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「免疫を通じたがんの予防 ― その過去・現在・未来」

オーストラリア・クイーンズランド大学
プリンセス・アレクサンドラ病院
ディアマンティナ・がん・免疫学・代謝薬協会局長

イアン・フレイザー博士

Cancer Prevention through Immunization – Past, Present and Future

Commemorative lecture at the 30th Honda Prize
awarding ceremony on the 17th November 2009

Dr. Ian Hector FRAZER

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The University of Queensland
Princess Alexandra Hospital, Australia

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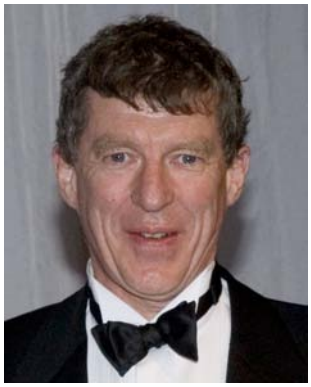

■生まれ

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■学　歴

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1994年～現在　クイーンズランド大学医学部教授

■受賞歴

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2007年　ノバーティス賞（臨床免疫学・リオデジャネイロ)、国際偉業サミット金賞、国際生命賞（科学研究分野)、メルク・シャープ・ハワード・フローレイ・メダル、クラニーズロス賞(科学技術工学アカデミー)

2008年　バルザン賞（予防薬)、ラマシオッティ・メダル、(オーストラリア）総理大臣賞（科学)、米皮膚病学アカデミー・リアグラバー皮膚病理学賞

2009年　オーストラリア医学協会金賞、ゴールドハロルド医薬健康賞

■現公職

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2003年～　オーストラリア科学技術工学アカデミー・特別研究員

2004年～　オーストラリア科学アカデミー・特別研究員

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1974 Bachelor of Science (Hons) Pathology, University of Edinburgh, Scotland

1977 Bachelor of Medicine and Bachelor of Surgery, University of Edinburgh, Scotland

1988 Doctor of Medicine, The University of Melbourne

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1978　Senior House Officer, Medical Renal Unit, Royal Infirmary, Edinburgh, Scotland

1980　Registrar, Medical Renal Unit, Royal Infirmary, Edinburgh, Scotland

1981-1985　Senior Research Officer, Walter and Eliza Hall Institute, Melbourne

1985-1999　Director, Div. of Clinical Immunology, Princess Alexandra Hospital, Brisbane

1989-1993　Associate Professor, Department of Medicine, University of Queensland

1991-present　Director, Centre for Immunology and Cancer Research (Now the Diamantina Institute), University of Queensland

1994-present　Professor, Department of Medicine, University of Queensland

■Selected awards

2006: William Coley Medal, Cancer Research Institute, N. Y., Distinguished Fellowship Award, Royal College of Pathologists, Australian of the Year,　Queenslander of the Year.

2007: Novartis Prize for Clinical Immunology, Rio de Janeiro, Golden Plate recipient, International Achievement Summit, International Life Award for Scientific Research,　Merck Sharp & Dohme Howard Florey Medal,　Clunies Ross Award, Academy of Technological Sciences and Engineering.

2008: Balzan Prize for Preventative Medicine, Ramaciotti Medal, (Australian) Prime Minister's Prize for Science,　American Academy of Dermatology Lila Gruber Award for Dermatology.

2009: Australian Medical Association Gold Medal,　Winner of the Gold Harold Health & Medicine Award

■Fellowships

Royal College of Physicians of Edinburgh, since 1988,

Royal College of Pathologists of Australia, since 1989,

Australian Institute of Company Directors, since 2002,

Australian Academy of Technological Science and Engineering, since 2003,

Australian Academy of Science, since 2004

このレポートは、2009 年 11 月 17 日 東京、帝国ホテルにおいて行われた第 28 回本田賞授与式記念講演の要旨をまとめたものです。

This report is the gist of the commemorative lecture at the twenty eighth Honda Prize Awarding Ceremony on the 17th November 2009 Imperial Hotel, Tokyo.

Cancer Prevention through Immunization – Past, Present and Future

Cancer is a challenge for the 21st Century

Ian Hector FRAZER

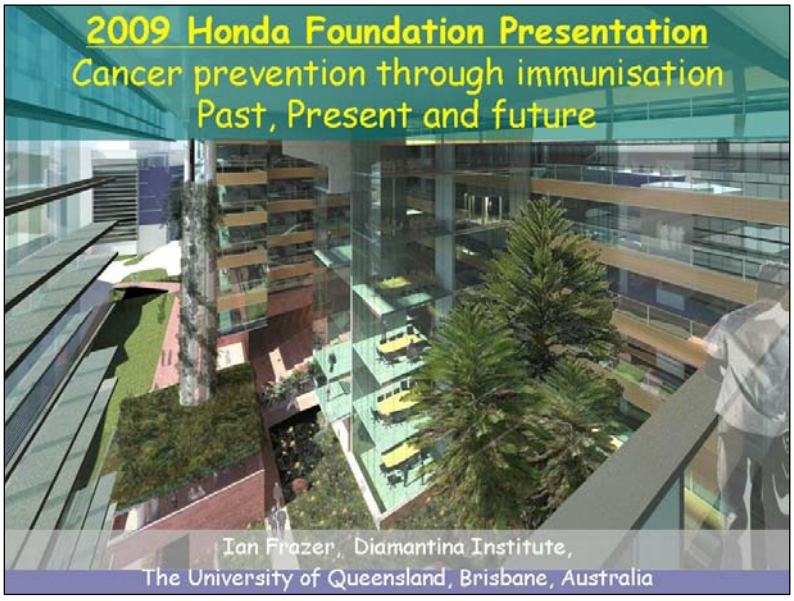

Fig 1

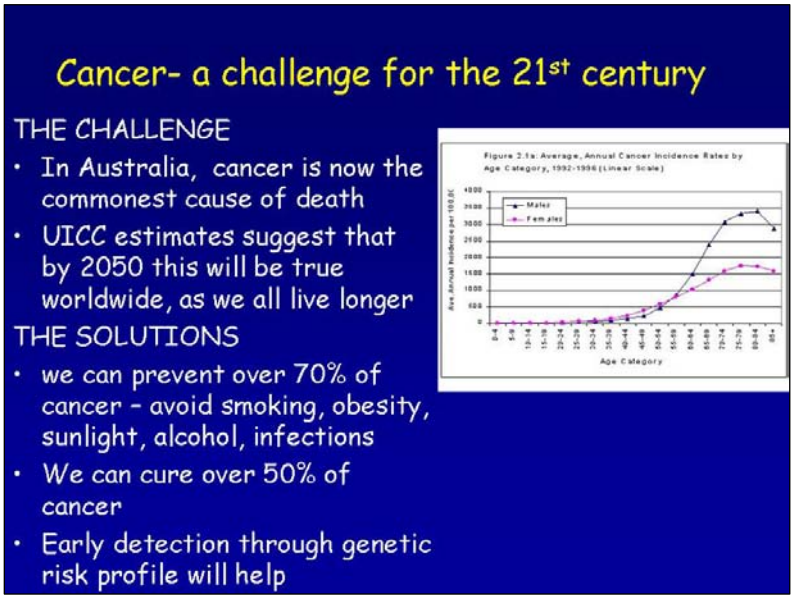

Fig 2

〈Fig 2〉 In Australia, cancer is now the commonest cause of death. The International Cancer Prevention Union suggests that by 2050 cancer will also be the commonest cause of death worldwide, as the common cancers, with the exception of breast and cervical cancer, are

predominantly diseases of over 50 year olds and we are all living longer. The solution to the challenge of cancer in the 21st century must therefore firstly be to ensure we do everything we can to prevent cancer. We have the knowledge already to prevent over 70% of cancer if we avoid smoking, obesity, excessive exposure to sunlight, excess consumption of alcohol and those infections we know cause cancer. We also know that we can cure over 50% of cancer, which is good news, because when I was a medical student it was only 10% of cancer that could be cured. We have the ability, for some cancers, to detect the disease early, and the chances are that in the future we will do better in this area, as risk profiling for people who are at particular risk of specific cancers will help us to work out who we should target for vigilant screening.

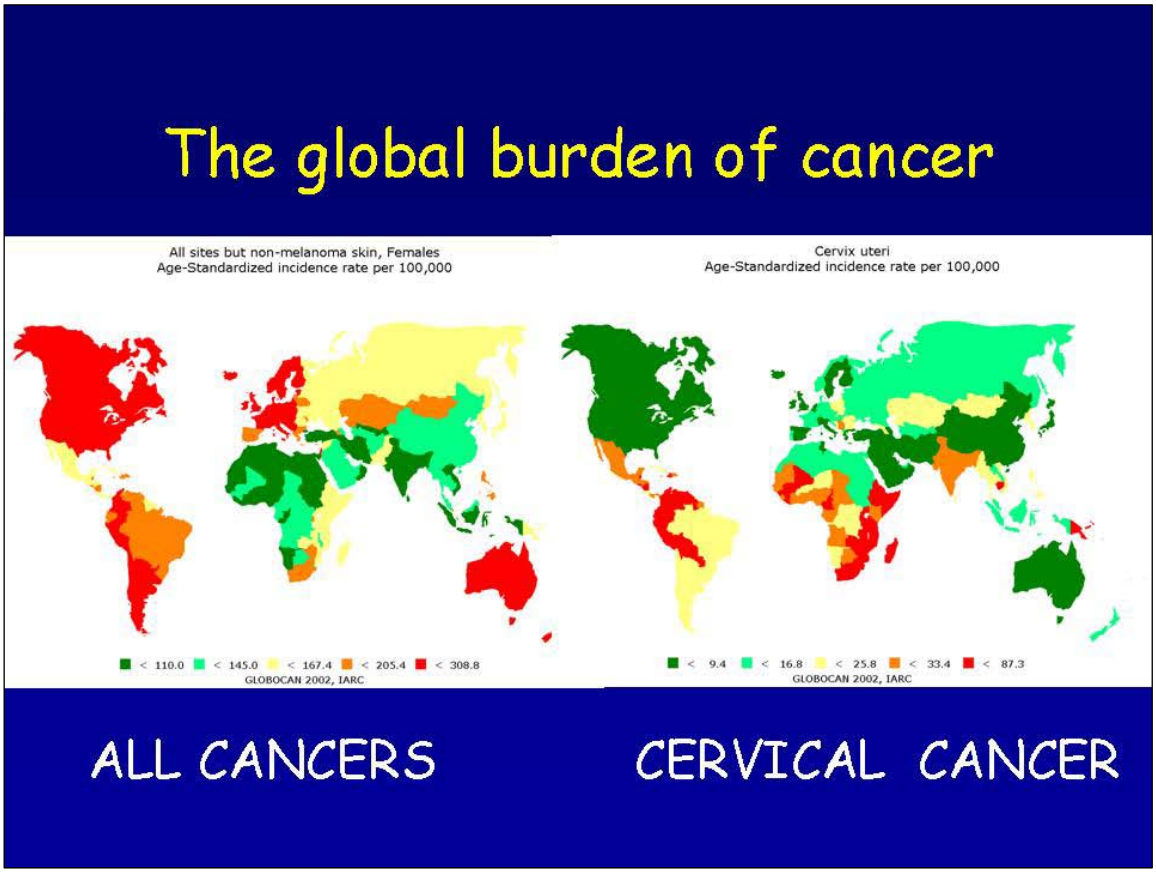

Fig 3

〈Fig 3〉 Globally, the burden of cancer is unevenly distributed with the majority of cancers occurring in the developed world. This is largely because we live longer in the developed world and therefore are more at risk. Cancers like cervical and breast cancer, on the other hand, are commoner in the developing world because these are cancers which occur in people under the age of 50, and the risk factors for cancer there are higher, and the ability to prevent the disease is less.

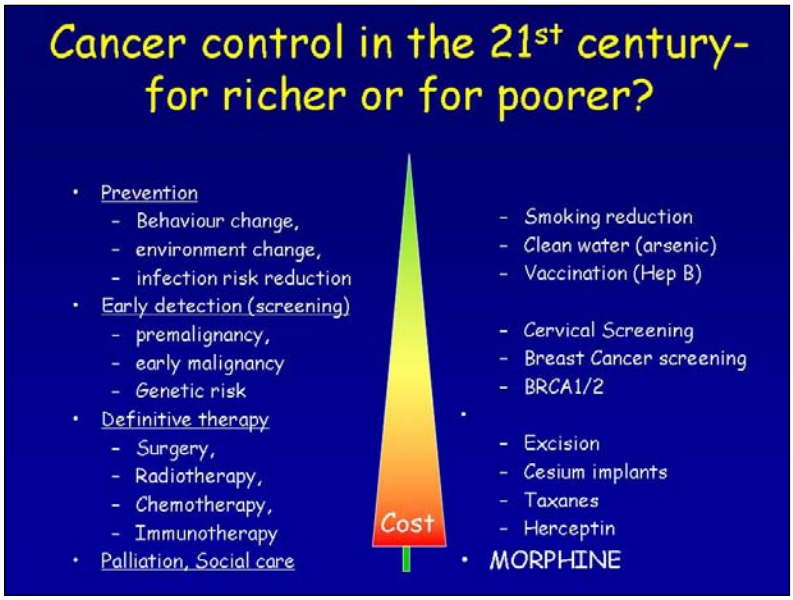

Fig 4

〈Fig 4〉　The critical challenge for the 21st century will be to find methods of preventing the predicted increase in cancer in the developing world, where expensive treatments are unlikely to be available.　Prevention is obviously the best hope.　Through behaviour change such as reduction in smoking, by removing carcinogens from the environment, for example arsenic from drinking water, and by reducing the risk of infection through vaccination we can prevent many cancers relatively cheaply on a global basis.　Early detection through screening is not likely to become available in the developing world in the near future - it will however remain a mainstay of cancer prevention for those cancers for which an effective screen is available in the developed world.　Screening for cervical cancer through PAP smears, screening for early malignancy through breast cancer screening and screening for genetic risk markers such as BRCA-1 and BRCA-2 will be the mainstay of early detection of cancer risk in the developed world.　Definitive treatment for cancer is well known and I will not speak further about that except to point out that as you go down the list from surgery to immunotherapy the cost of these treatments increases substantially and the new immunotherapeutics such as Etanercept and Rituximab will be not only very useful, and therefore very widely used, but also very expensive.　Of course, it is critically important that we also remember about palliation for those with uncurable cancer and one of the major challenges that we face is that in many of the countries in the developing world.　Where cancer is common and very little can be done for treatment, there is no available opiate analgesia for palliation.

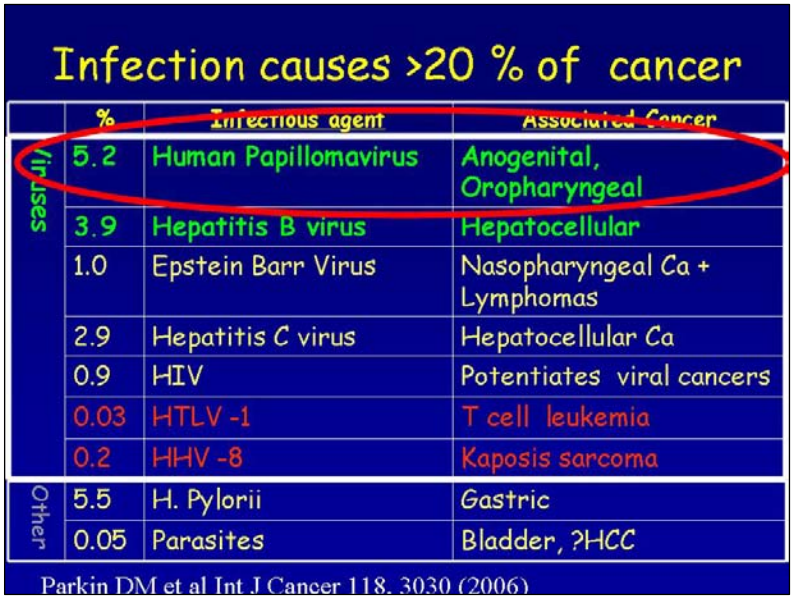

Fig 5

〈Fig 5〉　Today I am going to speak particularly about the prospects for preventing the infections that are responsible for cancer, and how we can use the body's immune system to prevent and control these infections.　Infection causes over 20% of the global cancer burden - viruses contribute the largest part of that - papillomavirus and hepatitis B virus at the top of the list.　Of course, and particularly in Japan, we must not forget about Helicobacter, a bacterium which is responsible for 5% of the global cancer burden, and particularly for gastric cancer.　The pathogens in green on the slide are ones for which we already have vaccines, while the ones in yellow are ones where vaccines are under development, and these are where the major breakthroughs in the 21st century are likely to emerge.　I am going to talk particularly today about human papillomavirus associated cancers, and while most of the talk will be about cervical cancer because this is the cancer most commonly associated with human papillomavirus infection, I would like to remind you that there is also a burden of disease due to papillomavirus at other sites particularly other anagenital cancers and cancers of the head and neck.　These problems are not unique to women - they also occur in men.　As for most of the pathogens on this list, infection with Papillomavirus is common, and as for all of them, cancer is a rare consequence of the common infection.

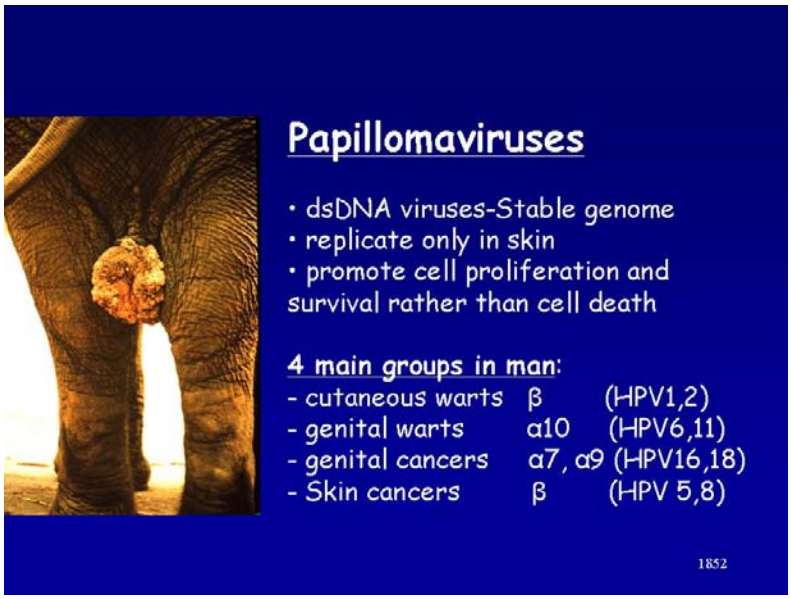

Fig 6

〈Fig 6〉　A little bit about papillomaviruses.　These are very common viruses and there are now recognized to come in over 200 different varieties.　They are double standard DNA viruses, which mean that they are genetically stable and do not change much with time.　They only can replicate in skin.　They are very much species specific and, unusually amongst viruses, they do not kill the cells they infect but rather promote cell growth and proliferation, conveying a risk of cancer development.　There are 4 major groups of these viruses in humans. One major group is responsible for cutaneous warts which all of us get and which do not turn into cancer.　An equally common group produce genital warts: again these do not turn into cancer.　A third group are responsible for genital cancer, termed A7 and A9, of which HPV types 16 and 18 are the commonest.　These viruses produce little visible disease apart from the risk of cancer.　The fourth group is associated with skin cancer, and includes HPV types 5 and 8, also beta viruses.　These viruses are very common, and infection only rarely produces cancer.

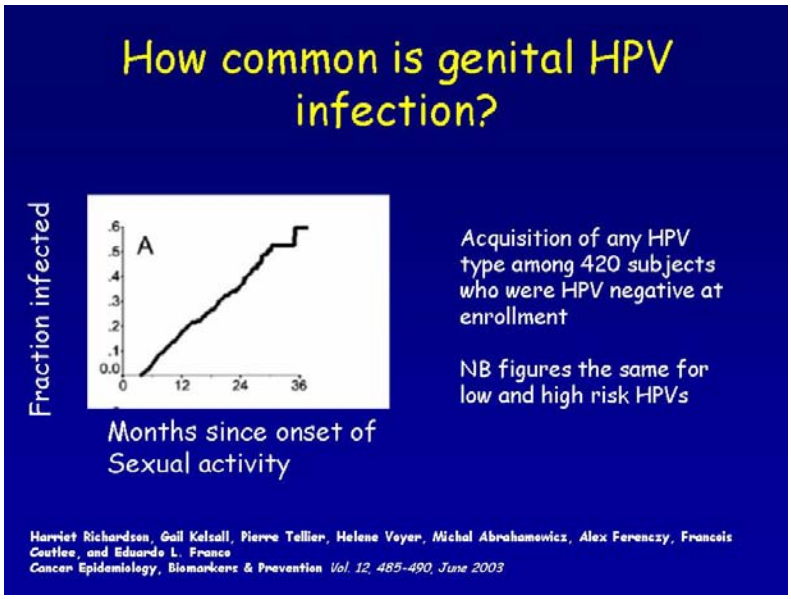

Fig 7

〈Fig 7〉　Infection with all papillomaviruses is extremely common - this graph shows the gradual accumulation of new papillomavirus infection amongst young people after the onset of sexual activity and you can see that over a period of 3 years after the onset of sexual activity more than half of this particular population acquired one or other of the papillomaviruses responsible for cervical cancer risk.

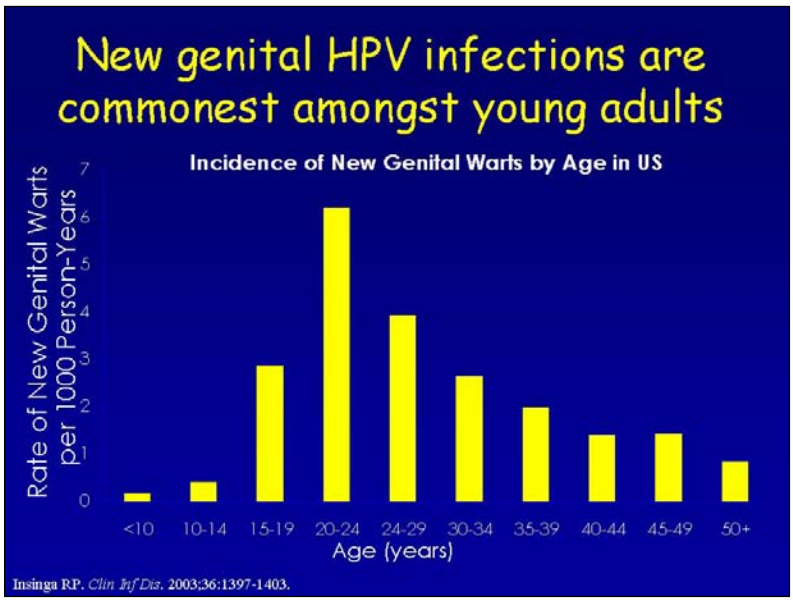

Fig 8

〈Fig 8〉　Unsurprisingly, the greatest instance of new genital papillomavirus infections are in young adults, but it is worth pointing out that this risk of acquiring new genital papillomavirus infections exist throughout life albeit at lower frequency, and there is no time of life when there is no further risk on a community basis.　Men also get human papillomavirus infections and

also therefore human papillomavirus associated cancers.

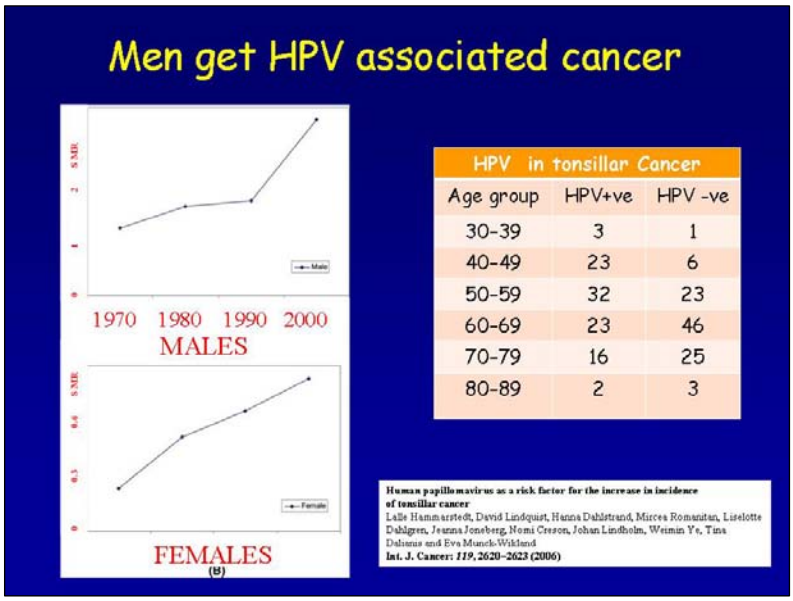

Fig 9

〈Fig 9〉 These are data for tonsillar cancer and you can see that both males and females have a significant risk of tonsillar cancer, and this is increasing. The interesting thing is that the increased risk is due to the increased risk of papillomavirus associated tonsillar cancer. There are two groups of people at risk for tonsillar cancer: elderly males who smoke and drink too much alcohol - these cancers are not increasing in prevalence, and younger men and women who acquire HPV infection and who do not have smoking or alcohol consumption as a risk factor. The papillomavirus associated tonsillar cancers are the ones that are increasing.

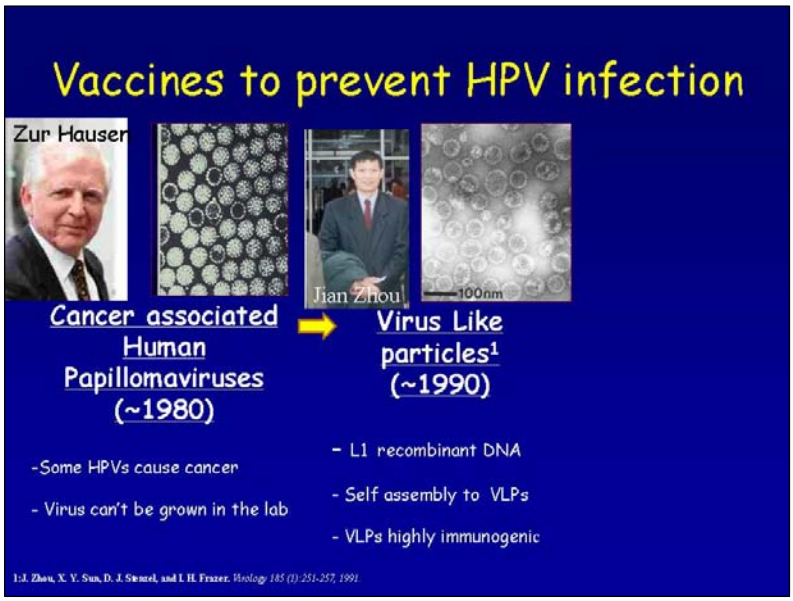

Fig 10

〈Fig 10〉　When it comes to prevention of human papillomavirus infection, Harold zur Hausen led the way by demonstrating in the early 1980's that papillomaviruses were responsible for cervical cancer.　He had the advantage of the new technology of molecular biology which enabled categorization of these viruses and the recognition that there were not just one or two papillomaviruses but over 20, some of which were associated with cervical cancer.　That gave rise to the idea that it was possible to prevent papillomavirus infection and therefore papillomavirus associated cancers.　Unfortunately these viruses could not be grown in the laboratory, precluding the normal approach for development of vaccines.　In 1990, my colleague, the late Dr Jian Zhou, and I came up with the technology for making papillomavirus virus-like particles using recombinant DNA technology.　The L1 protein assembles itself into these particles that you can see in the picture which look just like the virus and consist of 360 copies of the L1 protein.　Fortunately for us the process of the assembly of the L1 proteins into the virus like particles happened automatically and produced highly immunogenic virus like particles.

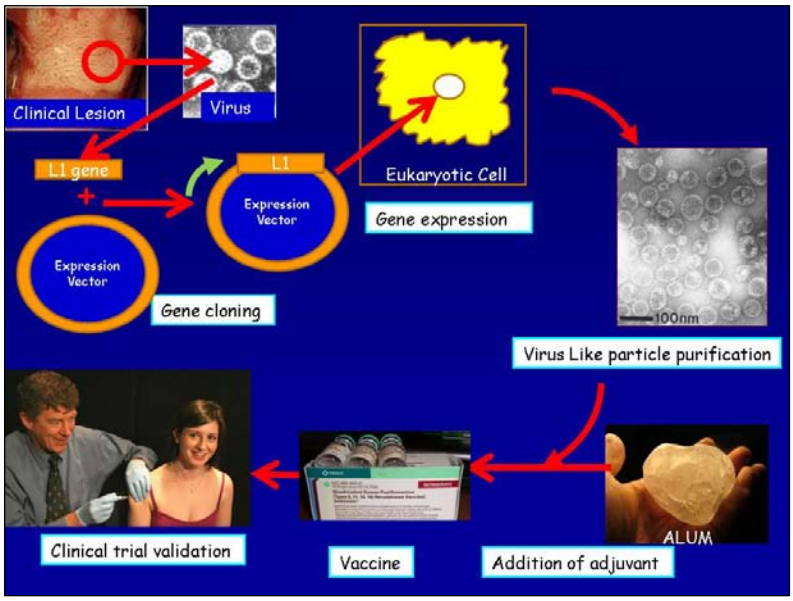

Fig 11

〈Fig 11〉　We achieved this by cloning the genetic information for the virus out of the lesion and demonstrating that we could express that protein in vitro using the recombinant DNA technology so long as this was done in eukaryotic cells, and the gene expression started from the appropriate place in the gene.　The net result was the production of virus like particles. These virus like particles combined with adjuvant became the basis of the vaccines that are now available to help prevent cervical cancer.

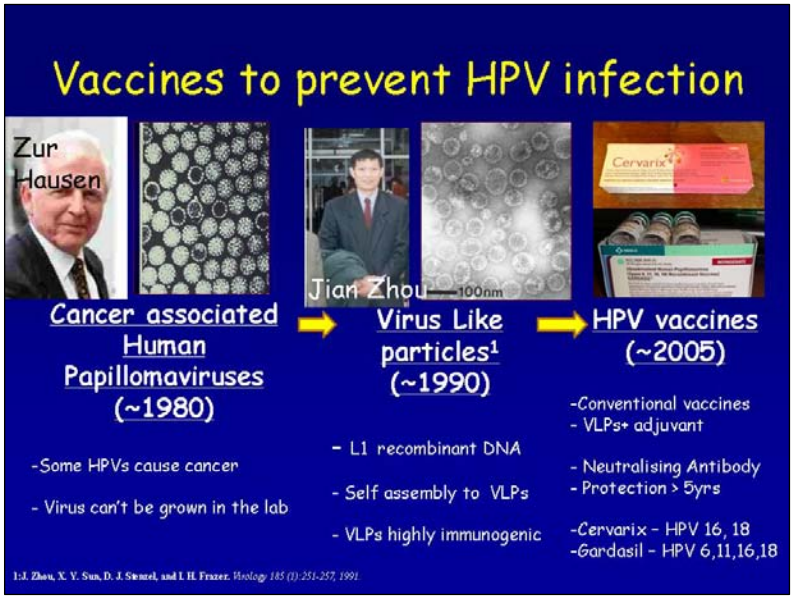

Fig 12

〈Fig 12〉　Of course there was a considerable amount of clinical research work that had to be done between the development of the virus like particle technology in 1990 and the availability of the vaccines in 2005.　That work involved some 2,000 scientists worldwide; 60,000 women taking part in clinical trials and the expenditure of about USD $1.5 billion.　So, clearly most of the work that was done on the development of these vaccines was done by others.　What has emerged are two very conventional vaccines based on virus like particles and alum adjuvant, which produce neutralizing antibody and give long term protection against infection.　The major difference between the two vaccines is that one prevents the two virus infections which are most commonly responsible for cervical cancer and the other additionally prevents 2 HPV infections which are responsible for genital warts.

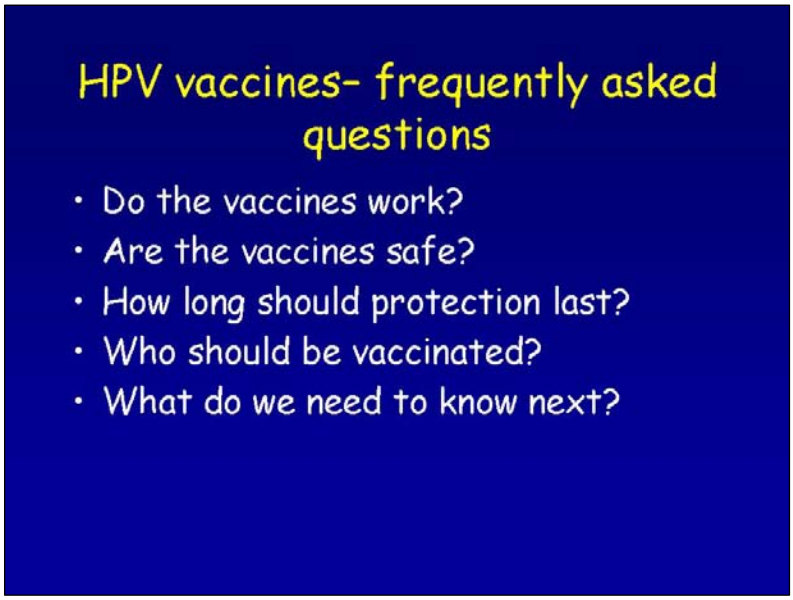

Fig 13

〈Fig 13〉　So, given that these vaccines are now available there are some questions that you should ask yourself including: do these vaccines work, are they safe, how long should protection last, whom should we vaccinate and what do we still need to know?　I will attempt to answer these questions over the remainder of the talk.

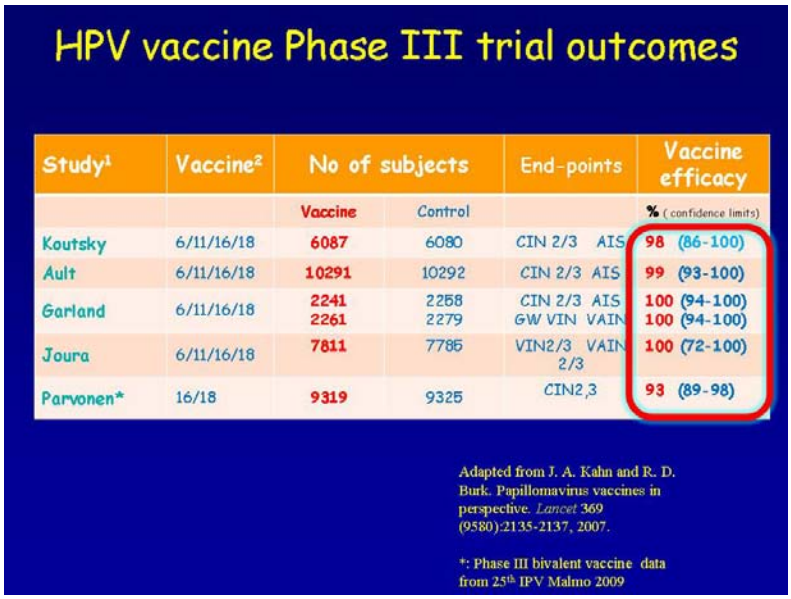

Fig 14

〈Fig 14〉　The first important observation is that, against the right criteria, these vaccines are extremely effective.　These data show the efficacy of the vaccines for preventing disease caused by the virus types in the vaccine in a woman who had not previously been exposed to these virus types so this is if you like an ideal situation and in this ideal situation cervical pre-cancer is prevented with 100% efficacy in the majority of the trials.

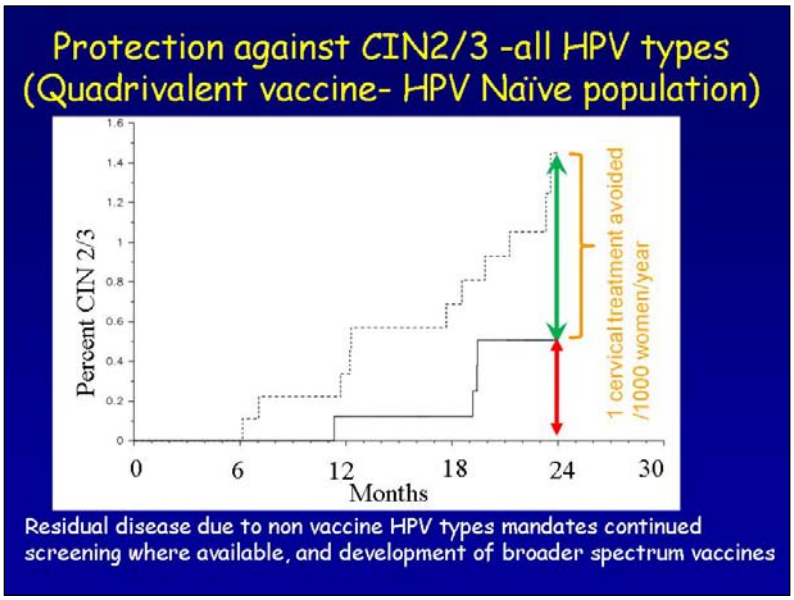

Fig 15

〈Fig 15〉　Of course, in the real world quite a bit of cervical cancer, about a third, is due to virus types that are not in the vaccine.　Therefore in the next slide you can see data showing that there is a steady accumulation of pre cervical cancer in the unvaccinated population and that this occurs with reduced frequency in the vaccinated population, but not with zero frequency.　The green arrow shows the reduction in disease burden due to vaccination.　The red arrow shows residual disease due to papillomavirus infection with virus types that are not in the vaccine.　For this reason vaccines are a part of the process of cervical cancer prevention and will be used along with cervical cancer screening - the PAP smear program, to help ensure that women stay clear of this disease.　Of course, the green arrow represents the major public health benefit that prevents one operation for cervical pre-cancer per 1,000 women per year in Australia, if the vaccines are used universally.

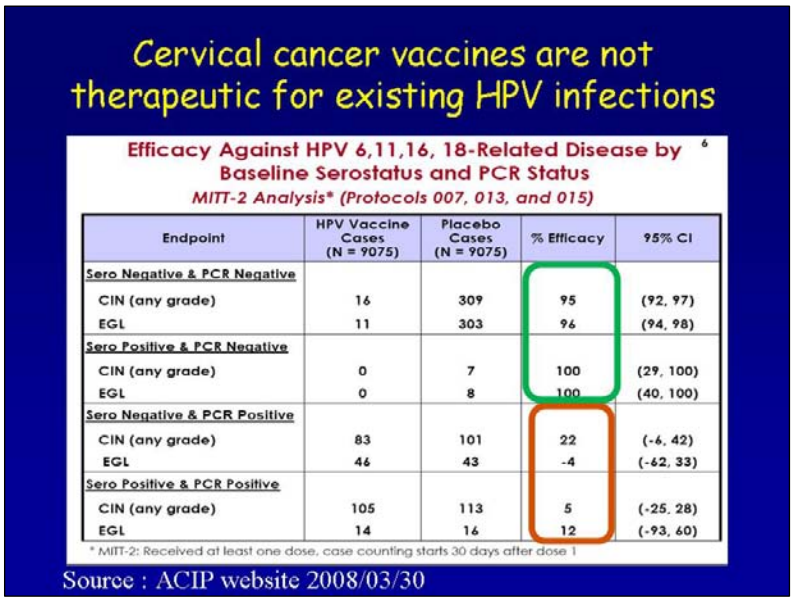

Fig 16

〈Fig 16〉　There is another limitation on the use of the vaccine.　This is a complicated slide but it shows basically in the first data box the efficacy of the vaccine for preventing cervical pre-cancer in women who have never seen the virus before, and as I have shown you previously this efficacy is about 100%.　The red box shows the efficacy of the vaccine in women who have already seen the virus, they have no disease but the virus is already there and as you can see here the vaccine efficacy is essentially zero.　So, the vaccines have to be given to women before they become exposed to the virus because once they already have the virus there is no therapeutic effect from giving vaccination.

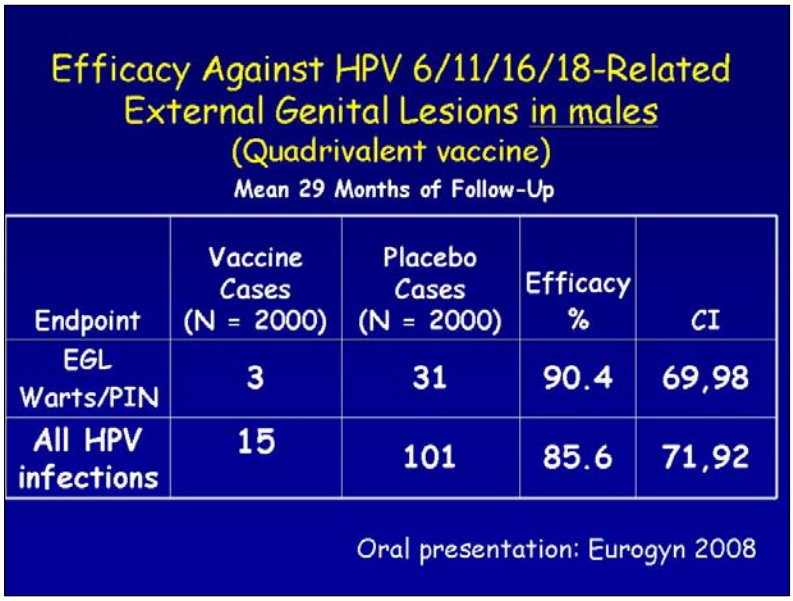

Fig 17

〈Fig 17〉　These vaccines are also effective in men and data shown on this slide here are for the prevention of genital warts in men vaccinated with the quadrivalent vaccine which also prevents genital warts and while the efficacy is a little bit less than for cervical cancer prevention, genital warts are prevented with at least 85% efficacy.

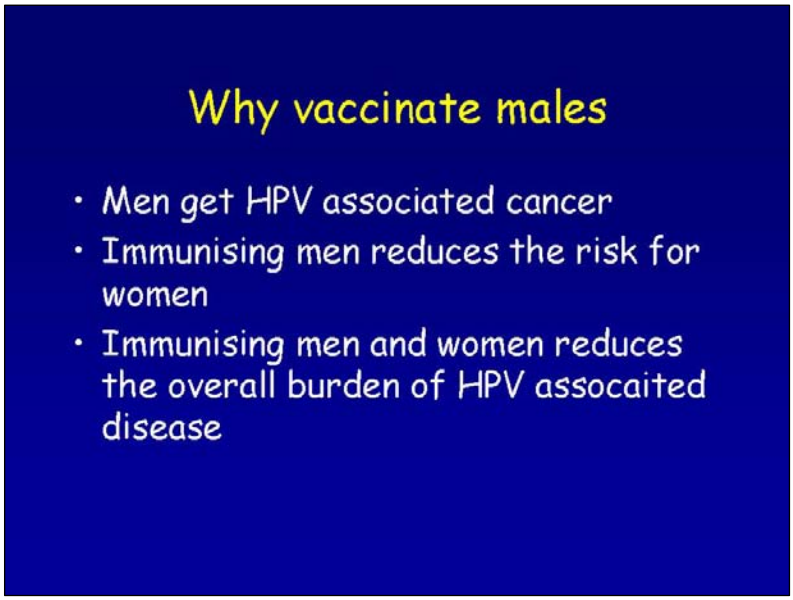

Fig 18

〈Fig 18〉　Why would you bother vaccinating men?　Well, the most obvious reason is because men get HPV associated cancer - about 10% of the global cancer burden caused by papillomaviruses is in men.　The second reason is because immunizing men reduces the risk for their female partners - if they don't have the disease they can't pass it on.　The third reason is because generalized immunization across the whole community will rapidly reduce

the overall burden of papillomaviruses in the community and therefore papillomavirus associated disease.　Of course, the ultimate decision as to whether to vaccinate men is based on cost efficacy and if all women are vaccinated then the added value for vaccinating men is relatively small but if less than 70% of the female population is vaccinated then vaccinating men as well significantly increases the protection for both men and women from papillomavirus associated cancer.

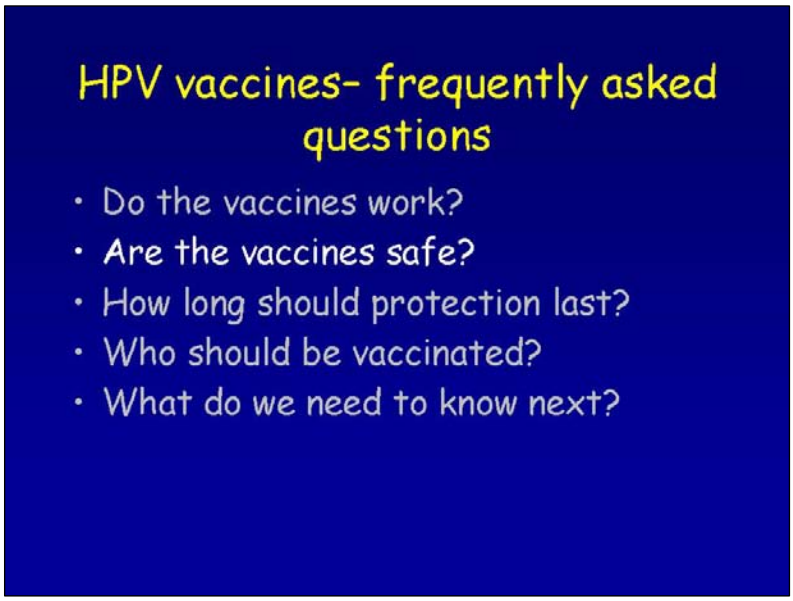

Fig 19

〈Fig 19〉　Are these vaccines safe?

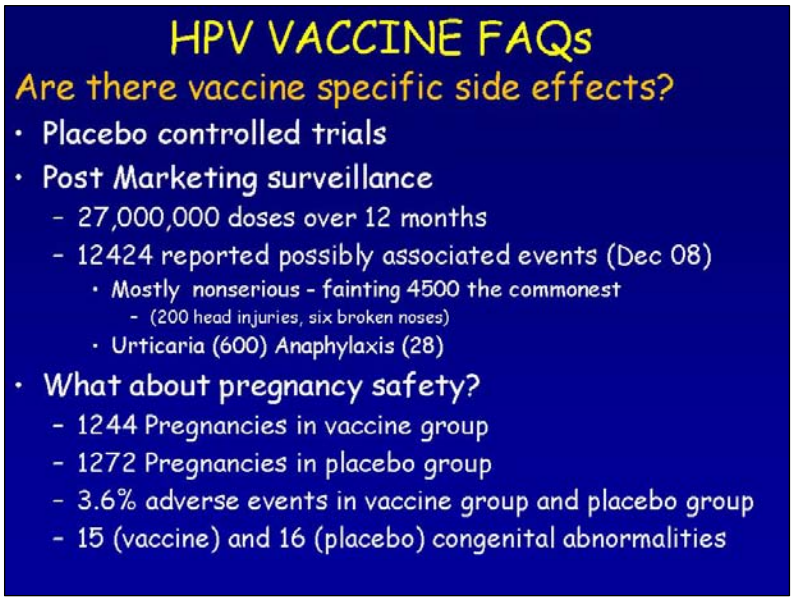

Fig 20

〈Fig 20〉 The extensive phase 3 clinical trials looked at the local side effects from vaccination and as with any vaccine there is a local pain and swelling to be expected at the site of vaccination in at least a small percentage of people vaccinated. This is not due to the papillomavirus - it is due to the adjuvant aluminum that makes the immune system switch on in response to immunization. As you can see, the placebo in the vaccine gives similar side effects whereas a saline placebo without adjuvants is relatively pain free. However, these effects are common and to be expected with all vaccinations. Rarer events are determined in post licencing studies. Over 40 million women worldwide have been immunized now. Amongst 27 million doses delivered over 12 months in the United States there were 12,000 reported adverse events. Most were not related to vaccination - and mostly they were not serious. Fainting was the commonest vaccine associated adverse event and a significant number of head injuries and broken noses resulted from fainting and falling. However, serious vaccine associated adverse events were pretty much limited to anaphylaxis and the frequency with which anaphylaxis occurred about 1 in a million is exactly the same as has been reported for most other vaccines. These vaccines will be given to young women of an age when they might become pregnant so pregnancy safety becomes critically important. Of course, women who take part in clinical trials should not become pregnant and are told to take appropriate contraceptive advice but nevertheless out of 12,000 women who took place in clinical trials, 1,244 became pregnant. There was a rumour indeed going around that these vaccines might be causing pregnancy but fortunately the placebo group did equally well at becoming pregnant showing that it was not the vaccine but just normal behaviour that allowed the pregnancies to occur. These data allow examination of the risk of adverse events due to vaccination and the risk of adverse events in the vaccine and placebo group were identical with about 3.6% of women developing an abnormal outcome from pregnancy and serious congenital abnormalities were equally frequent in the vaccine and placebo recipients.

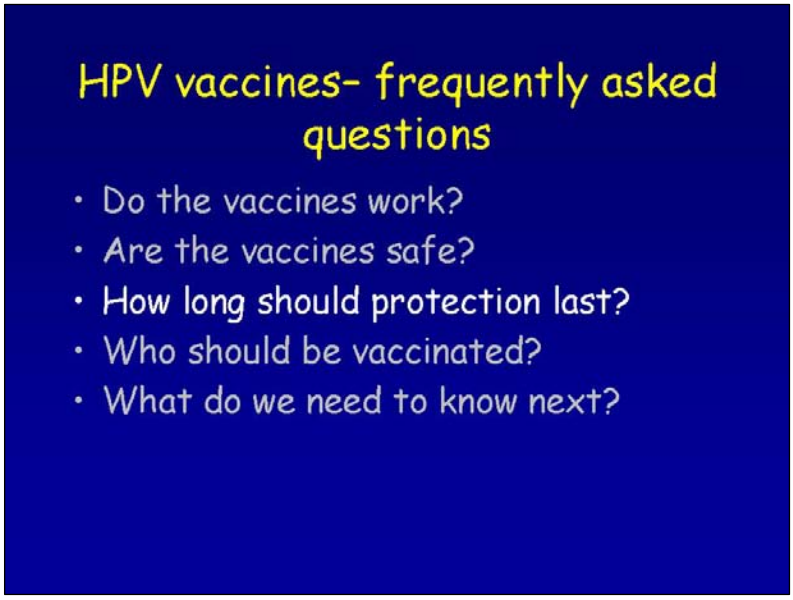

Fig 21

〈Fig 21〉　How long should vaccine protection last?

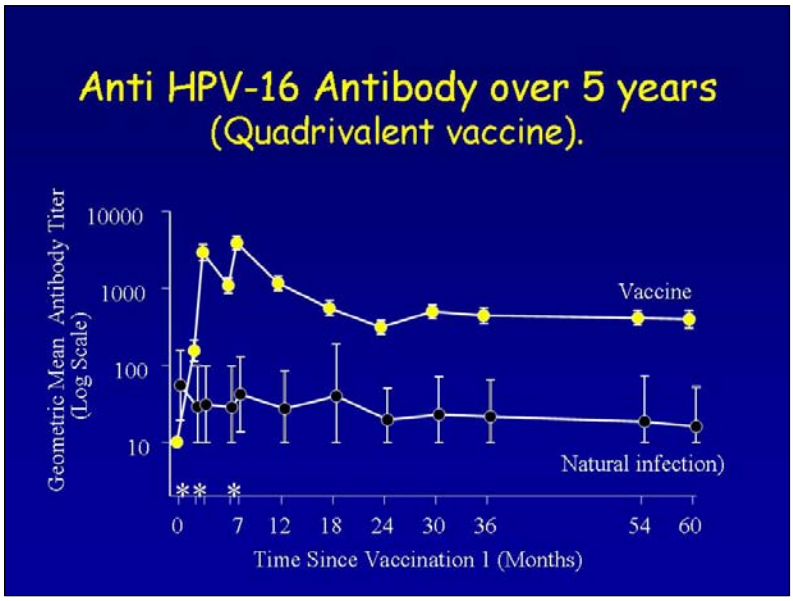

Fig 22

〈Fig 22〉　We don't really know the mechanism for protection against infection although we believe strongly that it is antibody, and therefore if we use antibody as a surrogate measure we can see from the data here that in fact antibody titres induced by vaccination, shown in the yellow circles, are high initially after vaccination and fall quite steeply over the first two years during which there may be a tenfold reduction of antibody levels.　Thereafter the induced antibody levels plateau and there is no evidence of decline.　Exactly why that should happen is uncertain but the bottom line is that the antibody responses are well above the background level that you see in natural infection for at least 5 years after immunization with all the

evidence suggesting that this will carry on for the lifetime for the woman.　So, it is reasonable to expect long term protection although clearly it is important that we continue to survey to ensure that that is achieved.

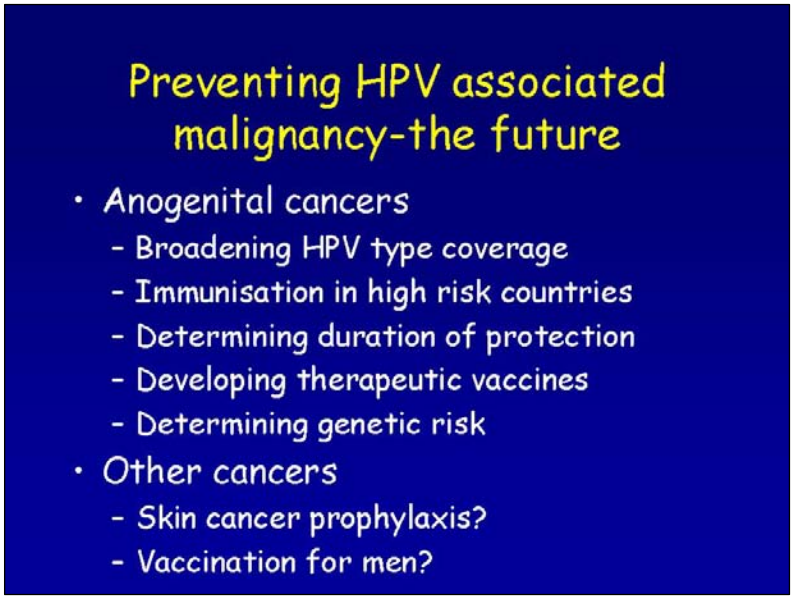

Fig 23

〈Fig 23〉　So, what do we need to know for the future?　Well, there are a number of issues that I could cover including whether we could get broader coverage against different types of HPV infections through increasing the number of HPV types in the vaccine, how we can best deliver these vaccines in the high risk countries where resources are limited, how long protection will last, whether we can develop therapeutic vaccines, whether we can determine who is at particular risk of HPV associated cancer and therefore more effectively target immunotherapy and whether we can develop vaccines for other cancers caused by papillomaviruses including particularly skin cancer.

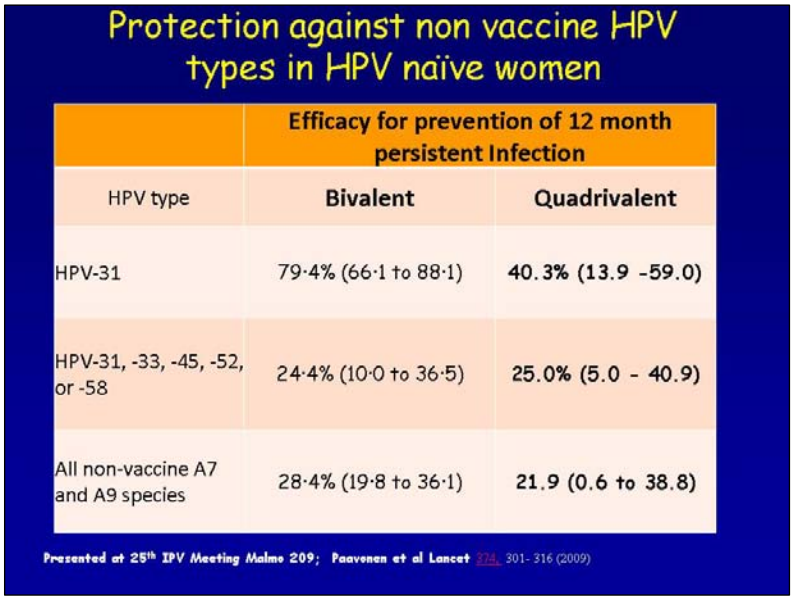

Fig 24

〈Fig 24〉　The data suggests quite strongly that there is some cross protection against HPV types that are not in the vaccines in women who have been vaccinated.　These data show several different HPV types there is some partial protection.　Of course, I have already shown you that the protection is not absolute and this is important because it is the reason that we have to carry on screening.　We can add further HPV types to the vaccine and a 10 valent vaccine is now under early stage clinical trial.

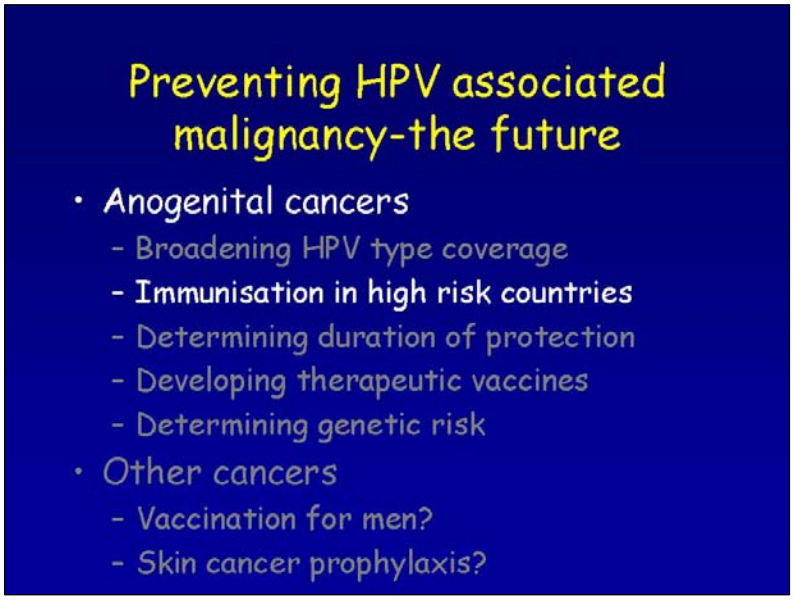

Fig 25

〈Fig 25〉　We are doing active research on immunization in high risk countries because we recognize that one of the critical parts of getting this vaccine where it is needed is to ensure it is made available in countries where there currently aren't the resources to enable purchase and distribution of the vaccine.

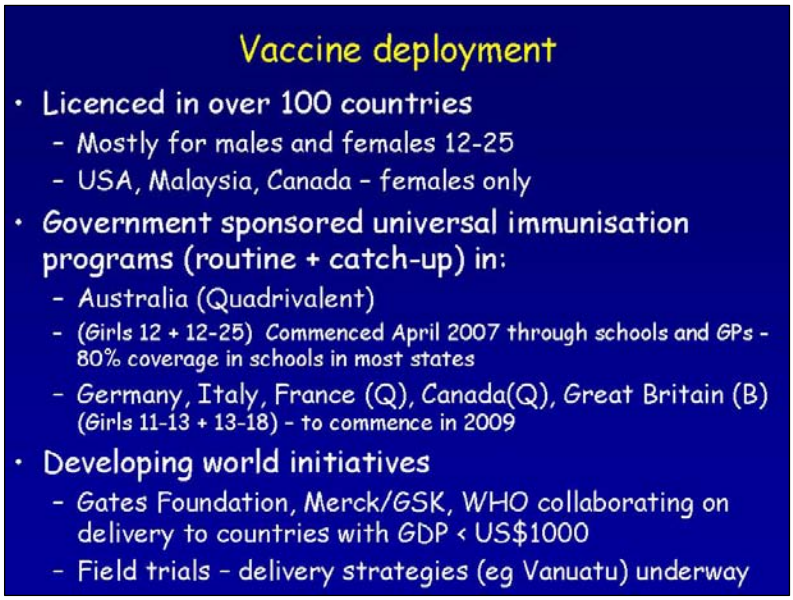

Fig 26

〈Fig 26〉　Worldwide the vaccine is licensed in over 100 countries - mostly for men and women, but in some countries only for women.　The Government sponsored immunization programs however, are limited to a rather smaller number of countries.　Australia was one of the first and has now immunized all girls between the ages of 12 and 25 with better than 80% coverage.　Most of the European countries, Canada and some parts of America currently have programs underway and the real challenge is for the developing world who have their licence but are not being used.　The Companies that make the vaccine are themselves putting considerable effort into ensuring that the vaccines are made available in the developing world free of charge or at much reduced cost and along with the Gates Foundation are planning to deliver vaccine across most of the developing world.　The most critical thing will be to develop programs which can effectively and sustainably deliver vaccines in these countries because the vaccines are designed to be given to 12 year olds shortly before they become sexually active and we have no vaccine programs targeted at this group at present.

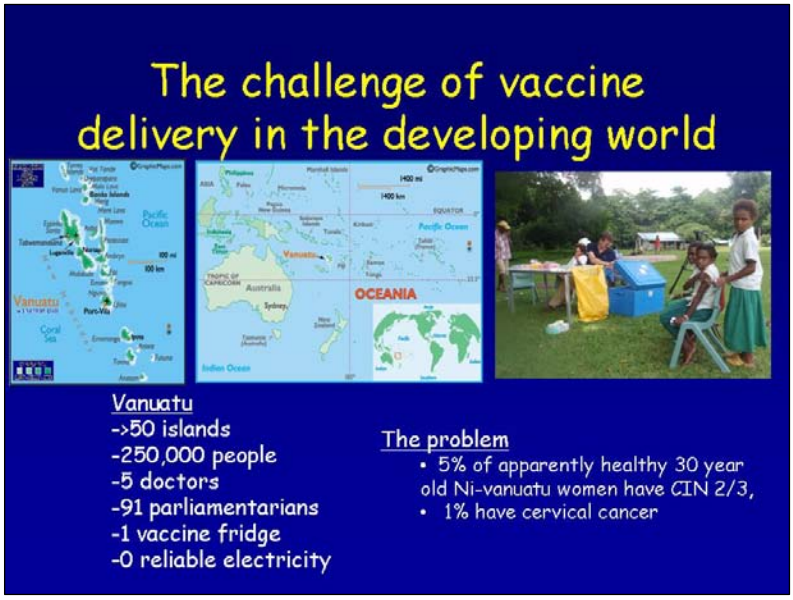

Fig 27

〈Fig 27〉　For that reason we are now doing field studies of vaccine delivery in Vanuatu and in Nepal.　Let me share a little of the data from Vanuatu.　Vanuatu are a group of Islands some 2 hours flying time from Brisbane in Australia.　The 50 Islands have a population of 250,000 and only 5 Doctors although they manage to have 91 Parliamentarians.　There is only one vaccine fridge for the whole islands based in Port Vila and reliable electricity outside of Port Vila does not exist.

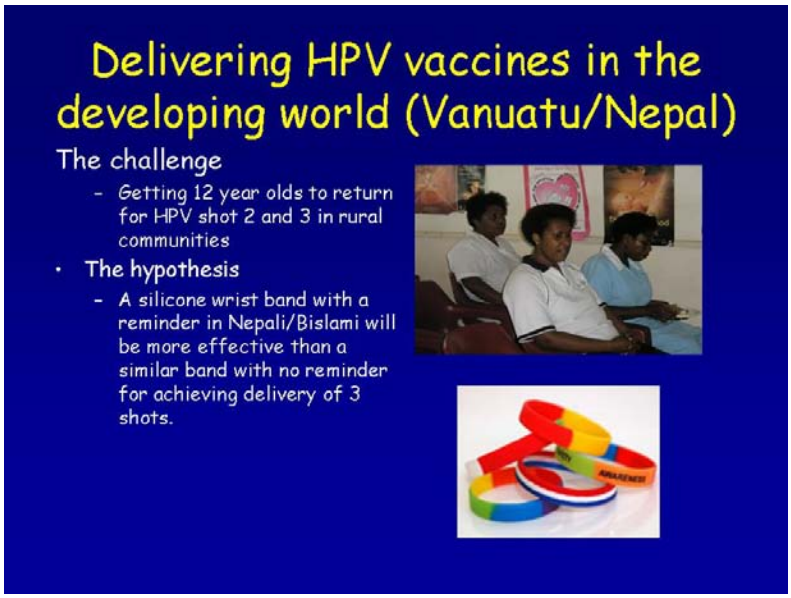

Fig 28

〈Fig 28〉　The problem clinically is that over 5% of apparently healthy 30 year old Vanuatu women have cervical pre-cancer and 1% of them are walking the streets with cervical cancer. So we set up a trial where we decided that we would try to deliver the vaccine to 12 year olds in

this part of the world.　The challenge being is that 12 year olds have generally left school in Vanuatu and we wanted to ensure that we could get them back for the 3 shots that they are required to have for protection.　We tested out the hypotheses that giving a silicone wrist band - one of these coloured bracelets, with a reminder on the band that they should return for their second and third vaccination would improve the chances that they would complete all three vaccine courses.　This trial is currently underway.

Fig 29

〈Fig 29〉　This is us educating the Vanuatu children under a Banyan tree in the north part of Efate Island along with their parents who are seen in the background there.

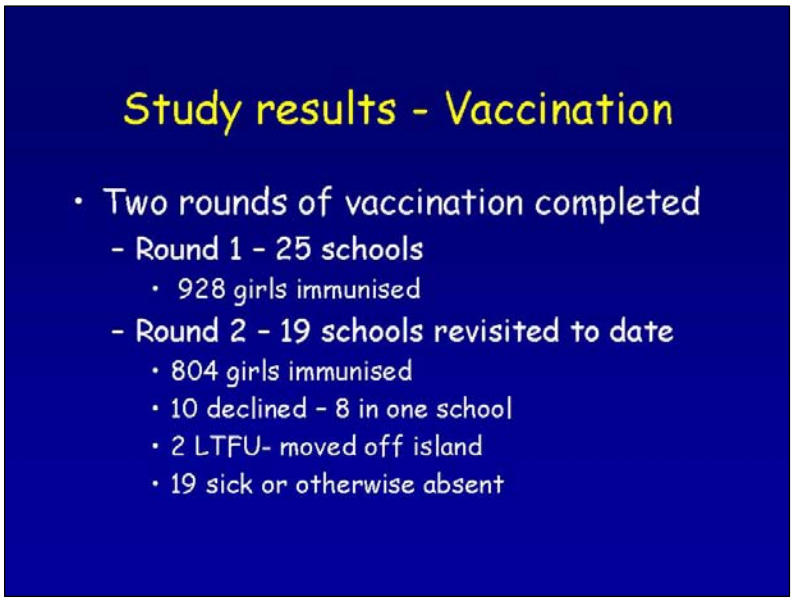

Fig 30

〈Fig 30〉　We have done 2 rounds of vaccination, immunized over 900 school girls in the first round and virtually completed the second round of vaccination.　Fortunately there is little loss to follow up and almost every girl immunized who received the first vaccine, of course the third vaccine which is six months after the first two will be the challenging one and we should be able to report on how that has done at the end of this year.

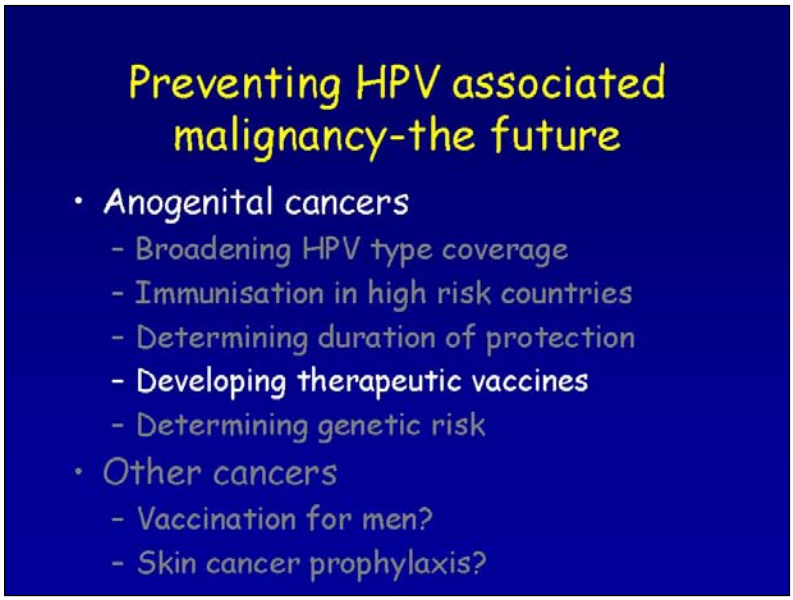

Fig 31

〈Fig 31〉　My major research interest these days is in developing therapeutic vaccines to treat the very many people who are already infected with these viruses who are not likely therefore to benefit from a prophylactic vaccine.

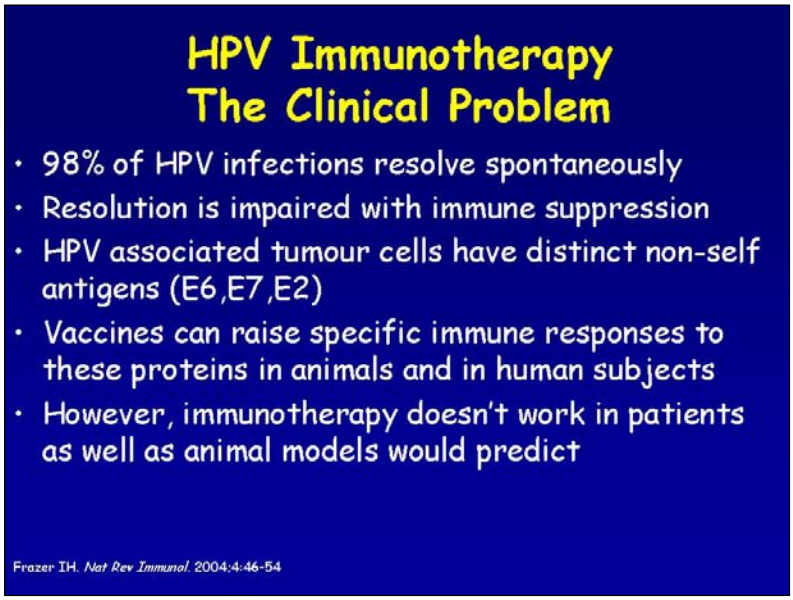

Fig 32

〈Fig 32〉　The challenge with this is that most people who develop these infections resolve the infections spontaneously although we know that a resolution is impaired with immune suppression and the virus induces particular proteins in the cells that it infects and vaccines can raise really good immune responses against these proteins in both animals and human subjects although, unfortunately the immune responses in human have not yet been shown to clear infection even though the animal models seem to suggest that they should.

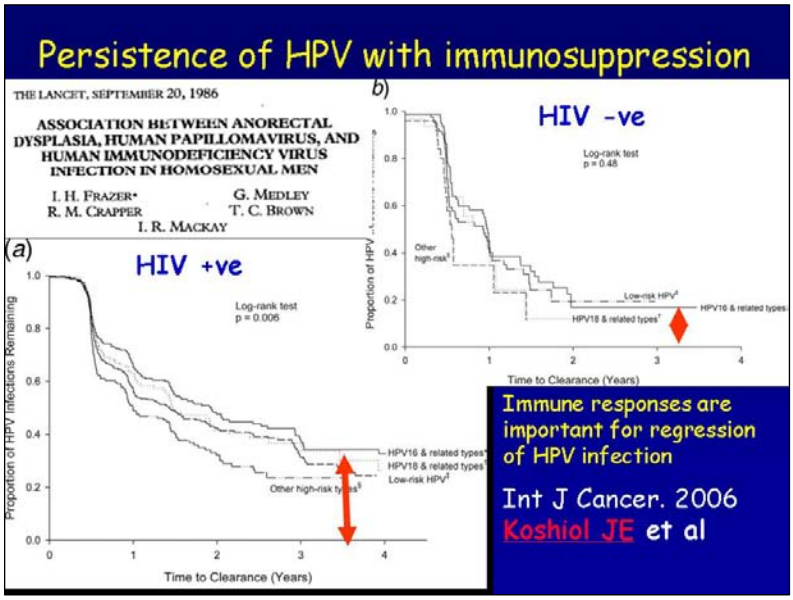

Fig 33

〈Fig 33〉　I got into this area many years ago, indeed the first study that I did looking at the connection between papillomavirus infection and immunosuppresion and what we showed was that immunosupression increased risk of anal pre - cancer amongs HIV and HPV infected males.　These studies have subsequently been confirmed and extended to show that what actually the immunosupression does is prevent clearance of the infection, so that HIV positive individuals take twice as long to clear the infection on average and a third of people who are HIV positive never clear the infection in comparison with HIV negative subjects where most of the infections clear and half of infections clear within a year.　Even if the infection does not clear, the immune system is clearly interested in persisting infection.

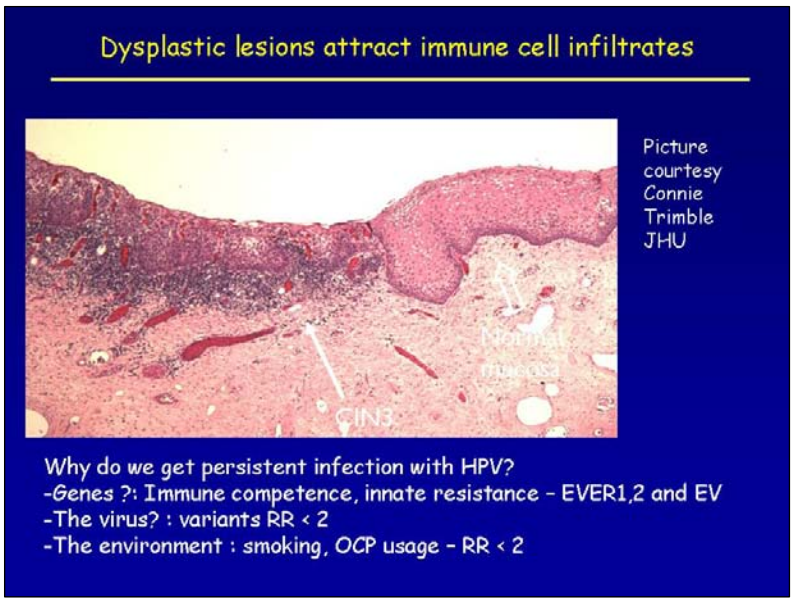

Fig 34

〈Fig 34〉　These pictures from Connie Trimble at John Hopkins University show a cervical pre-cancer lesion and normal epithelium - the normal epithelial is on the right and the cervical pre-cancer lesion is on the left.　What you can see is a significant immune cell infiltrate into the cervical pre-cancer lesion even though this lesion is not cleared.　So, the question really is why do some people get persisting infection with human papillomavirus.　It is not the virus because people have looked at the sequence of the virus and persisting and non persisting lesions and the viruses are the same.　It does not appear to be the environment because no epidemiological study has shown anything which increases your risk of persisting infection by more than double and yet clearly the risk of persisting infection in some individuals is very much higher than in others.　So, it must presumably therefore be genetic and it is likely that genes pre - disposed to the risk of persisting infection.

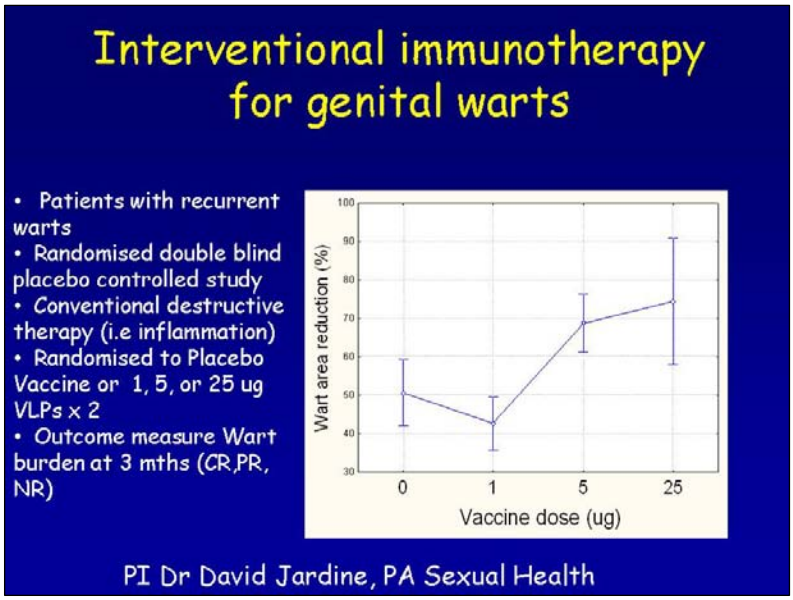

Fig 35

〈Fig 35〉　We undertook a study to see if we could clear people of persisting papillomavirus infection using an immunotherapy for patients with recurrent warts.　In a randomized double blended placebo controlled study we demonstrated that the addition of immunotherapy to conventional destructive therapy for genital warts significantly increased the chances of wart virus clearance over the course of the study so long as one or other of the two larger doses of vaccine were used.　These preliminary findings, not yet published, suggested immunotherapy may have something to offer in the clearance of infection but clearly we are not getting 100% clearance for the data that I showed you here.

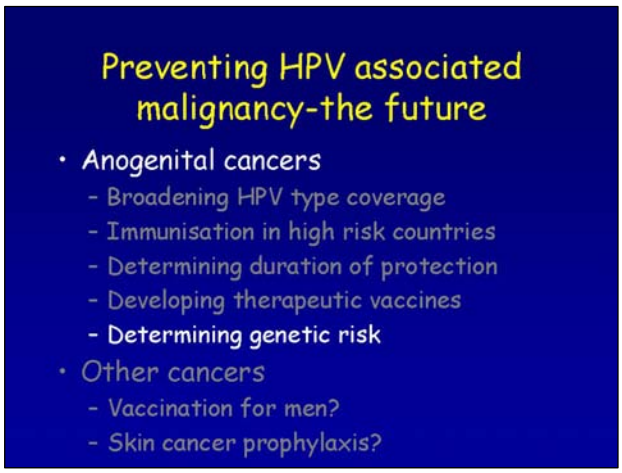

Fig 36

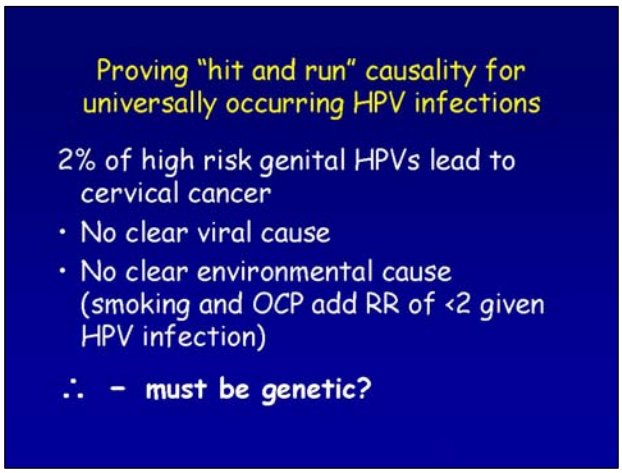

Fig 37

〈Fig 36〉〈Fig 37〉　To understand who is at particular risk of persisting infection and therefore might benefit from immunotherapy we have undertaken a study looking at the genetic pre-disposition in people who have persisting infection.

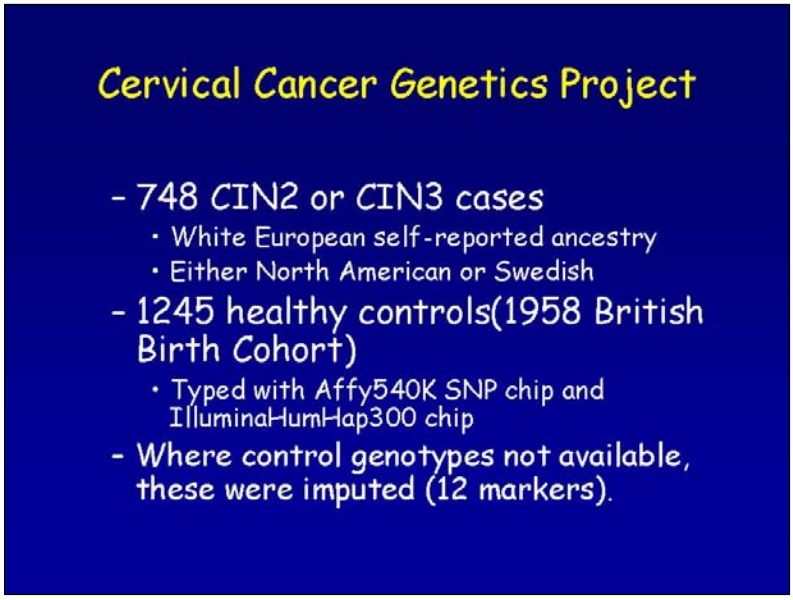

Fig 38

〈Fig 38〉　We selected 750 women with high grade pre-malignant lesions of the cervix and matched them up with control subjects from random population of healthy individuals. Basically both groups were typed for genetic polymorphisms across the genome in a so called genome wide association study.

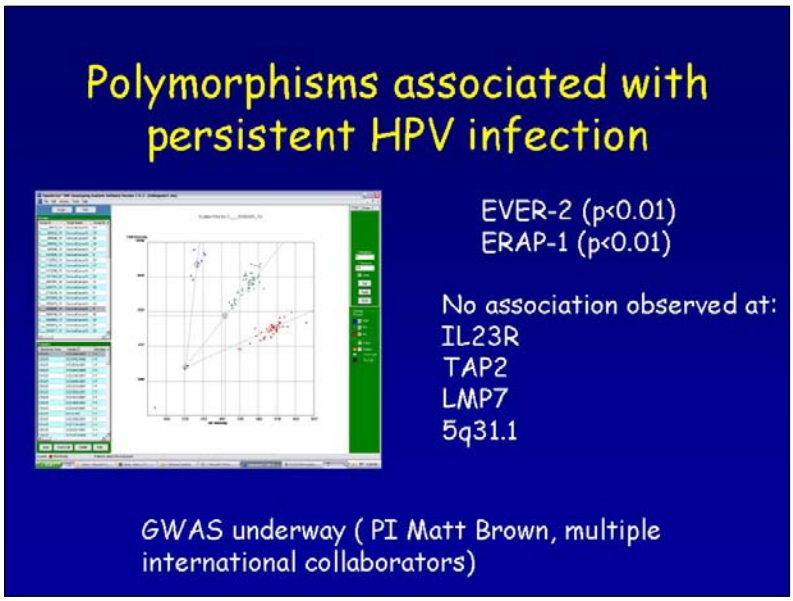

Fig 39

〈Fig 39〉　This study is underway but what I will report here is the findings with a limited number of pilot markers where we used genes where we thought that polymorphisms might be associated with persisting infection.　Of the 12 genes that we trialled in fact 2 came up positive.　One gene of our 2 is a gene which encodes for a protein whose absence is associated with persisting HPV infections as shown by Professor Gerard Orth some years ago.　A variant

in this gene significantly increases the risk of persisting the papillomavirus infection. Similarly another gene ERAP 1 which is associated with peptide processing in the Endoplasmic Reticulum is associated with persisting infection. A full study is underway looking across every gene in the genome and hopefully some results from this will be available next year.

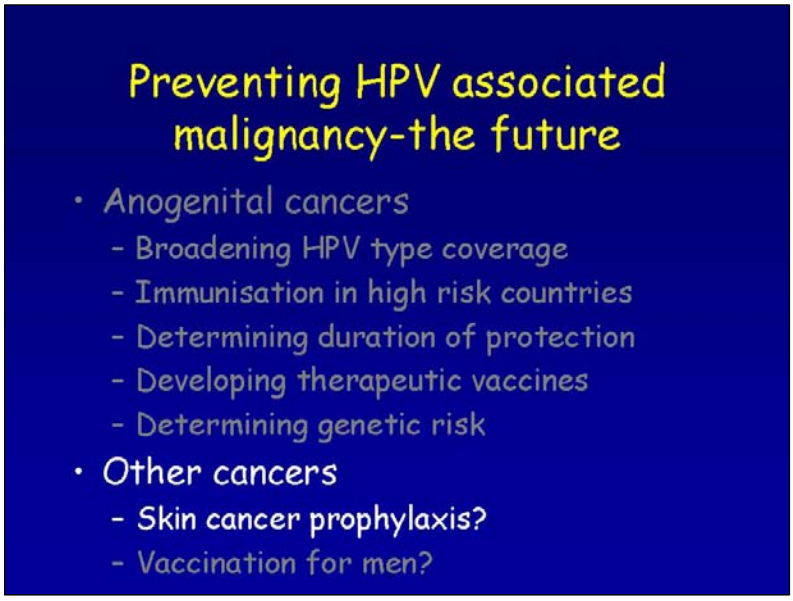

Fig 40

〈Fig 40〉 Finally, I would like to talk about preventing skin cancer through papillomavirus infection. Gerard Orth back in 1980, about the same time as Harald zur Hausen was describing the association between papillomaviruses and cervical cancer, showed that at least some skin cancers were due to papillomaviruses as well.

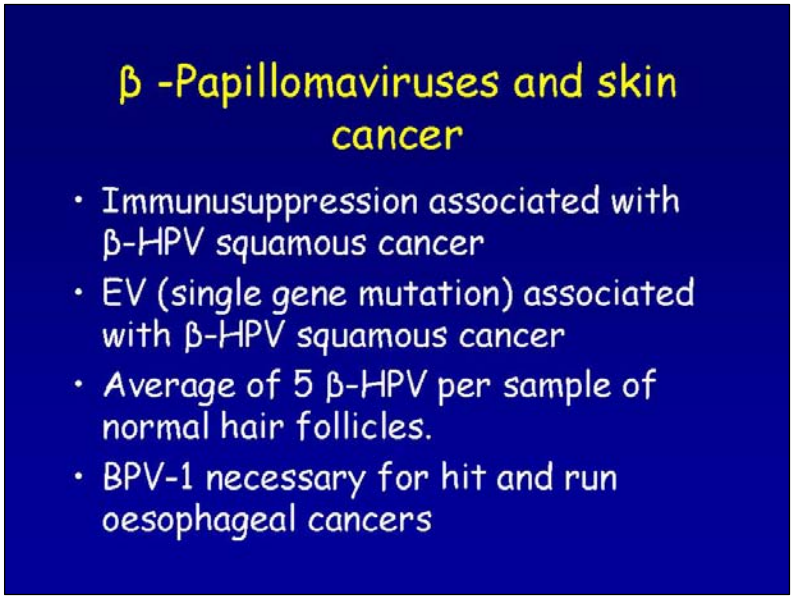

Fig 41

〈Fig 41〉　Immunosuppresion has always been known to increase the risk of squamous cancer of the skin and the genetic variation in the EV gene which I talked about previously increases risk too.　We know that most people carry multiple papillomaviruses of the beta papillomavirus family in their normal hair follicles so everybody is exposed to the virus and we also know that while papillomaviruses are very rarely found in the squamous cancers in the skin it is quite possible for papillomavirus to cause cancer through a hit and run mechanism. In cattle, bovine papillomaviruses are confirmed to give rise to oesophageal cancers in the cattle but while the virus is necessary it is never present in the cancers themselves.

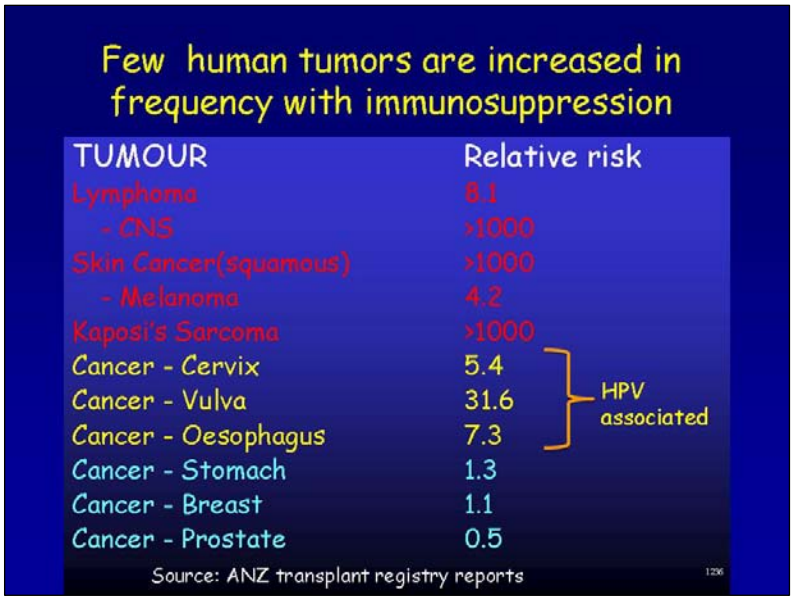

Fig 42

〈Fig 42〉　We also know that immuno suppression in humans is significantly associated with a risk of not only the cancers in the cervix and vulva that we know are papillomavirus associated but also squamous skin cancers with a relative risk of over 1,000.　So there is a smoking gun suggesting that papillomaviruses might be responsible for skin cancer.

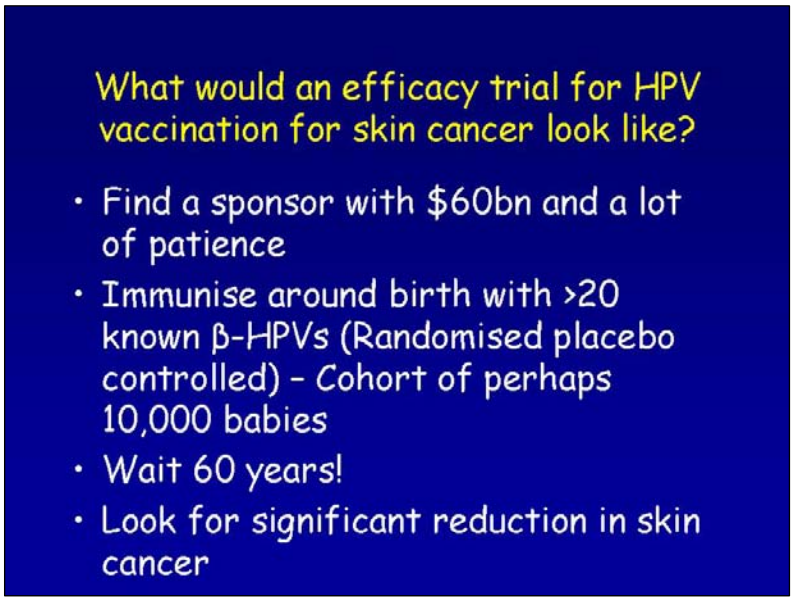

Fig 43

〈Fig 43〉　The problem is, of course, that the papillomaviruses responsible for the skin cancer are not the same types as in the cervical cancer vaccine so a new vaccine will be needed including the beta papillomaviruses.

A trial to prove that such a vaccine might work would be rather difficult however since the virus infections are acquired in early childhood and the cancers don't occur until late adult life and therefore an efficacy trial would last the life time of the individual, would cost a large amount of money and would not be feasible.

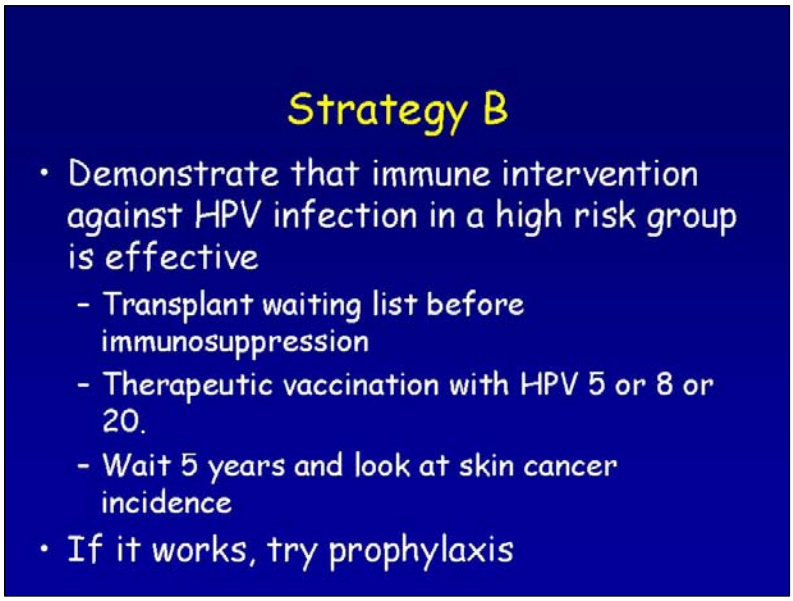

Fig 44

〈Fig 44〉　So, our alternative approach is to demonstrate that immunotherapy against HPV infection is effective at preventing skin cancer in a group of patients who are at high risk. The high risk group that we wish to examine is patients who are about to undergo renal

transplantation because we know that 5% or more of them will develop skin cancer in the first 3 years after they become immunosupressed. Basically, we will immunise them with immunotherapy targeted at HPV5, 8 or 20 and wait to see what happens with the incidence of skin cancer over the following 5 years. If we showed a significant reduction in the skin cancer due to papillomavirus infection this would be sufficient to justify a trial of a prophylactic vaccine.

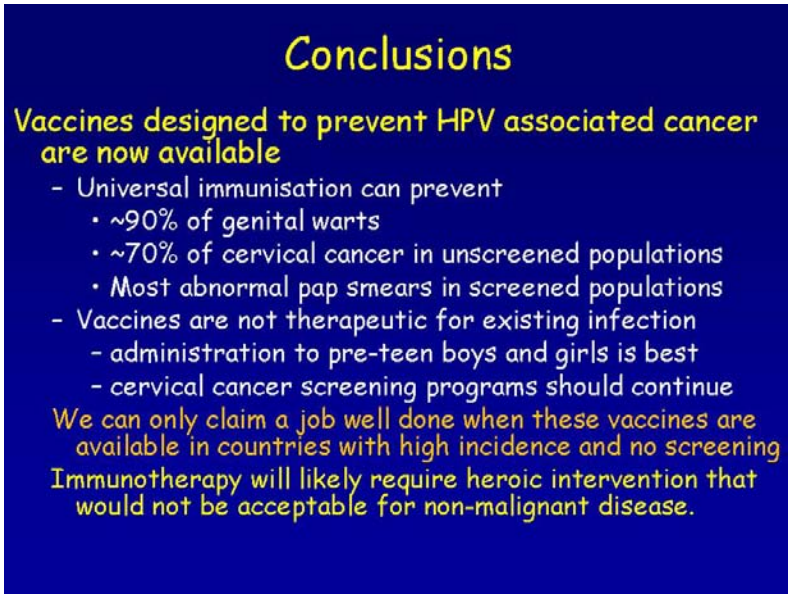

Fig 45

〈Fig 45〉 So, in conclusion I have told you that papillomavirus associated cancer can be prevented through vaccination; that we can prevent cervical cancer at the moment through universal immunization; that vaccines are not therapeutic for existing infection although we are developing these at the moment and therefore administration of these for cervical cancer is best for pre - teen boys and girls and we need to carry on screening but the big challenge is to get these vaccines into the developing world where they are really needed. Immunotherapy routinely for papillomavirus infection we require significant and heroic intervention which would not be acceptable for pre-malignant disease. On the other hand it can be used as a proof of principle to demonstrate that a prophylactic vaccine might be effective against skin cancer.

Similar strategies for the other infections associated with cancer will be necessary to enable effective prevention of the cancers through immunization.

Thank you for your time.

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