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Transcript

***[Margaret Stanley:** I've given talks at which there's been almost physical intervention, and particularly in Ireland where there was a vaccine scare, and the Irish Cancer Society put up a set of public lectures in which I talked. And it was quite tricky, and I'm not a shrinking violet, but I don't like the idea of getting a fist in my face.]*

Andrew Pollard: Hello, my name is Andrew Pollard. I'm director of the Oxford Vaccine Group at the University of Oxford.

Welcome to our podcast series, The Oxford Colloquy: Trust in Science, bringing you the stories, facts, and people behind the science.

On this episode, I'll be speaking with Professor Margaret Stanley, one of the world's leading experts on human papillomavirus or HPV, the virus that's the cause of cervical cancer, and her work has led to a point today where most cases can be prevented by vaccination.

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Andrew Pollard: Professor Margaret Stanley, OBE, Emeritus Professor of Epithelial Biology at the University of Cambridge and Fellow of the Academy of Medical Sciences, welcome to this podcast.

Margaret Stanley: Welcome. Thank you very much, Andy.

Andrew Pollard: So Margaret, you're a virologist and you've been working with viruses for all of your life.

But I'm interested to know, how did you start? Where did this idea come from, of working with these sort of organisms that are not even alive unless they infect a cell?

Margaret Stanley: Ah well it's like most of my career, entirely serendipitous. Because I did biochemistry as an undergraduate and did a PhD. Then I got married. And it was a very traditional marriage, so where he went, I went, and we went to Australia and I had to find a job. And in those days, women were paid less than men. So when I was

offered a job that was very attractive, but paid me two thirds of what a man did, I told them "Please no".

I was given a research associate job in the Department of Obstetrics and Gynecology. And the Department of Obstetrics in Adelaide was a really extraordinary place in those times because they had a really efficient cervical cancer screening and it was run by a Scotsman who'd learned his trade in Dundee from Betty Macgregor. And what he wanted me to do was see if I could work out if you could predict which of the pre-cancer cells were going to go on to invasive cancer. And this involved looking at their chromosome complement. Nobody had done this at this stage.

Andrew Pollard: So, this is now in Adelaide. So you're getting samples of cells from the cervix of women who are being screened.

Margaret Stanley: We got those, but we also got the biopsies when they were being treated.

Andrew Pollard: So they took samples from the cervix looking for signs of cancer.

Margaret Stanley: That's correct. And so I would be given these and under my boss's direction, we'd take out the bits of interest. And then I had to develop methods to try and work out what their chromosome complement is.

And at that stage, that was actually quite a big deal - because you have to understand that gynecologists were cutting women's uteruses out because they thought they had these pre-cancers. So this was quite useful. And it got me into the whole literature about cervical cancer, which was quite clearly a sexually transmitted disease.

Andrew Pollard: So what period was this, Margaret?

Margaret Stanley: That was the 1970s.

Andrew Pollard: So in the 1970s in Adelaide, there was some pretty severe surgery to treat pre-cancer lesions because they were known that they would go on to cause cancer.

Margaret Stanley: Not in the Department of Obstetrics and Gynecology, there was a very conservative treatment there. But in the wider gynecological community, there was this attitude.

Anyway, as I say, it got me into the whole literature about cervical cancer and the fact that it was a sexually transmitted infection, but nobody knew what the infection was. And this, of course, was the time when herpes came to the scene. And because I'd developed methods for growing cells from the epithelial surface of the cervix, I started to look at whether herpes viruses would transform. And they didn't.

Andrew Pollard: So, these are the viruses that cause cold sores that people would be very familiar with, but they can also cause similar types of infections in the genitals.

Margaret Stanley: It's a sexually transmitted infection, and that was why it was of interest. And so I'm into this area now of cervical cancer, and then the infectious cause, almost certainly a viral cause - what's the virus?

Andrew Pollard: Yeah, and you've proven that it's not herpes viruses because they didn't cause the cancer changes.

Margaret Stanley: They couldn't. So that's the first sort of step in the virological story. But I had to learn about herpes viruses. And I learned that by coming to Cambridge for a year on a Roosevelt fellowship. And I worked with the second person who made huge changes in my whole attitude, and that was the professor of pathology at Cambridge, Peter Wildy, who was a very distinguished herpes virologist. And so he actually made me a proper scientist.

So I learned about herpesviruses and learned that it couldn't possibly be them and the cervix. And then it was a question of, what is it? And that came from Germany. And that's the next transformation - because Harald zur Hausen, who got the Nobel Prize for this, was actually a great friend of Peter Wilde's. And we were informed about what was going on in his lab.

So he, in the early 1980s, had made this really remarkable observation that a new papillomavirus, which none of us had ever heard of, actually could be isolated, or its DNA could be isolated from cervical cancer in 100% of cases virtually.

Andrew Pollard: These are viruses that cause common warts, but within the family, there are some which can cause these lesions in the cervix.

Margaret Stanley: This was mind-blowing, because the papillomaviruses, you can't grow them - you couldn't then, and you can't really now. So it depended on technology, and it was the technologies that were coming along, how you could manipulate DNA, cut it up into bits, PCR was coming in, you could amplify it… All of this allowed the emergence. of papillomaviruses as a possible agent.

And if you sat back and thought about it, that was completely sensible, because they were the first DNA tumor virus ever demonstrated in the rabbit. Papillomaviruses in rabbits cause cancer. Not surprisingly they cause cancer in people.

Andrew Pollard: So with this new knowledge, what did you then do with the knowledge that the DNA from these viruses was found in the cancers?

Margaret Stanley: First of all, I got the isolates from Harald zur Hausen so I could then start to see if I could transform cells from the cervix with these viruses, which we could. I wanted to be able to make viruses *in vitro*. And that meant that I was trying to grow cells from infected cells. And I did, I developed a cell line which had the virus that causes cancer in it. And so in that way, I was able to make viruses, but I also developed animal models, which allowed you to look at the immune response.

And one of the great - you know, I said I had two things, going to Adelaide, then meeting Peter Wildy. This was the third major thing, joining the Department of

Pathology, because it had a fantastic group of immunologists. It really was stellar. So there was no way you could not be infected with the immunological virus in pathology.

And what I wanted to know was, what was the immune response? Why didn't the body's defences recognise this virus, which was there in large amounts? And so that set me off on the next phase of my career.

Andrew Pollard: So that sort of intersection between being a virologist and having the right people nearby who understood the immune system allows you to start thinking differently about that intersection between the infection and the immune response that might or might not protect you.

Margaret Stanley: Absolutely. And it also, again, it's technology. People forget how important the development of new ways of doing things is in science. And the technologies for handling cells, handling T cells, looking at different subsets of T cells. All these things were being developed. So it was a very exciting time to be in science.

Andrew Pollard: And what were the observations then once you started working with the immunologist? What did you learn about why doesn't our immune system get rid of these viruses?

Margaret Stanley: Because it was ignorant.

Andrew Pollard: Yeah. Because it was ignorant!

Margaret Stanley: This is a virus that hid itself incredibly efficiently from the immune system. It didn't kill cells. It in fact just made them behave in the way it wanted. It depended entirely upon the epithelium cells going from the immature state in the bottom of the epithelium up to the top when they're mature and about to go off. So every stage of that - it's a life, you're a baby at the bottom, you're a school girl in the middle, and you're a mature adult and then a geriatric at the top. And the geriatrics are packed with viruses and they're off to infect somebody else.

And all this is done very quietly. No cells dying, because they're going to die anyway. And it also evaded the major things that we now know are important, which is the innate immune system.

Andrew Pollard: So someone infected has no knowledge that they're infected because the virus has all these mechanisms to stop our bodies recognising that they're there and to hide from the immune system.

And as you say, I should explain that you're an epithelial biologist in terms of your title, and these are the cells that cover the surface of the cervix of the epithelial cells and there's lots of layers of them and what you're describing there is how the virus gets more and more packed with more and more copies of itself as it gets to the surface so it's then shared and it gets passed on to someone else.

Margaret Stanley: That's absolutely it.

Andrew Pollard: So now, I guess you're now moving through the 1980s, are you? Starting to work on the immune system. So when was it first understood then that there might be ways of preventing infections by using vaccines? Moving on from understanding that the virus can hide from us, to thinking about how we might stop infection in the first place.

Margaret Stanley: To be honest, if everybody had read the literature, they'd have known from the start, because Shope - of papillomavirus fame - demonstrated this in 1936. So it was clear that if you generated an immune response to the coat proteins of this virus, it's a little virus that has a coat with only two proteins in it, one of which the immune system, if it's given the right clones, will recognise.

And so that was clear, but could you do it in humans?

Andrew Pollard: So let's get this right, so 1936. Shope showed that you could stop infections and stop cancer in rabbits.

Margaret Stanley: Yes, you could stop infections. He didn't go to the step of stopping cancer, but it could stop infections.

Andrew Pollard: Yeah, which is remarkable given that it took until, what, 2008 before we had a vaccine that was being widely used to protect women?

Margaret Stanley: But then it was tricky to do the experiments. And that was something that we were starting in the 1980s in my lab, because we made - we cloned out the gene for this protein on the virus coat, and we put it into another virus, vaccinia. And so we made back what they call vaccinia recombinant.

Andrew Pollard: So then obviously things moved into the clinical trials and it was shown during the 2000s that these new vaccines protected against infection and against the precancerous lesions.

And now we have the first evidence that they are also stopping cancer in younger women.

Margaret Stanley: Absolutely.

Andrew Pollard: Which is an astonishing change, over the course of your career, starting with that first post in Adelaide.

Margaret Stanley: Starting back to when I was actually looking at women's cells and saying, oh, this is this, and then being able to tell them that they needed a surgery - to actually finding the cause. And then being able to stop it, and actually seeing that it does in fact stop cancer. It's been the most extraordinary journey.

Andrew Pollard: And over the years that you and I have known each other, actually your focus has been much more on understanding the immune response to the vaccines. I guess back in 2008 we thought you needed three doses of vaccines and very high levels of antibody to protect against these infections.

But over that period of time, the last, what, 16 years or so, we've learned that we don't need such high levels of antibodies. What's changed there? Why did we get it wrong at the beginning?

Margaret Stanley: We didn't get it wrong because you've got, as you well know, the manufacturers of these vaccines run these huge trials to get the information that they need for their product to be licensed and given to people so they can sell it, in other words.

And so when the manufacturers were deciding their trials for these vaccines, they took the best case scenario for the whole program of how many doses you needed, when you gave it, and all the rest of it. And they had a protocol from previous vaccines, particularly Hepatitis B. And so then, hepatitis B, what we call subunit, protein vaccines need the immune system to be shown again and again until it makes its maximum response.

Papilloma viruses seem to be different, and it is all about the fact that you're not delivering a protein just as a protein, you're delivering it as a particle structure, and these are intensely attractive and stimulating to the cell that's gonna make the antibody eventually. The other thing is - you seem to need just a sniff of antibody. Incredibly low levels of antibody protect, and again, we shouldn't have been surprised because this is actually true from all the natural infections in animals.

Andrew Pollard: Yeah, so these human papillomaviruses, there are other papillomaviruses that affect other species. And, as you say, we now know that you don't really don't need very much antibody to protect completely against infection.

Margaret Stanley: And that, I think, is the next really interesting thing. Why? Why is it that these tiny levels seem to be so effective? Maybe you could answer that.

Andrew Pollard: It's a good question. It may just be that the infection is a very small number of viruses, and so you just don't need very much to neutralise a small number.

If it was a big dose, you might need a lot more antibody. Maybe?

If you think about that period, we're talking about 16 years, we started with three doses, and we moved to two doses, and now we're just giving a single dose today. And in some ways, the thing that I find more astonishing is that with a single dose, with a lowish level of antibody, it's still protective and it lasts for such a long time.

Why is that, Margaret?

Margaret Stanley: It's all about what happens in the first encounter of your vaccine immunogen. In other words, the particle and the B lymphocyte, which is going to go through its paces and at the end of the day, make a cell only secreting antibody.

Now memory. Now we're talking here about immunological memory, which, in this case is about the constant presence of antibody throughout decades, maybe your lifetime, is dictated, certainly in mice and almost certainly in people, by specialised cells secreting this antibody, living in specialised homes in your bone marrow. And they're either kept alive because the other cells are in contact with, or they periodically redo themselves. I don't think that's been worked out yet.

But it looks as though viruses that cause a lifetime immune responses, give you lifetime memory, it's about making these changes - these so-called long lived plasma cells, in the right amount, in the right first encounter. Once you've got them stuck in their niches in the bone marrow, you don't dislodge them unless something better comes along.

Andrew Pollard: And so there's something about these vaccines, unlike other vaccines, where immune responses can sometimes be very short, that produces the right sort of long lived plasma cells that make these antibodies. And we know now for decades later that people who are vaccinated still have the antibodies. And it certainly looks as if even with a single dose, that's also true.

Margaret Stanley: We know it lasts at least for 18 years.

Andrew Pollard: So we've got, now in this country, people were vaccinated, or girls were vaccinated from 2008, but with a catch up campaign. So nearly everyone under the age of about 35 or so should be protected, or at least have been offered the vaccine to protect them against this terrible disease, cervical cancer.

So what does that mean for the future? Can we give up screening? Is that the end of cervical cancer or is it still going to be a problem for years to come?

Margaret Stanley: Logically it ought to be the end. But it won't be, because you can't give up these widespread interventions without backlash - backlash from the consumers. So I don't see us giving up screening, but you can reduce the number of times you take a sample.

Now, you're asking, will the vaccines get rid of cervical cancer entirely? No, because they're only dealing with The two, of seven now, most common, types of HPV that can cause cancer. You've still got others - so there'll still be an argument to continue screening. Then you have people who haven't been screened. Migrants. Specific ethnic groups. You can't ignore them and they will have to be able to have the secondary intervention of detecting these pre-cancers.

So you aren’t going to get rid of screening, but you ought to reduce the interval. So you don't need women to be screened every three years - every five years, every ten perhaps.

Andrew Pollard: So we're reaching a point where with the current vaccines, we might be preventing approaching 90% of the cancer causing infections, but we still got 10% left. And then, of course, as you were saying, not everyone is taking the vaccines, so they're not going to have the protection directly themselves, although

because the vaccines work so well, they are actually reducing the overall rates of infection in the population, even in those who are unvaccinated because they're less likely to come in contact with the virus.

Margaret Stanley: The so-called herd protection, really is important for these vaccines.

Andrew Pollard: So we're in a very good position at the moment.

Margaret Stanley: Yes we have a good screening program. We have an excellent immunisation program. The only thing you need to do is come up for your shot, and come up for your screen.

Andrew Pollard: If we look over the next 50 years, are we going to see cervical cancer just disappear or because we've only got people under 35 vaccinated, does cancer still remain as a major player?

Margaret Stanley: It won't be a major player in countries which have good screening programs, because they will still be highly efficient at pulling out the pre-cancers.

Andrew Pollard: Because the early treatment of pre-cancer is quite effective.

Margaret Stanley: Yeah, that's very effective. With our current issue in the UK, we've virtually prevented cervical cancer in the under 30s.

We've got the younger women under control. It's the older women who've not had the benefit of vaccination, who will need to be screened, but providing they're screened well, maybe 80, 90% at least coverage - then it should disappear.

Andrew Pollard: Now, as the World Health Organization is very focused on trying to roll out the vaccine to certainly girls everywhere, and in some countries, boys as well, to reduce the rates of cancers in the decades ahead.

But actually, the projections are it's going to take for cancer to disappear to the levels that we're talking about, to very low levels, most of the next century - which is pretty horrific because of the slow pace of rollout. And of course, the large number of people already infected, so there's a lot of work to do.

So perhaps, although we vaccine people think we've dealt with the problem, the screening is going to be needed for most of the next century.

Margaret Stanley: Absolutely. If you can introduce it, but screening is an exponential increase in investment and sophisticated resources compared to immunisation.

Andrew Pollard: So in poorer countries, it's very hard to implement.

Margaret Stanley: It's a tough call. It's a tough call.

Andrew Pollard: The other thing I wanted to ask you about was, we talked about the potential, if you're vaccinated, to have about a 90% reduction in cancer causing

viruses in our population. Is that true everywhere in the world? Is it 90% coverage of the current vaccines everywhere or, does that vary?

Margaret Stanley: Oh, it varies enormously. There are countries, high income countries, developed countries in which only 40 to 50% of the 12 to 13 year olds are being vaccinated, then every now and again you have a vaccine scare and the numbers drop like a stone. And the best example of that is Japan.

Japan introduced the HPV vaccine, I think it was about 2010 or something like that, and they had excellent coverage, 70-80% of their girls for the first two or three years. Then there was a scare and the numbers dropped like a stone. And now, until there was a change recently, only 2% of girls were being vaccinated.

And they don't have a really good screening program. So women in Japan are still vulnerable and I feel quite strongly about this because this is an issue about women's health and why isn't it being taken more seriously.

Andrew Pollard: So that's a whole generation of girls in Japan who will be at risk of cervical cancer because of an unfounded scare about the safety of the vaccine.

Margaret Stanley: And one quite strongly supported by groups of doctors.

Andrew Pollard: Yes, but I think it is true to say that things are moving on in Japan and coverage is going up.

Margaret Stanley: The Japanese experience is an excellent illustration, an exemplar of things that you shouldn't do and things that are absolutely essential if you're going to get a decent national immunisation program.

And one is political will - the government was pusillanimous. In Japan, they didn't withdraw the vaccine, but they withdrew their promotional support for it. If you went to your gynecologist and asked for a vaccine for your daughter, they would say, “Oh no, the government doesn't recommend it.”

Andrew Pollard: And you've been very strong in advocacy around these vaccines, as you say, because of the importance for women's health, but the vaccines are also being used for boys because there are cancers that are caused by the same virus that affect men.

Margaret Stanley: Oh, there are. And the immune response in men is really interesting because - women are slow to make an immune response to a cervical infection, but they do eventually, they make antibodies.

Men do not make an immune, an antibody response to genital infection, nor, it would seem, to infections in the mouth and throat, which is another target for them. And that's an interesting biological question. Why are men and women different in this respect? I can't answer it. But it means men have to be vaccinated.

Andrew Pollard: Certainly with vaccines, women generally, it's not true for all of them, but generally respond better to vaccines than men do. And it's thought that's because of oestrogen receptors on the cells of the immune system which actually help stronger immune responses.

Margaret Stanley: We've got to be good for something.

Andrew Pollard: Exactly. Estrogen is good for something!

Margaret, you've been very vocal and spoken a lot in public about HPV vaccines. Have you faced challenges in doing that?

Margaret Stanley: Oh, yes. I've given talks at which there's been almost physical intervention, and particularly in Ireland, where there was a vaccine scare, and the Irish Cancer Society put up a set of public lectures in which I talked. And it was quite tricky.

The people who opposed this strongly were in the audience and they were physical, and I thought the Irish Cancer Society actually had hired security guards. I'm not a shrinking violet, but I don't like the idea of getting a fist in my face…

There is opposition. The thing is that people aren't rational, they don't think through things, they react emotionally. So nobody should expect a rational response to this, it's an emotional one. And that's the challenge. How do you respond to that?

Andrew Pollard: And has that feeling intimidated in that way? Has that stopped you from being an advocate for the vaccine?

Margaret Stanley: Absolutely not!

Andrew Pollard: I think a really important role that you've had has been in promoting the good science and good communication around HPV vaccine and the importance of the vaccine for defending women's health.

Margaret Stanley, thank you very much for speaking to us on this podcast.

Margaret Stanley: Thank you. It's been a pleasure.

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Andrew Pollard: That was the Oxford Colloquy Trust in Science, bringing you the stories, people, and facts behind the science. So you might be wondering, what is a colloquy? A colloquy is a discourse or conversation, and I hope you'll agree that's what we've been having.