10-24-1978

"The Story of Tumor Immunity"

Peter Brian Medawar

Sir Peter Medawar
"The Story of Tumor Immunity"
October 24, 1978
Portland State University

PSU Library Special Collections and University Archives
Oregon Public Speakers Collection
http://archives.pdx.edu/ds/psu/11438
Transcribed by Nia Mayes, March 30, 2021
Audited by Carolee Harrison, September 2021

LEON J. RICHELLE: Ladies and gentlemen, it is indeed a pleasure, to present and introduce to you, Professor Sir Peter Medawar. Yesterday, Sir Peter delivered the first of the 1978 Morden lectures, entitled “Is Human Understanding Finite?” It was a rewarding experience. We learned why elephants cannot get bigger than they are. We also learned that in Sir Peter's opinion, there are limitations to what science can discover. The most interesting part of the evening was when Sir Peter invited members of the audience to join him on the stage, after the conference, to visit with him, ask questions, and say hello. Today again, Sir Peter has asked me to invite members of the audience to join him on the stage after the conference for an informal post-conference seminar.

For those of you who were not here yesterday, let me state briefly that Sir Peter was educated at Oxford. He holds more than a dozen honorary degrees from universities in Europe and the United States. He is currently Professor of Experimental Medicine at England's Royal Institution, and is on the staff of the Clinical Research Center at Northwick Park Hospital in Middlesex. Elected a fellow of the Royal Society at the age of 34, Sir Peter was awarded the Nobel Prize in 1960 for his basic research in acquired immunological tolerance. Sir Peter has written many books, including *The Future of Man*, *The Art of the Soluble*, *The Hope of Progress*, and in 1977, *The Life Sciences*, which he co-authored with his wife, Lady Jean Medawar, who is with us tonight. Today his lecture is entitled “The Story of Tumor Immunity.” Sir Peter Medawar. [applause]

SIR PETER MEDAWAR: Mr. Chairman, Mr. President, Mr. and Mrs. Morden, ladies and gentlemen. I do not plan this to be a conventional scientific discourse, but rather a history and critique of the ideas underlining the modern conception of human immunity, ending, I hope, in the forefront of modern research.

The story of tumor immunity begins with the discovery of the transplantability of tumors, its discovery made by a Danish veterinary pathologist, Carl Oluf Jensen, 'round about the first turn of the century. May I have the first slide please? I have a number of portrait slides prepared for me by the photographic department of the Royal Institution and delivered to me without the indication of who was who, but I'm *almost* 100 percent certain this is Carl Oluf Jensen. [laughter] …Because he is the only member of my gallery who looks like he could be a character from the plays of Ibsen.

Now, what [pronounced "Yensen"] Jensen or [hard "J"] Jensen, as we all call him, discovered was that tumors which arose spontaneously in rats or mice could very oft be transplanted to other rats and to other mice. And so on serially, *ad infinitum,* as it appeared. Jensen himself made an important contribution to this observation that what was being propagated from one mouse to another, or one rat to another, in this process of tumor transplantation, was a living tumor cell and not an infectious agent, as it could so easily have been, and many people hoped at the time it would turn out to be. If cancer was a consequence of infection by an infectious agent then one could do very much more about it than what one is able to do at the moment. This research on the transplantation of tumors was recognized everywhere to be extremely important. It was taken up all over the world. In England, it was taken up by the pioneer scientists of The Cancer Research Fund in London. It was taken up in America by Leo Loeb, and in Germany by Paul Ehrlich.

The general rule was and still is for a transplanted tumor to grow—first to grow and get quite large, perhaps the size of a pea—and then to regress, diminish in size, and dwindle away. It came to be recognized by all people who worked upon the subject of tumor transplantation that a mouse in which a tumor had first grown and then dwindled away was absolutely refractory to the growth of that tumor if it were transplanted on a separate second occasion. This phenomenon, this absolutely refractory state, to a second growth of tumor which had once grown and dwindled away was referred to by an assistant of Ehrlich's, Georg […], as tumor immunity. And this is the subject I'm going to talk about.

It soon came to be recognized, in all the laboratories in which transplantation work was being carried out, that tumor immunity, this refractory state I am talking about, could be aroused not only by the prior transplantation of the tumor, but also by the inoculation into mice of various

normal tissues, including even blood. Prior inoculations of blood could sometimes make mice refractory to the transplantation of tumors.

Research on tumor immunity, therefore, began in a blaze of high hopes and high expectations, because this work seemed to hold within it the promise of prevention, possibly even of the cure, of tumors. Well, this blaze of high hopes very rapidly died down because results of research on tumor transplantation became utterly inconsistent and unreproducible from one time to another in the same laboratory, and from one laboratory to another. Sometimes even transplantation didn't work; sometimes even the transplantation of tumors upon which the whole exercise was founded didn't work. And one of the early research workers of the Cancer Research Fund in London, Wilhelm Kramer, spoke about *seasonal* influences in the transplantation of tumors.

Now there are many experienced scientists in this audience, and they will join me when I say that matters have reached a very low ebb when we have to appeal the seasons to account for variations in our results. You may wonder why, faced with these dilemmas and these utter inconsistencies and un-reproducibility of results—what drives the scientists out of their minds more quickly than anything else—you may wonder why they didn't go mad, but your wonder will be sensibly abated when I tell you one of them did go mad. [laughter] Though, the chivalry that operates among scientists prohibits my telling you what his name was. He had a long and fruitful life writing pretty mad papers. [laughter] And no wonder.

This deplorable state of affairs continued until about 1910, when the world's foremost experimental pathologist, Peyton Rous, working at the Rockefeller Institute, exploded what we can see now in retrospect to have been a bombshell. He asked, in an innocent-sounding kind of way: This tumor immunity that everybody speaks of, is this an immunity directed against the tumor *as* a tumor? Is it really anti-tumor immunity, or is it immunity directed against the tumor as a graft? You see, in all these transplantation experiments, of course, the tumor is being transplanted from one mouse to another. Or one rat to another, as the case might be. We now know that the answer was the latter, namely, this so-called tumor immunity that people were spending several hundreds of thousands of dollars in studying, and several hundreds of thousands of hours, was immunity directed against tumor graft as a graft. The tumor grafts as grafts were rejected much the way that kidney transplants are rejected today, unless one treats the recipient to prevent tumor grafts… kidney grafts being rejected. All of the grafts were simply foreign grafts and were rejected in the way the foreign grafts are rejected.

We can see now why this was so. The early cancer research workers worked upon a bizarre miscellany of mice. They worked upon what they called “the white mouse,” “the black mouse,”

“the gray mouse,” or even “the spotted mouse,” and various products of miscegenation among them all. Sometimes they even spoke about “the Berlin mouse” or “the Tokyo mouse,” which by modern standards is nearly comic, because these mice, though they might resemble each other in color, were madly heterogenous. They were all as different one from another as human beings are different one from another. And therefore, the grafts were being rejected, as Peyton Rous surmised, merely because they were what we now call “allografts,” grafts exchanged between individuals of different genetic makeups.

Matters continued in this state of dignified chaos until it became possible to provide tumor biologists with pure strains of mice, which I’ll explain how they formed in a moment. Up ‘til now, working with “the white mouse,” “the black mouse,” “the gray mouse,” you name it, any old kind of mouse, heterogenous mouse, was analogous to chemists working on the melting point of the “white crystal,” the melting point of the “green chemicals,” and so forth, equally ludicrous.

It came to be seen by a number of distinguished pioneers, notably Dr. Little, the head of the mouse… the laboratory known as the Jackson Memorial Laboratory in Bar Harbor, Maine—well-known as the shrine of mouse genetics—that unless mice could be purified genetically, made genetically uniform and homozygous, it would be useless to continue to try to prosecute research on tumor transplantation. May I have the next slide please? Dr. Little, the head of the Clarence B. Jackson… *Roscoe* B. Jackson Memorial Laboratory. There is no mistaking that fine old Yankee face for a character from Ibsen, is there? That's definitely Little. Little and his colleagues, Snell and Lionel Strong, developed pure strains of mice by inbreeding them for very many generations of brother… repeated brother-to-sister matings or parent-to-offspring matings. This procedure is well-known to make mice genetically uniform, this systematic inbreeding; “uniform and homozygous,” as geneticists say, but don’t give that another thought. Using… and the strains that they developed, Strong and Snell and Little, are still used; two or three hundred generations of strict inbreeding are still used in laboratories, cancer research laboratories, throughout the world today.

Another very important figure of this day was Dr. Peter Gorer. Next slide please? A professor of immunology at Guy’s Hospital Medical School. He's an exceedingly intelligent chap, as you can see. [laughter] What you can’t see was that he was a very fine athlete and he represented England at the foil, at Olympic level. That is totally irrelevant, that’s merely to add local color to my lecture. [laughter] Now, Little and his colleagues and Peter Gorer and his colleagues worked out the genetics of tumor transplantation in mice. They found that in mice, transplantability of tumors was controlled by genes present in a lengthy chromosome segment called the major histocompatibility complex. As, subsequently, it has been discovered that an exact analogous

chromosomal segment in human beings controls the outcome of transplants of hearts and kidneys and other organs that get transplanted. The existence of these different tissue groups you may think of as analogous to blood groups though they are in reality they are quite different and don't overlap.

The existence of these different tissue groups instead is a genetic differentiation among human beings which has made it possible for us now for the first time to work out the genetic basis of susceptibility to such diseases as multiple sclerosis, ankylosing spondylitis, and also juvenile diabetes. Because of our full knowledge of the existence of these different tissue groups, we know the members of these different groups have different susceptibility to MS and to ankylosing spondylitis and to juvenile diabetes. What is profoundly interesting about these subsequent discoveries is they could not have been premeditated by any active mind. They could not have been foreseen, and they could not have been programmed. They could not have formed part of a research project, submitted in the attempt to solicit funds. What advice could one possibly give to a young man who said, “I'm going to work out the genetic basis of differences in susceptibility to multiple sclerosis?” You couldn't very well say, “Well, first spend 4 or 5 fruitless and maddening years studying the transplantability of tumors. And when you are nearly out your mind, make a systematic study of the genetics of transplantation of tumors, and then you will find in mice that there is a genetic differentiation, which, if extended to and applied to human beings, will provide you with the kind of genetic differentiation you need to sort out differences of susceptibility to human disease.”

See, it absolutely doesn't make sense. If anybody had said to Peter Gorer—who worked in my branch of University of London, called University College London—if anybody said to Peter Gorer, “You may think you'll start in the transplantation of tumors; in reality you’re working out the basis, the genetic basis of susceptibility to multiple sclerosis in human beings.” He would have said—I knew him very well, I know exactly what he would have said, I knew him very well—"I'm not a bit surprised.” [laughter] “I know my work is enormously important and bound to bear fruit [laughter] in the future.” Well, you try to tell that to a grant-giving body.

What I am trying to illustrate—this is all in parentheses—is that scientific discovery cannot be premeditated, but that the ordinary processes of scientific discovery, just the way we jog along from day to day, although it's extremely expensive and messy and unpredictable, nevertheless, does produce the goods, obviously variably. I don’t think I'm likely to exceed myself… the time, but I must give you another example of this. Those of you who are in the position of having to solicit grants from time to time may derive some satisfaction from thinking of it. They say that plagiarism is the highest form of flattery, and I want to flatter my friend John McMichael, Professor of Medicine in the post-graduate medical school in London, who has produced an

absolutely marvelous example of the same kind, of the inability to premeditate discovery. He says, "What do you suppose the reaction would be if, 'round about… if the grant-giving system that prevails today, prevailed in 1900?" And some young surgeons, aware of the great limitations upon that craft imposed by the fact they couldn't see into the insides of the body, put in a grant project for making human flesh transparent. You can imagine the slow, gray shaking or wobbling of wise old gray heads from side to side as they pronounce the project utterly ludicrous. And you can imagine what peer reviews would say about such an idea. And in fact, one could not undertake to make such a discovery, yet in the ordinary course of scientific research, this discovery was made. And its medical potentialities were recognized very rapidly by Roentgen, and so x-radiography, which does make human flesh transparent, though not burned, fortunately, came to be accepted in into medical diagnostic practice. Another example of discovery which could not possibly be premeditated.

Well now, this is a long digression, for which I simply have to ask your forgiveness. With the development of inbred strains, it became possible at last to answer Peyton Rous' question in a satisfactory way. Is there an immunity directed against tumors as such, or is it merely directed against tumor grafts as grafts? The answer is, yes. It came to be discovered by Foley in America and Ludwik Grass… or Gross, in America, by Sjögren and Klein in Sweden, and Habel, that there is indeed such a thing as an anti-tumor immunity. Because if tumors arise spontaneously in one member of an inbred, a pure strain of mice, and this tumor is transplanted to another member of that same strain, and if it then arouses immunity, this cannot be an ordinary anti-graft immunity, the kind of immunity directed against a graft which is genetically foreign. Because these mice are, as near as they can be made, genetically identical. And so it is indeed the case autochthonous tumors—autochthonous, I'm sorry about that—A-U-T-O-C-H-T-H-O-N-O-U-S, get it?

Autochthonous, a tumor living in the soil in which it arose. Autochthonous tumors do arouse an immunity reaction. Which is not, as I say, I do emphasize this, an immunity directed against the graft as a graft, against tumor grafts, or tumor as a tumor. Now this kind of immunity, you must know, is called cell-mediated immunity; it is an immunity very similar to that, ironically enough, which does cause the rejection of grafts. It is worked by a cell called the lymphocyte; cells called lymphocytes. Very like… Tumor grafts are destroyed by mechanisms very similar to the way in which kidney grafts are destroyed. This close similarity led a number of people, notably the very ingenious Dr. Lewis Thomas and my friend Macfarlane Burnet, to propose a theory of why graft rejection reactions occur. Why, when kidneys are transplanted from one human being to another, does it come about that these kidneys are rejected? He says the graft rejection reactions are a by-product, merely a by-product—and indeed a very tiresome by-product—of the existence in the body of a body-wide monitoring or surveillance system of which the basic

purpose is to identify aberrant, miscreant cells, tumor cells. Spy them out and irradicate them before they can gain a foothold and do harm.

This is the famous theory, first thought of by Lewis Thomas and popularized since by Macfarlane Burnet, of immunological surveillance. It is an extremely attractive theory and I believe it to be essentially right. There are unfortunately some grave snags in it, one or two of which I should just very briefly mention to you. Mice which have been deprived of the power to mount cell-mediated immunity reactions are yet very resistant… are still very resistant to the development of tumors as a result of the injection of cancer-producing chemicals such as methylcholanthrene, which I shall tell you about later. They ought to be very susceptible, of course, they should be deprived of a surveillance mechanism, but they haven't been; they're still pretty resistant. As against that, mice in which cell-mediated immunity has been deliberately boosted, which can be done in a whole variety of ways, do have a heightened resistance to tumors, and this is the basis of some forms of tumor therapy today in which attempts are made by inoculation, such as BCG, for example. To stimulate, potentiate the patient's immunological responses in the in the hope of increasing its ability to reject tumors.

However, the dots raised by the nude, or as you folks say, "the nude mouse" and other difficulties are grave enough to have made people question whether there's any natural defense against cancer. There is however, epidemiological evidence, which I think many of you may not know about, epidemiological evidence of variations in susceptibility to cancer, which make it, to my mind, pretty clear that there is a natural defense against tumors. I'm thinking of breast tumors in human beings and the magnificent work of the Harvard School of Public Health under the chairmanship of Dr. Brian MacMahon, who has collated the results of a worldwide survey of the susceptibility of women to breast tumors considered as a function of their reproductive history.

Let me show you a slide of his own, epitomizing his results… the next slide please? This slide, which—I'll show it to you again, so don't try to comprehend all it says straight away—illustrates a woman's risk of contracting breast cancer as a function of the age at which… the age at birth of her first child. When I say the age at birth of her first child I mean, of course, the mother's age at birth, not the child's age at birth. [laughter] It was at first thought that women who had vast numbers of children, as is common in some religious sects—and among, for example, Canadian Roman Catholic farming families who have 12 or more children, just as a matter of course—it was thought that women had very large numbers of children were especially resistant to breast cancer. But further analysis showed that the number of children born is not the important parameter—as people say when they don't know what the word parameter means—it is not the important independent variable, let me say. What is important is the age

at birth of first child, and of course if women are going to have 12 or 14 children in their lives, they pretty well have to start rather young in life. And this is the important independent variable, the age at birth of the first child.

In this graph here, MacMahon's graph here, the baseline is taken to be the risk of contracting breast cancer of childless women. Or, for example—and this is where it all started—or, for example, women who take holy vows and are therefore precluded from reproduction on religious grounds. Taking that as the baseline, you can see, although it has implications bordering on impropriety, that if women… [laughter] …that if women have their first children as teenagers, their risk of contracting breast cancer is very much less than those of childless women, and enormously less than women who have the first children at the age of 30 or over. I will try to… these results are explicable, as I shall try to explain. These results are generally accepted, and the world's leading cancer epidemiologist, Richard Doll—the man mainly responsible for establishing the connection between smoking and lung cancer—says of these results, "These results are clear and convincing." And he's not a man given to squandering praise unless there is a good reason for it. And the question is, how are they to be interpreted?

I think what will be the main take-home from this lecture is what I believe to be the correct interpretation of these results. Now, some people look naturally to an endocrinological interpretation, others to an immunological interpretation. Endocrinologists tend to think in terms of endocrinological explanations; immunologists in terms of immunological explanations; now, this makes people young enough to be still cynical, it makes them laugh. They think it just goes to show. It doesn't go to show anything except that scientists would be *mad* not to look, not to seek first to where the light is before they stumble around in the dark. Immunology and endocrinology are both brightly-lit domains of medical science and of course we look first where the light is before we grope around it in explanations which we don't, perhaps, fully understand. It could indeed be either, immunological, endocrinological; that is an admission on my part of what I regard as evidence of singular greatness of mind, because I shall wish to convince you the explanation is in reality immunological, not endocrinological.

The main burden of this lecture is to try to explain *why* these findings are immunological in origin and why they do offer some hope, even if it is a most remote and very distant hope, that one day it will be possible to divise anaphylactic methods effective against tumors. The modern story of tumor immunity in these later developments turns upon the phenomenon of anaplasia. May I have the next slide please? Anaplasia is no longer a very familiar word in medical scientific circles; when you start talking about it, people think, as you may be thinking, that I'm talking about a bogus claim on the imperial throne of Russia. [laughter] Now, anaplasia is the name given to a tendency of tumors to revert, in some respects, towards an embryonic

type. I've collated a number of examples of the reappearance in tumors of substances normally formed in embryonic life, and of which the formation is normally turned off before the adult stage is reached.

The most famous of these substances is carcinoembryonic antigen; speaking in acronyms, C.E.A., which is a glycolprotein which appears in fetal… in some fetal tissues, notably fetal gut, and which is formed anew tumors of the colon and intestinal tract, generally, and are tumors of what we call… of what embryologists call endodermal tissues. Another such substance is alpha-fetoprotein, which is an albumen-like, functionally an albumen-like compound which appears in the body fluids of all amniote embryos of which it's being sought. And which also appears, as a number of Russian scientists have shown, in tumors of livers of mice, and liver tumors of human beings also. One of the most characteristic features of liver tumors is the production of alpha-fetoprotein. Then there are other by-chemical similarities that have been reported between tumor tissue and embryo tissue.

… are made to … with… in studies of RNA has shown that there is a similarity between the transfer RNAs of some tumor tissues in human beings and some fetal tissues. Dr. Leese and his colleagues working at the Chester Beatty Research Institute in London have demonstrated close similarities between the isoenzymic profiles of lactic dehydrogenases in tumor tissues and embryo tissues. I'm going to say that again, so you fully realize what a very high-grade lecture you are listening to. [laughter] My thoughts had turned towards the isoenzymic profiles and lactic dehydrogenases. I was saying that Leese and his friends had shown that there was a similarity between embryonic and tumor tissues in respect to what I said. So, there is plenty of evidence of embryo-like characteristics in tumors, which extend, incidentally, as I shall now explain, to embryonic antigens.

It is the most interesting and totally… and was a totally unexpected fact, well-attested by a great variety of research workers, that embryos are sufficiently unlike the animals which they grow up into to be able to arouse an immunity reaction in them. That's if adult animals are inoculated with embryonic cells of the same genetic composition, so when it's the same genetic composition, an anti-embryo immunity will be aroused. An anti-embryo cell-mediated immunity very similar to that which occurs in graft rejection reactions. In the sense that if you inoculate into adult mice cells taken from a 9- to 11-day-old mouse embryo, the mouse will be immunized against these embryonic cells, and lymphocytes will form in it which are capable of attacking those embryonic cells in tissue culture, just as if the embryonic cells were foreign grafts. The experiments I'm talking about, these and all the others I shall mention, are done within an inbred strain. And we are not dealing with genetic differences at all, except in the very restricted sense in which embryos are genetically different from the animals they grow up

into. Of course, a different constellation of genes is activated in the embryo from those that are activated in the adult. There is a rather special sense in which you could say that embryos are genetically different from adults. They are, anyhow, to antigenic adults, this is the crucial part.

Now, the crucial step, the *experimentum crucis* as they used to say in ancient Rome, is this: the scientific reasoning is if anaplasia occurs, if, that's to say, embryonic substances reappear in tumors, and if these embryonic substances include embryonic antigens of the kind that can arouse immunity from adults, then the inoculation into mice or other animals of embryonic tissues should protect mice against tumors. This is to say that there's a long roll of honor of people who that have demonstrated that this is the case. I put first, in my own personal roll of honor, knowing the industry from the inside, Joe Cogan and Norman Anderson, working at Oak Ridge National Laboratory and in the University of Tennessee. Edward Boyse who works in… who was a pupil of Peter Gorer's, whose name I already mentioned, who works in Guy's Hospital, London. And George Klein and Richmond Prehn, now the head of the laboratory of which Little was the head.

All these have demonstrated that this is the case, they have… nearly all of them studied transplantable tumors to try to demonstrate that the inoculation into mice of embryonic tissues produces anti-tumor immunity. But my group and I working at the clinical research center thought it would be more satisfactory to raise tumors by the use of chemical carcinogens and notably, methylcholanthrene, which I shall now… if we've reached that stage; please may I have the next slide? It is always thought by chemists to be especially edifying to see the structural formula of any chemical substance that is referred to. That is methylcholanthrene. I'm showing it not because I think anybody here is going to be deeply edified—of course, those of you that haven't done chemistry for a great many years still like to be reassured you recognize a methyl group when you see it. [laughter] And that is… that used to be called 3-methylcholanthrene, but chemistry is a very rapidly growing science; it's now called 20-methylcholanthrene. The difference is not constructive, but in nomenclature only. Now, the hypothesis of my colleagues and I, my research that I have been trying out is—and all our experiments are based essentially upon it—will the inoculation into mice of embryonic tissues produce resistance to the growth of methylcholanthrene-induced tumors?

I will show you the first experiment we did, for a special reason. May I have the next slide please? Here is an experiment illustrating results of our first experiment. Two very large groups of mice were each injected with 50 micrograms of methylcholanthrene, and one-half of these mice received inoculations of mouse fetal tissue, at about the time at which… about the time which we would expect tumors to arise. And the other half did not receive such

inoculations. The time scale is weeks, as you can see. Or is it days? It's days. Indeed, our experiments… our experiments all last a year; it's one of the reasons I think why some of my friends professed to discern a tinge of grey in my hair. Anyway, if you look at this experiment, those of you who are experienced scientists will see it is an experiment of unmistakable authenticity, because it was designed in the hope and in the expectation that would show a protective effect of fetal tissues on the growth of tumors, and it demonstrates exactly the opposite. [laughter]

This is science for you, my friends, I do assure you. But we were not down-hearted, because we knew there must be some mistake. I knew this must work. What is wrong with this experiment is, first of all, we injected […] methylcholanthrene, and then later on we injected fetal tissue. We thought that the first variation we must try is to arouse… if tumors spring up very rapidly after the injection of methylcholanthrene, or if the malignant transformation occurs very soon after the injection of MCA, as I am going to call it now, partly for familiarity. If we injected fetal tissue first and then later injected methylcholanthrene, we might hope to see some protection. May I have the next slide please?

And indeed, this turned out to be the case. Same design of experiment, just different timing of the injections of MCA and of fetal tissue. In this experiment, fetal tissue was injected 14 days before injections of methylcholanthrene. And here are the two groups, the control group and the ones who received fetal tissue. There's a profoundly significant difference in the final total number of tumors formed and in the rate of formation of tumors. And this difference between the results of injecting fetal tissue before or after methylcholanthrene struck us as being a potentially important one. Nothing has occurred to shake us in that opinion. So we did a rather bigger trial of the same kind, varying the time of inoculation into mice of fetal tissues in relation to the time of injection of methylcholanthrene. May I have the next slide, please?

This was an enormous experiment which nearly drove us out of our minds, in which… in all these five—I think it's five groups of mice—methylcholanthrene was injected on the same day, which we called day zero. While the fetal tissues were injected on the same day, that's day zero itself, or seven days after, or 14 days after, or seven days before, or 14 days before. What you see from this experiment is that injection of fetal tissue at the same time or after the injection of methylcholanthrene has no protective effect whatsoever. There's almost solid protection if one injects fetal tissue 14 days before methylcholanthrene, if the mice are already in an immuno-olfactory state before you inject them with methylcholanthrene. Now, this has not got that of unmistakable air of authenticity that I referred to a moment ago, because the protection there is too good to be true. Now, scientists don't like getting results that are too

good to be true. The first thing they think of, if everything goes exactly according to plan, if all their theoretical anticipations are confirmed, as we say, is that they made some mistake.

So, my assistants and I exchanged long meaningful glances at each other… [laughter] …signifying the unspoken question, "My god, did we forget to inject these mice with methylcholanthrene?" [laughter] "Oh dear." We're pretty old hands at scientific research, you see; you can't fool us very easily. But to our enormous relief, at about the time when you might have expected, some tumors started to appear in this group of mice, showing that it was okay. We had injected methylcholanthrene. But notice the difference, the knife-edge on which we work. We work here on a knife-edge between inhibiting the growth of tumors or enhancing them, as immunologists say. "Enhancement" being a phenomenon… an abstract noun used to explain any phenomenon that is otherwise inexplicable.

These results with tumor immunity appear to me to explain quite easily why it is that so many attempts at specific tumor immunotherapy don't work. One has to introduce… prophylaxis works, is what I'm saying. If you can set up an immune state before the malignant process begins, then you can get protection. So, prophylaxis works, therapy or treatment seems not to work. Now, a second connection, a second connection to thoughts I'd like you to put together in your minds, please?—this isn't going on forever, have no fear—is this. If embryo tissues, and as is indeed the case, pregnancy produces anti-embryo immunity, should not pregnancy, the bearing of a litter, produce anti-tumor immunity? I didn't make it sufficiently clear, which is a euphemism saying I didn't make it clear at all, that anti-embryo immunity is aroused also by natural pregnancies. If I forgot to say that, I'd like this opportunity to apologize abjectly. It has been shown by many people, rather especially a worker called Braun and the Hellströms that work in Seattle, that normal pregnancy produces anti-embryo immunity of just the kind that you get by deliberately injecting into mice embryonic tissues.

Having cleared up that point, with a renewed apologies for not having said it before, the two things that I want to put together are this: if normal pregnancy arouses anti-embryo immunity and anti-embryo immunity is tumor protective, then should not ordinary pregnancy be tumor protective? This is a problem which I asked some young colleagues of mine to investigate in rats. May I have the next slide please? This is an investigation by Pinto, an exceptionally brilliant Ugandan-Haitian colleague who's joined me. After Amin kicked him out, much to my delight, since I have now acquired him on the staff. What is the effect upon the susceptibility of rats to mammary tumors induced by dimethylbenzanthracene of parting or bearing a litter? And the answer is, that it depends on when the rats have the litter. In rats which have no litter at all, nulliparous rats as they're called in the trade, as you can see, a fairly high proportion, 19

out of 25, contracted tumors over the period of the experiment after being given 20 milligrams of dimethylbenzanthracene by mouth.

Now, if they are given this dimethylbenzanthracene first, and then mated, so that they go through their pregnancy after dimethylbenzanthracene, this has almost no effect at all. It doesn't make matters worse, it hardly has any effect at all. 10 mice out of 25 got tumors, and that is what you would expect from that big timing experiment which I illustrated in the last slide. If, on the other hand, the dimethylbenzanthracene is administered after the rats have borne one litter, then there are very significant protections indeed. Only one tumor arose in 20 rats, which I take to be only five percent as opposed to something between 50 and 65 percent. Thus far, these experiments confirmed our theoretical anticipations. If rats go through a pregnancy before they're exposed to a cancer-producing stimulus, in this case one that pretty regularly produces mammary tumors, then they are, to a fairly high degree, protected. Well, that's all right for rats, who cares about rats, I hear you cry? What about human beings? May I have the next slide, please?

Well, I believe this is the comparable experiment. You've seen this before; if you have a sense of *déjà vu*, you are absolutely right. [laughter] This is what happens in human beings. These are MacMahon's, Brian MacMahon's epidemiological investigations on the influence on susceptibility of breast cancer of women who have a completed pregnancy, it has to be, either early in life, or not at all, or later in life. And these are exactly the results that one would have predicted. If the event of malignant transformation occurs fairly early in reproductive history, as it does seem from these data to do, then an early pregnancy confers protection. A late protection produces that dire phenomenon of enhancement. It makes the situation worse, as you can see here. So, thus far, the results in rats and in human beings support, in my opinion, an immunological interpretation. And this does raise in my mind and in my colleagues working at Memorial Sloan Kettering Cancer Center in New York, the possibility, the remote possibility that if we could devise for use in human beings an immunological simulation of pregnancy, something which would produce an anti-embryo immunity, a specific anti-embryo immunity in teenagers, for example, this would confer the kind of lifelong protection which MacMahon has observed with teenage pregnancies. I believe it would take about ten years to devise a preparation which might be reasonably expected to simulate pregnancy immunologically, and the clinical trial, supposing it were to be feasible at all, as I believe it would be, would take between 50 and 60 years.

Because it's one of the strengths of MacMahon's epidemiological investigations; he has shown that a pregnancy at the age of 15 confers a virtually lifelong high degree of resistance to mammary tumors. For 60 or 70 years. Mammary tumors are less frequent in such teenage

pregnancies. Now, I do exhort you, because there are many laymen here, not to look at those results and take them personally. No one can look at this graph and tot up their own chances of contracting a breast tumor. These are statistical epidemiological figures based upon the collations of vast amounts of data. Now, a woman should no more look at that graph and predict her likelihood of getting a breast tumor than a man should expect to die on the very day on which he reaches the mean expectation of life at birth as it was when he was born. There are very considerable variations; many other factors affect susceptibility to tumors. This is merely one of them, so please don't take it personally.

Now, in the midst of these remarks I have forgotten about tumor immunity. I am now reaching the home stretch in my closing remarks, so be reassured, ladies and gentlemen. What about tumor immunity? Is it right or wrong, the theory of tumor immunity? One cannot say of theories whether they are right or wrong, black and white. That belongs… only historians of science ever do this kind of thing. They describe the supersession of wrong theories by right theories, but in science it doesn't happen this way; there aren't right and wrong the way that English school children were told that the kings of England are either good kings or bad kings. King John was a bad king, but King Stephen was a good king. [laughter] It's not like that with scientific theories, I do assure you. There's a lot of truth, obviously, in the theory of tumor immunity. Unmistakably, a lot of truth.

We really distinguish, in science, fertile from infertile theories. Now, fertile theories are theories which arouse an enormous amount of interest, stimulate discussion and controversy, and prompt people to make observations they would not otherwise have made, and do experiments they would not otherwise have done. I think everybody here who knows about this—there are a fair number who do—will admit the theory of tumor immunity has been enormously fertile. Thanks to it, we know a great deal more about tumors than we would otherwise have known. So, let us go on and call it a good theory; it is a good theory, because it is conducive to the discovery of the truth. Thank you. [applause]

RICHELLE: Thank you very much, Sir Peter. I am not sure that I can draw a conclusion from Sir Peter's conference. If my understanding is right, however, he has suggested an extremely pleasant way to avoid cancer. [laughter] As I said before, Sir Peter has offered that anybody in the audience who would want to come and ask questions, say hello, or just meet him, please do come use the stairs on the right of the auditorium and we'd be very pleased to have you. Thank you.

[direct audio concludes; some background noise and conversation for about two minutes; program ends]