago. This was a trip on the way to Crete. This is a sign from a park that's outside St Petersburg and it basically is trying to tell you what you should not do but as you can see the messages that are put there are somewhat confusing. I kind of liked the second one down on the right-hand side because that's a very Australian message, it says "It's not a good idea to keep your red wine too close to the bar-b-que". But some of the other ones are a little harder to interpret and I'm particularly interested in the one down at the bottom left and then other interpretations for the one at the top left which obviously could be interpreted simply as that certain sorts of dancing are not allowed but I think they have other things in mind.

At any rate, we need to get consistent messages out if we

want people to understand what we're supposed to do and not do and I guess that's a problem that wouldn't have been helped there even if that bit at the top was translated from Russian into English. So this is a list which has been conveniently drawn up by a colleague of mine, Professor Bruce Armstrong in Sydney about what we can do in the Australian environment to help reduce our risk of cancer.

It's no surprise that at the top of the list you will find **smoking** and the World Health Organisation, the International Cancer Union and all governments recognise that smoking is a very major public health problem they wish they could do without. 29 per cent of all the avoidable cancers are due to smoking - 29 per cent - 43 deaths a day in Australia. So, clearly, this is something we have to do something about and, indeed, as you are well aware, legislation has been put in place around this country to make our environment safer from the point of view of smoking.

But we've got a long way to go yet. We've managed to reduce the percentage of people that smoke in this country from 25 per cent down to 14 per cent over the last 15 years, that's why we get a green light for performance there. But Canada can manage 11 per cent and, in principle, there's no reason why that figure shouldn't be zero. It certainly would be a good idea from the public health point of view if it were.

The next one on the list - and I hate to say this in a function like this evening when I'm sure we're all going to enjoy a drink - is **alcohol**. Alcohol contributes quite significantly to the cancer burden, particularly head and neck cancer and liver cancer but not exclusively those cancers. The

trouble is to know exactly how much alcohol you're allowed to drink. The general rule for that is less than your doctor so given the number of doctors present in the room that may be quite difficult to achieve.

But realistically the National Health & Medical Research Council has set some guidelines out about that. They're under revision at the moment. I preferred the old ones which were that men were allowed four standard drinks a day and women two. The new ones have halved those figures. I'm not quite sure what the evidence base for that is but clearly we're going to have to look at it pretty closely because they are just draft guidelines at the moment and I suppose that once they're introduced and become guidelines I might have to feel obliged to stick to them, so I'll have to decide whether the evidence really justifies the cause. But come what may, there's no doubt that excess consumption of alcohol increases your risk of cancer.

Of course we have to balance that off against some fairly good epidemiological evidence that a certain amount of alcohol increases longevity: one to two glasses of red wine a day are supposed to decrease our risk of cardiovascular disease and there was an interesting published study recently looking at the consumption of alcohol in old folks' homes and showing that the woman - and it was "woman" in this particular study - who had one to two drinks every afternoon on average lived longer by about two and a half years in the nursing home than the woman who had none at all. I would have liked it to have been randomised to the alcohol group but clearly it's nice to see such studies coming out to show that there are some benefits from alcohol consumption as well.

Overweight and obesity is a significant problem in this country and it contributes about four per cent of the preventable cancer burden, particularly colon cancer, bowel cancer, ovarian cancer and a number of other cancers as well. Unfortunately, this is one area where we're not doing well. Our weight on average is increasing and, of course, it's not just cancer we need to worry about for that. Physical inactivity gets a green light where obesity gets a red light. There's a sort of dichotomy there, which isn't easily explained except that the weight is absolute, you can measure that, whereas the physical inactivity is what people report they do and that's in the census. So, in the census we're all taking more exercise but in practice we're gaining weight nonetheless.

More fruit and vegetable intake. We do fairly well on that and it's not a major contribution to cancer but nevertheless there's fairly clear evidence that you increase your fruit and vegetable intake you can reduce the instance at least of bowel cancer.

The ones down at the bottom of the list are perhaps less important but the one that we can't put an exact figure against, because many of these figures are derived from international studies and then applied to the Australian setting, is the **excess sun exposure**. This is clearly one we really need to think very carefully about. We tell our kids correctly that they should keep out of the sun and we encourage "slip slop slap" and our kids do it until they reach teenage years and then they go down to the beach - and there was a nice report in one of the journals recently that a quarter of all teenage children in this country get sunburnt regularly at the weekends and that's why we

have one in 16 people coming down with melanoma.

It also concerns me very considerably that solaria are still quite legal in this country where sun exposure is very easy to get for free. And promoting a solarium use to teenagers as "a healthy tan" in my mind is as bad as promoting smoking and yet we still encourage it and allow it to be advertised and although states are beginning to think about introducing compulsory legislation we have a little bit to go in that area yet, particularly in Queensland it seems ridiculous that on the Gold Coast of all places there are several solaria working and selling their wares to a community that can go outside and get a full day's worth of exposure in five minutes.

So, moving on from all the bad news, if you like, the things you're not allowed to do, let's think about the other side of things and what we can actually do to help prevent cancer through medical research. I'm going to focus particularly on infections in cancer because that's the area that I'm most interested in but we don't want to forget the other things that can be done and I'll come back to them at the end.

For the non-medicals amongst you, you might be somewhat surprised to learn that your bacteria outnumber your cells 10:1. You may be approximately 10 billion - that's UK billion - that's 10,000,000,000 - cells but your micro-organisms are ten times more than that. They crawl all over the surface of you, they are inside you, and they're doing a very good job, they defend you against attack from a whole range of other much nastier micro-organisms and they also help you to digest your food and keep you working as a person. Eventually, of course, they'll

consume you at the end of the day, too, but in the meanwhile their job is actually there to defend you.

It's not surprising, given that number of organisms, that some of them actually can cause trouble as well as protect us and, indeed, that's what we actually observe. Worldwide more than 20 per cent of all cancers are caused by infections. The one that I'm particularly interested in is at the top of the list there, human papilloma virus, and it's responsible for about five per cent of cancers worldwide.

I'm going to talk a little bit about cervical cancer but while we do that just remember that these viruses are responsible for a range of other cancers in humans, in men as well as in women and, for example, head and neck cancer, about 20 per cent of it can be attributed to infection with these viruses. So they are a particularly nasty group of viruses. They're green on that list because we now have a vaccine to help prevent them and you can see also hepatitis B virus (which is next on the list) we have a vaccine to prevent that, too.

Both of these viruses are very commonly a cause of infection. Fortunately, the infections don't often lead on to cancer but, nevertheless, collectively they contribute these two viruses ten per cent of the cancer burden worldwide and while we would like to think that the vaccines that we have available at the moment will be used, until their actually deployed effectively worldwide - and the hepatitis B vaccine has been around for 30 years now and still only a half of the world's population has been immunised. We won't really be doing as much as we can to help prevent cancer, particularly in the developing world.

The next three viruses there are in yellow because we're trying to work on vaccines for those but we haven't yet got them. The big challenge is going to be hepatitis C virus which is probably the most important to get a vaccine against. And then down at the bottom in the other category - I don't think Barry Marshall would be very pleased that I put his discover as "other" helicobacter. Now helicobacter is a bug not a virus but Barry Marshall and Robin Warren were given the Nobel Prize for describing the association between that particular bout and gastric ulcers but we recognise also that it's a major cause of gastric cancer and I'll talk a little bit more about that at the end if I have time.

So, we're going to focus mostly on human papilloma virus from now on and cervical cancer for a bit. It's a disease of the developing world. The countries and the red on the map there are the countries where cervical cancer is common and the green ones is where it's rare. The only anomaly on the map there is China which is shown in green, it should actually be red, it's just that China hasn't until very recently reported to the World Health Organisation on its instance of any cancers and particularly not on cervical cancer.

However, this is predominantly a disease of the developing world. In most countries on the map there it is the second commonest cause of cancer death in women after breast cancer. It causes a quarter of a million deaths, half a million new cases every year. Interestingly and uniquely amongst that was the viruses that I showed you on the previous slide. The cancer that causes is entirely attributable to infection of the virus. If there were no papilloma viruses there would be no cervical

cancer so that we can potentially eradicate this cancer by getting rid of the infections.

Two types of the virus are together responsible for about 70 per cent of the cancers and as I'll show you in a moment unfortunately there is a very large number of types of virus. Fortunately for us, although these infections are extremely common, they very rarely lead on to cancer: about 30 to 50 per cent of us will be infected with the highest risk virus out of the list HPV16 in our lifetime sometime. But 98 per cent of us get rid of it on our own. We don't really need any help to get rid of it. It's only the two per cent with persisting infection that are at risk of cancer.

However, there is a long lag time between the time when we get the virus infection and the time when we get the cancer and that's just as well because that allows us to screen for cervical cancer, that's what the pap smear program that we use to screen for cervical cancer actually does, it screens for evidence of persisting infection with the virus. Dr.Gabriele Medley, who is the medical secretary for the Society, has spent her life developing effective screening programs in Australia and has ensured that Australia actually has one of the best screening programs in the world for cervical cancer.

The problem is not so much the screening program but getting people to take part in it. The 250 deaths from cervical cancer in this country every year and the 500 new cancers mostly occur in women who have not taken part in the screening program as recommended by the NH&MRC. Worldwide, of course, there are screening programs in most developed countries, not nearly as effective as the ones in Australia but in the developing world

where most of the cervical cancer deaths occur there are no screening programs and there are no reasonable prospects of there being screening programs within the next 25 to 50 years. So, cervical cancer is a disease that we can control in the developed world if we use these screening programs but for the developing world, where most of the deaths are, that will not be sufficient.

So how did I get into all of this business? Well, as you have heard, I was born in Glasgow although, according to that very reliable source of information Wikipedia, I was actually born in Moe in Victoria. That must have come as a real surprise to my mother because she was definitely in Glasgow at the time. So I was brought up in Glasgow as a typical impoverished researcher's son, I only had a bucket to live in and, indeed, no clothes. But you can see it was at least one of the sunny days in Glasgow, that must have been the only one that year I think. I was quite a cheerful chap until I got into research but times have changed and I've got a bit more serious looking since then.

At any rate, I started off my research career in Scotland and I just want to make a couple of points about research and where it fits into the medical profession. This is me and two of my colleagues in Edinburgh in 1975 when I was a medical student. I won't tell you which of those three was me but I can tell you for free that I haven't changed my skin colour or my sex since those pictures were taken.

Anyway, with Induiki and Margaret Lane who were two of my co-conspirators if you like, I was allowed as a medical student to do research and the message I would leave you with out of this particular observation is that I think all medical

students, indeed all health care professionals should be encouraged to do research while they're in training because we really need research to inform the correct decision-making process. What do we do next? How do we improve the profession? You can only find that out through evidence-based research.

We did a little clinical study that actually ended up about two years later being published in the British Medical Journal, their standards were not so high in those days and they actually let the paper in. It had to be rewritten by the editor about 16 times before it actually got in but at least it was published. That actually got me going in research for two reasons: one was because it was interesting to do the research and, secondly, because it had an immediate impact on clinical practice. The hospital that we did this study of how to give fluids after surgery to change their practice as a result of the study and save a lot of patients sore arms from infusion phlebitis, so that from my point of view that was a lesson well learned and I basically would leave you with the lesson that we need to build research into the training of medical students and healthcare professionals across the world.

I came out to Australian in 1981. It wasn't easy to come here. I was keen to come because the Walter & Eliza Hall Institute was the centre of medical research in Australia, particularly in my field of immunology and I wanted to meet with the people there. But, as I say, it wasn't that easy to come. You got asked when you came into the country to fill all these forms. They asked about my criminal record and I told them I didn't realise it was still necessary to have one to come here. Nevertheless, they let me in and I came and worked with Ian

McKay who's the gentleman in the middle of the three people in the picture up there, that was a very young Ian McKay, he's now in his 80s but he still goes surfing and skiing and he's still active in medical research, too, I might add. What I learned from him was the importance of clinical observation. It underpinned the basic research that I was doing at the time.

I won't go through all the history of what I was doing then but I'll just try and outline how I ended up working on this virus that causes cervical cancer. I was working on liver disease and a particular sort of liver disease which Ian McKay as a gastroenterologist was interested in. He was interested in when the body turns on its own liver, if you like, and tries to destroy it and I found this a very hard area to work in and I also didn't like the smell of cooked liver very much so I decided I would get out of that area and work on another virus, hepatitis B virus which also infects the liver because that seemed a little easier to understand.

One of the observations that we made in the men that we were studying who had problems with chronic infection with hepatitis B virus was that they had some damage to their immune system and it wasn't entirely clear to us why that was until a colleague from the United States came to visit - this was in the early 1980s - and said that they had been seeing this problem with men who had sex with men, that they were having real problems with their immune system and we realised that in fact that was the reason why we were saying the same thing in Melbourne.

So that taught me a couple of things. First of all, if you make a chance observation like that it is worth trying to follow

it up and also that you don't always know what the answers are to the problems at the time but they often become clear through the research of other people. At any rate, we did this study and found out that there were a significant group of men with immune suppression and, indeed, that led to my first contact with the media because when we first published and announced the results of our finding that there was a significant problem with HIV AIDS in Melbourne, of course all the television channels found this extremely interesting and I found myself bailed up outside the Hall Institute one evening when I wasn't expecting it by all the television cameras coming to see what this was all about. So, I learned to deal with the media a little bit at that time, too.

But what we also observed from that cohort of men was that they had terrible trouble getting rid of wart virus infection and that led to the interaction with Gabriele Medley which led to me getting involved in the papilloma virus area because she had the idea that it would be a good idea to look to the cells in the back passage of these men to see if they were infected with human papilloma viruses and, indeed, it turned out that they were and that they were having troubles with the virus persisting and leading to cellular changes pre-cancer which, indeed, was also the case. So that intrigued me enough that basically I've made that the subject of my research for the rest of my career.

So that I was fortunate in Melbourne to have a number of mentors: Ian McKay, Gabriele Medley and others - Ian Gust particularly who helped me develop an interest in this particular area and, as I said, that led on to all that happened

subsequently. Eventually the Hall Institute decided it was time for me to leave. I seem to remember that the then director told me in his nicest way that he wanted me to go and start a branch of the Hall Institute somewhere else which was a polite way of saying "It was time for you to get out and go", which I did and I went up to Queensland. When I left Melbourne they told me that my move to Queensland would improve the average intelligence of both states. I took that on the chin, it was all right, and I'm sure there are a few people who followed me up to Brisbane who might have felt that that was perhaps a bit of an overstatement.

At any rate, that led me to meeting with this guy, Professor Harald zur Hausen who drew the connection between human papilloma virus and cervical cancer. He did that back in about 1979/1980 as a hypothesis and it was possible for him to do that because of the tools and molecular biology that were becoming available at that time. This virus is a difficult virus, it doesn't grow well and it's hard to grow it in the lab so that he used molecular tools to find out about the sequence of the virus and found that, rather to his surprise, instead of there just being one papilloma virus which caused warts rather it was a whole family of these viruses and that some of them seemed to be associated with cervical cancer.

We recognise now that there's one particular group that are associated with infections in the genital tract and specifically with the ability to cause cancer and type 16 and 18 are the commonest ones of those. They're the ones that are in the vaccines that are now available to help prevent cervical cancer. But, unfortunately, they're not the only ones. There's a whole

family of these viruses. In fact there are about 350 now sequenced and characterised and about 20 of those have been associated with cervical cancer. So that this is important because each of these different genotypes, each of these different virus types is in fact seen by the immune system to be a different virus and so that while these two viruses which together are responsible for about 70 per cent of the cancers are the two common ones and they are the ones that the vaccines will protect against. The other ones can still cause cancer so that at the moment we can't protect against all cervical cancer by vaccination - only against 70 per cent of it.

So that the technology that Jain and I developed - my colleague the late Jain Zhou and I developed - came out of the knowledge of how the virus worked as a virus and this is a couple of pictures of the virus, the pink football is basically what it looks like. It's made up of 360 copies of one protein called L1. That doesn't matter too much but what does matter is the trick that Jain and I came up with back in 1991 which was how to assemble a shell of the virus out of those proteins.

Now we didn't set out to make a vaccine. I must stress this. We set out to understand how the virus worked as a virus. But what we wanted to do was to build a virus because we couldn't grow this virus in the lab and we set out to build the building blocks, this protein called L1, and much to our surprise when we did that, we played around with it for a while before it worked, we actually found that it assembled itself into the virus-like particle, the shell of the virus.

So these pictures in the middle here are of empty virus - they're virus-like particles but these are made using the common

DNA technology in the lab so there's nothing infectious there. The important thing is they look just like the virus to the immune system and therefore the immune system responds to them in the same way as it would respond to the virus by making neutralising antibody to protect against infection. So we can use these virus-like particles to make the vaccine.

It is worth pointing out in passing that we didn't really expect that these virus-like particles would assemble like that. It was a bit like getting a set of Lego blocks and throwing them into the corner and then coming back in the morning and finding that they'd built themselves into the Sydney Opera House overnight because we really didn't expect that to happen at all. But it's just as well from the point of view of developing a vaccine that it did because that meant that the process was relatively easy to do, it could be done in a lab on an industrial scale. If we'd had to work to build the thing up into the virus-like particles then we would never have got a vaccine.

So that the self-assembly was pretty critical and these things are seen by the immune system very effectively and they make a very good vaccine so that from 1990 through to 2005 the vaccine was developed. That little yellow arrow, the second one there, looks kind of small and insignificant but what it actually represents is the work of 2000 scientists and doctors worldwide, 60,000 women who volunteered to take part in clinical trials and about US$1 billion of expenditure so that this was a very big exercise to turn the technology that was developed in the lab back in 1990 into a vaccine that could be actually used to prevent the disease.

At the end of the day it's a very conventional vaccine. It works like every other vaccine that you had as a kid, it produces these neutralising antibodies which will protect you against infection. Perhaps the most important thing is exactly that: it only protects you against infection, it does not treat the existing infection. So that these vaccines are, of course, now available and indeed there are two of them: one called Gardasil, one called Cervarix - one made by Merck and sold by CSL in Australia, one made by GSK. They both work just the same way, they're both just as effective.

So I'm going to show you some data to show they're effective so I've got to make a disclosure of conflict of interest. This is the bit where I have to spill the beans and say yes if these vaccines are sold, which they're being sold, I will make some money off it and that's very nice for me but to distract you from that nice idea I've put up a picture of me becoming Australian of the Year instead.

But moving right along, as they say, what do we need to know about a vaccine? We need to know whether it works, how long it works for, is it safe and who should get it. So, I'll just go through these ideas with you just now for this vaccine. This is a complex slide so we just need to focus on this bit on the side here and we really only need to look at the red numbers. This is just vaccine efficacy and those trials are 60,000 women worldwide and there are only two comments that I need to make about this. First of all the vaccine, as you can see there from those red numbers, is between 95 and 100 per cent effective in all the studies but effective according to the rules that were used for the studies and the rules that were

used for the studies were that the women had not to be infected with the virus when they came into the study and efficacy was only measured as protection against disease caused by the viruses that were in the vaccine, which I told you only 70 per cent of the viruses cause cervical cancer.

So the vaccine is extremely effective at preventing cervical pre-cancer caused by the viruses that were in the vaccine - 70 per cent, if you look at it overall, only 100 per cent if you narrow it down to the disease caused by those viruses. So that was encouraging, to put it mildly, when we got those figures back. It was really very nice to see. There are no other vaccines that are 95 to 100 per cent effective. Most of them were between 85 and 90.

This is translating the data into the real world. This is sort of a complex graph but I'll kind of make it simple. The dotted line, the staircase there on the top, shows the gradual accumulation of cervical pre-cancer in woman that have been given the placebo in the trials and this is over a couple of years and a certain percentage of them come down with the pre-cancer that we normally treat if we find it in a pap smear.

The green arrow shows the reduction that is due to the vaccine. So the solid line shows the amount of cervical pre-cancer in vaccinated women and you can see there's about a 70 per cent reduction, which is what you predict. By the way, that 70 per cent reduction translates in this country alone into 20,000 operations for cervical pre-cancer that do not have to occur ever year, so that’s really the benefit of vaccination, you don’t have to have surgery to cure yourself of cervical pre-cancer.

The red arrow is the residual pre-cancer that's caused by other virus types and that's why we have to carry on doing pap smears because to protect women against the disease caused by the other virus types, we have to carry on with the pap smears. So that's how effective the vaccine is.

The next question is how long will it work for? And the answer to that is we don't know, clearly, because we've only been doing studies for about eight years. But this slide, which again I will not expect you to you to absorb all the details from, just look at the dotted yellow line up at the top there, that's the level of protection in your blood against infection, it's antibody against the virus.

After you're immunised the level of antibody goes up and then it falls for a little while and the most important part is that from two years out to five years and, indeed, now to eight years that level stays absolutely constant and that means that the protection level isn't diminishing with time. And that's true for quite a lot of vaccines and it seems to be true for this one as well. So, the best guess at the moment is that once you've been immunised the protection will last life long.

The next question, of course, is is the vaccine safe? And the answer to that is from placebo-controlled trials with 60,000 women we can find out about the common side effects of the vaccine and the answer is that you get a sore arm when somebody sticks a needle in, that's go great surprise and some people faint when they get the vaccine and that's no great surprise except to the media who find it quite interesting when women faint when they get the vaccine.

As you know, Catholic schoolgirls, particularly in

Victoria, seem to be prone to that, but nevertheless, the instance of fainting was exactly the same in the placebo arms of the trials as it was in the vaccine arms. It's not of course the vaccine that makes you faint, it's the fact that somebody threatens you with a needle that makes you faint and, indeed, army recruits fall over like ninepins when you get the needle out and suggest you're going to immunise them and you don't actually have to do the immunisation, they just pass out.

At any rate, there's no side effects that were significantly more common at least with the Gardasil vaccine for which the best data is available in comparison between the vaccine and the placebo recipients. Post-marketing surveillance tells you about the rare side effects after vaccination and this is always the area that's contentious because now you have no placebo arm and therefore you don't have a good comparative for the frequency of things.

20 million women have been vaccinated worldwide to date over the last two years. There have been a number of reported adverse events, which might have been associated with vaccination. Mostly they're fainting and, indeed, one broken nose was due to the fact that somebody fainted and fell against a table so I don't think that really counts. But, obviously, people are concerned about whether there are any serious adverse events and there have been a number reported but nothing at more frequency than you would have expected by chance

There are a number of groups out there who would like you to believe that vaccines are dangerous, generally or specifically, and there's no evidence to support that but nevertheless the evidence is used because somebody died and they

had received a vaccine at that hospital, the vaccine that caused the problem.

What about pregnancy safety? Well, the vaccines are given in trials and nobody should actually get pregnant. As you can see there, the instructions we give out that you shouldn't get pregnant when you're on an experimental drug don't work very well. Indeed, there was a rumour going around that the vaccine actually caused pregnancy but then, of course, that's what you have a placebo group for and the placebo group got pregnant with equal frequency so we could be quite safe and say that it wasn't the vaccine that was causing pregnancy but, more importantly, we can look and see whether there are side effects from the vaccination in pregnancy and the short is there are not. So that pregnancies go wrong occasionally but they go equally wrong in vaccine and placebo recipients. No evidence that there was any problem due to the vaccine itself.

Then who should get it? Well, you need to know a few things. These vaccines will not cure you of infection you've already got so basically you want to get the vaccine before you get the virus so you have to say who gets the virus and the answer is young people get the virus when they become sexually active. Do they need to get the vaccine before they become sexually active? No, so long as they get it before they get the virus and most people get the virus within the first three to five years after they become sexually active so the earlier the better.

Does it matter if you've had the infection in the past? No. You won't get rid of it because you've had the vaccine but it doesn't make it any worse, so there's no reason to test for

it and, indeed, we can't test for past infection, you just give the vaccine to everyone.

What about the best age to give it? Well, basically, this is looking at the immune response, depending on how long you are at the time. What you can see here is that basically young people do get a better immune response to the vaccine than older people do. So, maybe that's no great surprise because most vaccines work better on younger people but the bottom line is that if you want to get the best immune response to the vaccine you're best getting it when you're twelve. I hate to say it, but after that, immunologically speaking, it's kind of all downhill, as you can see from this line there. Indeed, I'll show you a little bit more and point out that as we get older still the immune response gets less. Don't look at all the details, just the graphs all slope down this way and we're now looking at 45 year olds at the end of the graph there.

Should older women get the vaccine? Does it work in older women? Well, this is looking just to see at what age people get infection with this virus and it's no surprise, as I've told you already, that the majority of people get the infection at the ages of between 15 and 19 or 20 and 24. We're using warts here as a substitute for catching the infection - genital warts I'm talking about - because they come very quickly after you get these viruses and therefore they're a surrogate measure, if you like, for what age you get the virus at.

But the interesting thing is that you're still quite significantly at risk, at least in this American study - you can argue Australia might be different from America - in getting the infections between the ages of 25 and 50. So there is still a

risk there that you can protect against. And the bottom line, if you actually look to see if the vaccine works in that age group is it works just as well as it does in the younger people. I'll not go through the data, I just put the slide in to remind me to tell you. That's the nice thing about giving a talk is I can use these as a prompt.

But the bottom line is the vaccine is at least 95 per cent effective at protecting against new infections in older women who have not previously been infected but the instance of new infections in that older age group is quite low and therefore while you might well as an individual want to protect yourself at an older age group there is no obvious and immediate public health benefit from generalised immunisation.

Where next with these vaccines? Well, we need to know how long protection lasts. Is it lifelong? We need to know how effective the vaccine is in men because we don't have any data and we need to know how to get it into the developing world, which is my major interest. Basically, the vaccine is now licensed for use pretty much worldwide. Japan and China are the last major countries that haven't licensed it. We have a very good program in Australia which you've probably read about where the government is paying for the vaccine to be given to girls between the ages of 12 and 25 for the next couple of years and the really good news is that where that's been looked at, the uptake on the vaccine has been over 80 per cent in this voluntary vaccine program. Not so good in the 18 to 25 year olds where they have to go and get something done, better in the schoolgirls where they're offered the vaccine at school.

Other countries are following our model and Germany, Italy,

France, Canada and Great Britain will all introduce programs in the course of this year basically targeted at the same age groups. But, of course, the big problem is to get this vaccine out into the developing world and that's where it's most needed because that's where the biggest incidence of the cancer is.

The vaccine is quite expensive but the biggest problem in the developing world is working out a program to deliver this vaccine to women of an appropriate age. We give healthcare to young girls in the developing world; we give them vaccines up to the age of about four; we don't see them again until they first become pregnant at the age of between 18 and 25 and, clearly, this vaccine needs to be given before the onset of pregnancy and that's a real challenge.

So, what we've been doing is some trials in Vanuatu and now we're going on to do these in Nepal as well of what would be necessary to get vaccine into the communities by basically finding out from the communities themselves what they understand about vaccination, whether they want this vaccine, whether it's helpful to them to know about it or whether it's just better to say "This is a great vaccine you should take it" and these studies which hopefully will allow us to develop policies for these countries about vaccination should enable the vaccine to be delivered there if we can find the funding. The funding will come from the World Health Organisation, the Gates Foundation, the vaccine manufacturers and anybody else we can get it from but it will be a big challenge to get this vaccine out there in under 25 years I feel.

I don't have very much more I want to say to you, to be quite honest. I just want to tell you one other final story and

that's about gastric cancer because it's another infection that I think you should know about. These little green things crawling over there are not worms; they're bugs in the surface of your stomach and they're the ones that cause gastric ulcers and gastric cancer. Barry Marshall and Robin Warren were quite rightly given the Nobel Prize for finding out that association. Indeed, anybody that drinks their own bug in order to prove that it causes a disease deserves every prize that there is going.

It's an interesting bug because we actually all carry it around with us - well, 70 per cent of the people in this room have actually got it but not everybody gets sick with it because only one of many species of this bug can actually give you trouble. It's an interesting bug because it injects things into your cells. It's got a little needle and syringe on the end of it. It's born that way and it injects into your cells things which change their behaviour which shoot the bug but also cause the cancer.

So this is another cancer that, in principle, we can eradicate. This one you don't need a vaccine for, you need antibiotics and this is an important disease to get rid of because in South East Asia gastric cancer is the commonest cancer in men. It kills more men than lung cancer even in countries where smoking is common. So this is one we really do want to get rid of.

Basically, I've told you about a number of infections this evening that can cause cancer. I could go on and talk for a lot longer about that but I shall save you that because it's dinnertime and I realise that I am the entrée between the starters you had upstairs and the soup that you're waiting for

and I don't really want to spoil the soup, so thank you very much for your attention.

DR MEDLEY: Ian has graciously agreed to answer questions. Just a few before the soup in case anybody has anything they would like to ask.

QUESTION: Thank you very much. My name is Jane and I might say already my darling daughter has already had your wonderful vaccine so thank you very much. But as a medical student I remember those horrible oesophago-gastrectomies that I had to assist with, I've hated surgery ever since, and I just wonder what you think about would you vaccination be good for all of us here even though oesophageal cancer is much more infrequent.

PROFESSOR FRAZER: I guess that the question can be sort of summarised by saying what about all the other cancers these viruses cause? The issue is getting the vaccine into people before they get the infections. Oesophageal cancer is caused by a lot of different things and not all oesophageal cancers, of course, are caused by papilloma virus. In some parts of the world the frequency is much higher, in China particularly.

I think the bottom line is this is a great vaccine for preventing cervical cancer but by the way we'd better give it to everybody because there are a lot of other things we can't really prove it will prevent but we know in the long run that it will. The reason we can't prove it is because if you get the infection at the age of 16 and you don't get the cancer until you're 60 then there are not too many benevolent organisations will sponsor 45 year studies to find out whether the vaccine works, so that the easiest way to do it is just to immunise people and then see what happens the instance of the cancers

and, in due course, we'll find out where this virus is really causing trouble.

It's not going to be the cure for oesophageal cancer any more than it will be for head and neck cancer but the instance of the diseases should go down.

QUESTION: Will it have a role in preventing prostate cancer?

PROFESSOR FRAZER: Yes, okay. As a mere male I also feel concerned about prostate cancer. We're all destined to get it if we live long enough, the males amongst us. At the moment I think it would be fair to say that all the vaccines for treating prostate cancer are experimental. The nearest one to market is something in the United State called Provenge which is not a cure for prostate cancer and it's not even a prevention for prostate cancer, it's a means of treating existing prostate cancer.

But perhaps the most interesting thing is the idea that papilloma viruses themselves may be responsible for at least some prostate cancer as well and there are certainly a group in my institute who are directly studying that.

One of the difficult things is that while we can see the fingerprint of papilloma viruses in a number of cancers we also recognise that papilloma viruses can cause cancer by what we call a hit and run mechanism. In other words, they come in, do the damage and then disappear and they leave no trace behind that they've been there.

If papilloma viruses cause prostate cancer it must be a hit and run mechanism. We know there are definitely cancers in animals where a papilloma virus works that way. If it turns out to be the case in prostate cancer that will be a great step forward because prostate cancer will then be effectively a

disease we can prevent by vaccination. So, we're doing our very best to find out if that's the case but at the moment I'll have to say the evidence is not one way or the other, we just don't absolutely know.

QUESTION: Should males also be vaccinated at an early age?

PROFESSOR FRAZER: It's widely known, at least in Queensland, that my male sons got the vaccine for their Christmas last year. It wasn't the only thing I gave them for Christmas, I'm not that mean, but I believe that men should be vaccinated but - and I stress "but" - there is no evidence base at the moment that the vaccine prevents disease in men.

It's certainly safe, it's immunogenic, in other words it produces the right immune response but the men are reluctant to take part in the trials. You see, the trials involve biopsies every three months from that part of your anatomy and when you suggest that to men they sort of lose interest and say "Well, I'd rather go to the footy this afternoon, thank you".

So these trials are under way but they're slow for recruitment and it will probably be the end of 2009 before we have a definite answer whether the vaccine works in men. At that point then the push will be to recognise that we should be immunising the men as well, if it works.

It will be like rubella. We started off by vaccinating only women. After about five to ten years the public health people pointed out it would actually be cheaper and more cost effective to vaccinate the men as well and I'm sure that will be true for this virus, too.

QUESTION: Does cervical cautery completely eliminate the virus?

PROFESSOR FRAZER: Well, of course, if you've got it in the cervix

then that gets destroyed in the course of treatment of an abnormal cervix. 98 per cent of people get rid of it and for the other two per cent we have a number of treatments which we think help but there's no definite way you can get rid of it, certainly not an immunological one. Most of the time the virus is harmless. We carry it around. We're infectious for other people, sure, but we don't know we've got it and it doesn't cause any problems, it's only when it changes the cells in the cervix does it become pre-cancerous and it's a real problem.

End

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