Immunology and the Host Response
The Biology of Cancer: Part Three
Uptodate: Cancer Research Today: Programme Four
A series of Programmes from the Institute of Cancer Research

With Dr A J S Davies and Professor Peter Alexander.

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Black-and-white
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<Opening titles>

<Dr Davies to camera>

This is the third of a series of three programmes which are broadly concerned with the biological approach to cancer research. In the first two programmes, we talked about cell division and cell growth and invasion and metastases. On this occasion, we're going to do something rather different, we're going to talk about tumour immunology and the people who are going to do the talking are Professor Peter Alexander and myself, Dr Tony Davies.

<Dr Davies and Professor Alexander are seated for discussion. Camera moves from one to the other during discussion>

<Davies>

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We're going to try and stage a dialogue; both of us are immunologists, Peter's a tumour immunologist and I'm perhaps a rather more fundamental immunologist. We have a rather different viewpoint about tumour immunology and we're going to try and talk about it from a discursive point of view.

Peter, if tumour immunology is to be a real thing, then tumours must be antigenic. Is it formally possible to demonstrate that this is so?

<Alexander>

In most experimentally induced tumours, which have been adequately studied, there's really clear evidence that they have antigens, that is, macromolecules which the body sees as foreign on their cell membrane.

<Davies>

Is there a, what shall we call it, a cancer-specific antigen, something which uniquely characterises cancer cells?

<Alexander>

No, I think these new antigens are more complex. There isn't just one type.

<Davies>

If there are to be more than, if there are several types of antigens which characterise malignant cell populations, would you like us to tell us a little about these things? What are they?

<Alexander>

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Well, what I'm saying now really refers entirely to experimental animal situations and there one can distinguish really between three types of these new macromolecules on the surface. There are those which are induced by a virus, that is, if you produce a tumour by inoculating an animal with a virus, then one has new components on the cell membrane; the information, the genetic information of which is introduced by the nucleic acids of the virus. That's fairly simple and reasonably straight forward.

<Davies>

Are these viral antigens coded for exactly by the virus? Are they to be regarded as the antigens which characterise the virus, or are they something new which relates to the virus in a particular cell?

<Alexander>

There's the possibility of that latter situation occurring, but we definitely know that some of the entrants at least are directly coded for by the DNA or RNA in the virus. Whether they also switch on some hidden host information is debated, but that isn't so clear.

<Davies>

I see. And are all virally associated tumours antigenic?

<Alexander>

Yes, I think that seems to be very clear and there's great cross-reactivity, therefore all tumours induced by one particular virus, even in different species, will have the same type of new antigen on their surface.

<Davies>

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So as far as, so that this is a very interesting characteristic of the antigenistic tumours with viruses: that for a particular kind of virus, you'll always get the same kind of antigenistic property.

<Alexander>

That's right, that by and large is true. There may be a fine structure superimposed, but that's the general pattern. Now, the second type of new antigen is the re-occurrence of an early foetal antigen, presumably material which is normally only made in early foetal life before the animal has learnt to recognise self, and therefore the material is seen as antigenic. Those recur and reappear on the surface of tumour cells. Now, these tend to be, these have only been discovered relatively recently, but they are quite widely distributed and they really offer biologically an interesting sign because it really is a direct biochemical manifestation of the fact that tumours and embryo have something in common. So the tumours retrograde to something of early embryonic life.

<Davies>

So you could, you could perhaps think of these embryonic antigens as being sort of an aspect of dedifferentiation?

<Alexander>

That's right. I don't really like the word dedifferentiation because if it's a highly specific product made only in one part of the cell cycle, one might call it differentiation, but I like to think of it simply as the switching on of silent genes. The bulk of our genes tend to be silent and this is the inappropriate switching on of a gene that shouldn't normally be switched on.

<Davies>

It was a, the gene was switched on during embryonic life…

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<Alexander>

… life, and then switched off.

<Davies>

I see, so that it is, it's the expression of these embryonic antigens could be thought off as de-repression…

<Alexander>

That's right.

<Davies>

… rather than de-differentiation?

<Alexander>

That's right, yes.

<Davies off camera>

That's the word you'd prefer?

<Alexander>

Much prefer that because you see tumours will also make highly specialised products like hormones and so on and there it's the same phenomenon. It's again switching on a silent gene, but one clearly wouldn't call that dedifferentiation to make a highly specific product.

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<Davies>

So that we've got viral antigens where there's an extrinsic agent, we've got these embryonic antigens, what about anything else?

<Alexander>

Well, now the third type is really the, in some ways the most interesting and also the most puzzling, the chemically-induced tumours, tumours induced by chemical carcinogens…

<Davies>

What sort of things?

<Alexander>

Oh, the carcinogenic hydrocarbons, azo dyes, almost all types of chemicals that induce carcinoma and sarcomas and leukaemias in experimental animals. The tumours induced by these chemical agents have in addition to the embryonic antigens, which we've just discussed, another neoantigen on their surface, which has a quite unusual characteristic that it seems to be almost tumour specific. Each individual tumour will have its own; for example, if you take a rat and put two pellets of benzpyrene, one on the right flank, one on the left, you'll get two sarcomas. And these two sarcomas will both have the cross-reacting embryonic antigens plus an individual antigen which is, however, different, so that the one on the right will won't cross-react with the one on the left. Now, the origin of these no one knows, except it's possible that this is really a mutation induced by the mutagenic carcinogenic agents…

<Davies>

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Most carcinogens and mutagens, I suppose?

<Alexander>

That's right and so that's a possibility, but the fact that it happens so invariably isn't a very attractive hypothesis. The other thing is that it's also the switching on of a silent gene but then one has to postulate that there are a whole battery of silent genes that can be switched on and they're sort of switched on – different ones are switched on in different tumours. This is quite a challenging situation, but these are perhaps the most, these are more important from a host-interaction point of view because these are very strong antigens and can, in fact, lead to a powerful host reaction.

<Davies>

I see. You said that if you induce two tumours in the same animal with a benzpyrene pellet that very often you will get different antigenicity, in fact, you will always get different antigenicity in the two tumours. What about within a single tumour cell population? Don't you get heterogeneity in relation to antigens there?

<Alexander>

Well, the data isn't clear. People have sort of cut up tumours into different parts and the data hasn't been very, very clear. I think one would on experimental grounds, I think it would be difficult because if this had occurred fairly early in the genesis of a tumour then one would expect them to get muddled. Really clean experiments on this, as far as I know, haven't been done.

<Davies>

Good. So we've got three kinds of antigens: we've got viral antigens, the embryonic antigens and we've got these, what can we call them, neoantigens, if you like, which are little bit less well defined?

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<Alexander>

Yes, the individual tumour-specific.

<Davies>

OK, individual tumour-specific antigens. Now, can you tell me a little bit about the methods of detection of these tumour antigens?

<Alexander>

Now, the first ones to be detected were the last type, the individual tumour-specific ones. And the evidence that they existed came from transplantation experiments within pure-lines, pure-bed animals.

<Davies>

What do you mean by pure-lines?

<Alexander>

Well, that means groups of mice or rats, or guinea pigs now, which have been brother-sister mated for many generations so that each individual in the group is, in fact, genetically identical so that they behave like identical twins. Now, of course, grafts between animals within such a group are automatically accepted. If you take a skin graft on, it will stick on as it will amongst an identical twin, but what was found is that if one suitably immunised… well, let me start again… is if you now induced in one member of such an inbred colony of mice or rats, a tumour, and then one adopted suitable immunisation procedures, that tumour could not be transplanted from one animal to the next if the recipient had been immunised against the tumour, showing that the tumour was antigenic and this was nothing to do with ordinary histocompatibility antigens that prevent acceptance of grafts between normal people.

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<Davies>

For example, in relation to kidneys, it's the…

<Alexander>

Yes.

<Davies>

OK.

<Alexander>

No, it was something in these inbred, it was really the failure of a tumour which arose in one animal to fail to grow in a genetically identical animal after this had been immunised. And that really provided absolutely watertight evidence for the existence of a new macromolecule on the surface of the tumour cells, which must be absent from all the normal cells of that animal, and that the body reacts against that and that there was an immunological rejection.

00:10:31:20

<Davies>

And these kind of antigens which were defined in this way were called tumour-specific transplantation antigens?

<Alexander>

Yes they were called tumour-specific transplantation-type antigens. TSTAs, they're often referred to. But those were ones first, and that was how it was first recognised

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that these individual tumour-specific ones were unique because if you immunised against tumour A, the animal was only able to resist tumour A and not tumour B.

<Davies>

And you'd imagine that a non-malignant cell population, a benign cell population, which was nevertheless hyperplastic, would not have these antigens on its surface?

<Alexander>

Experiments to show that were done, yes.

<Davies>

Good. So that one of the methods by which these tumour antigens were detected was the methods of transplantation. Are there any other methods?

<Alexander>

Yes, of course, people then immediately started looking for signs of an immune response, antibodies and cytotoxic cells, a point which I'm sure we'll return to in a moment. And in vitro tests were set up to find these and they were, in fact, demonstrated. Most convincingly of all, perhaps, was that resistance to tumours could be transferred from one animal to another by means of lymphoid cells. Demonstration for antibodies came rather later and for a number of technical reasons is still a difficult technique except for virally induced tumours.

<Davies>

I see, but it's perfectly common for a tumour which can be shown to be antigenic, by transplantation tests, for you to be able to demonstrate under these circumstances that there are antibodies produced which are specific for the tumour cells, specifically

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can attach to the tumour cells, and also that there are cytotoxic cells which you can demonstrate will attack specifically the tumour cells.

<Alexander>

Yes, particularly the cells. The antibody side is often more tricky, but the cells, the data there is certainly very solid.

<Davies>

Yes, that's fine. Now, so far you've talked almost entirely about experimental animals. You've described transplantation techniques, particularly as these are obviously the best ways of characterisation of these tumour-specific transplantation antigens by definition. This would relate to experimental animals. What about in man? Because there one must have a different kind of situation. The only in vitro tests are available to you are for fairly obvious reasons…

<Alexander>

Well, we haven't got 60 generation brother-sister mated human populations for a start…

<Davies>

They're not easily available.

<Alexander off camera>

No, no, that's <*laughs*>…

<Davies>

What are…

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<Alexander>

Well, there you see only in vitro tests are available and so the general test system is that one takes cells from the tumour of a patient, establishes these in tissue culture and then sees whether the patient, either before his tumour's been surgically removed or while the tumour's still in situ, has antibodies or cytotoxic cells by doing tests in vitro. And these in vitro tests have revealed that there are antigens on the surface too because one can in many cases find antibodies, but again, these are the more difficult ones to be sure of specificities, but also cytotoxic mononuclear cells from the blood are found and will kill, with a certain degree of specificity, tumour cells. But there is a very interesting difference in that the human tumours, that the specificity of their antigens is quite unlike any of the three specificities we've seen in experimental animals, in so far as there is a histogenic cross-reactivity. That means that tumours which occur in any one organ all cross-react. For example, if you have a bladder carcinoma, your patient will have mononuclear cells in the blood that kill bladder carcinoma cells, but they will kill all bladder carcinoma cells. They won't kill kidney tumours cells, they won't kill melanoma cells, but they'll kill all bladder carcinoma cells.

<Davies>

Quiet independently of the patient from whom the bladder carcinoma cells have been taken?

<Alexander>

That's right. So there's total cross-reactivity, rather as in the virus situation in the animals, but it's confined to one organ site. You come to melanoma and you find that, by and large, the lymphocyte or the mononuclear cells from a patient with melanoma will destroy all melanoma cells but will leave other malignant cells in vitro alone and so on. And this is: it seems to be confined not so much on the actual morphological criteria of the cells but on the histological origin so that if one has even

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histologically different tumours so long as they originate in the same site, they will cross-react. Now, this is a very puzzling situation because one doesn't, it clearly isn't like the chemically induced tumours. If one said that it was like the viral situation, one would then have to say that there was a unique virus for each site: that there is a melanoma virus, a bladder carcinoma virus, a hypernephroma virus and so on. And there's no … and that doesn't make good biological sense because all the viruses found in experimental animals that produce tumours don't behave in that pattern, so the origin of these isn't clear. It could again be something to do with an early embryonic differentiation antigen. Maybe in early embryonic life, organs carry a macromolecule which they don't carry later, but that's hypothesis, but it's an important difference.

00:16:12:15

<Davies>

So that you've got a bit of a problem here because in experimental animals you can characterise tumour-specific antigens in a variety of different ways, including transplantation; with man, you can only do this in vitro. And in man, unlike the situation in experimental animals, you get this cross-reactivity between cells from like organs, which is a rather strange phenomenon.

<Alexander>

Yes.

<Davies>

Are you never a little bit worried when you do these experiments with human tumour cells in vitro that to some extent, the changes that you are finding relate to the transfer of the cells into a glass vessel and that changes don't take place subsequent to the transfer which complicate the issue?

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<Alexander>

Yes, I think this is a real hazard and one really relies on really rather a large body of data being internally consistent for giving one the answer, but there if somebody comes up and says that the whole thing is an in vitro artefact, it would be very difficult to argue with total confidence against that, but then, of course, one is still there, why if it is an in vitro artefact, why should all melanoma cells differentiate to have that antigen and so on? But certainly these in vitro tests are much less convincing than the transplantation tests, but there's now so much of it. And there's also some ancillary data on the late hypersensitivity and so on, which is corroborating but not terribly convincing yet.

<Davies>

You're quite sure that all these tests that are done on human tumours aren't tests on the HeLa cells? <*Laughs*>

<Alexander>

Well, yes, I think so. Mind you, there is a lot of nonsense in the literature when people have worked with long transplanted lines, and as a purely technical point, I maintain that these human studies must be made on short-term cultures obtained from primary surgical specimens, not only because one might confuse a HeLa with a normal cell – with a cell one wants, but also infection and other things. And, in fact, to answer your first question about in vitro artefacts, some of these have been done on very early cultures, on the cells immediately after they have been dispersed, and the same sort of answers have been got.

<Davies>

So whilst clearly the situation is not ideal, there are certain broad answers which indicate that human tumours are antigenic and can be demonstrated to be so in vitro?

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<Alexander>

Yes.

<Davies>

Now, perhaps, we should go on, as we've considered the fact that tumours are antigenic, the methods that have been used for the display of this antigenicity in man and in experimental animals, perhaps we should go on to consider, for a little while, the mechanisms of immunity. And it seems rather strange now that in the last 10 to 15 years, there've been probably three kinds of lymphoid cell, or three kinds of cell from the lymphoid system, the reticuloendothelial system, involved in anti-tumour immunity. There are those lymphoid cells which people call T-cells to indicate their thymus origin and there are lymphocytes, lymphoid cells too, which are called B-cells – I'm not quite sure why, perhaps to indicate a bone marrow origin or to distinguish them, at any rate, from cells of thymic origin. And there are the other cell population, which I think you're particularly interested in, which are the macrophages. And correct me if I'm wrong, but I think that it's been demonstrated that T-cells in vitro can be cytotoxic against tumour cell populations.

<Alexander>

Yes.

<Davies>

And that their cytotoxicity does not require complement?

<Alexander>

Yes, that's right.

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<Davies>

And it is furthermore blocked by the presence of antitumour antibody, for reasons which we shall perhaps come on to later.

<Alexander>

No, I wouldn't accept that.

<Davies off camera>

You wouldn't accept that?

<Alexander>

No, no.

<Davies>

All right. Well, at any rate, T-cells can be cytotoxic.

<Alexander off camera>

Oh, yes.

<Davies>

So these cells of thymic origin, which are themselves not antibody-producing cells, but which nevertheless can probably cooperate with B-cells in the production of antibody can kill tumour cells. Whether they do in in vivo situations is a little bit more problematic, probably. I think there are some experiments which demonstrate this.

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Now, whilst initially they thought that the other kind of lymphocyte, the antibody-producing lymphocyte, the B-lymphocyte was not a killer cell, it seems as if it may well be so, as long as the target cell has been in some way sensitised, probably with antibody or something of this kind? Would you accept this?

<Alexander>

Absolutely. I'm not sure whether one would call that a B-cell. I would rather like to think that the B-cell, by virtue of having antibody on its surface…

<Davies>

Is already blocked.

<Alexander>

… can, well, is now a killer cell,…

<Davies>

Oh I see.

<Alexander>

… that, in fact, you can have a cell coated with antibody which can then interact and, so to speak, the cell's interior provides the complement, and the antibody coating provides the specificity for binding to the target.

<Davies>

Good. There's a problem, isn't there at the moment about this? Whether the B-cell, which has characteristically got immunoglobulin on its surface and which

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characteristically would transform into a plasma cell when appropriately stimulated, whether that can be a killer cell or whether it's another cell which derives from the bone marrow which is called a K-cell, I think?

<Alexander>

Well, I think that terminology, yes, I think that there really isn't an argument. I think both apply. I think an early primitive plasma cell can kill by virtue of the fact that it's already got antibody on its surface, possibly in conjunction with complement, and then you also have other rather featureless mononuclear cells, which carry antibody on their surface, and which can also kill, and the simplest way of looking at this, I think, is just to say that antibody leads a killer cell to its target and thereafter there's a relatively non-specific killing mechanism which, however, is not effective until you've applied some way of attracting it to the target.

<Davies>

So the antibody's the focusing device?

<Alexander>

Yes, that's right, absolutely and the [unclear word].

00:22:10:10

<Davies>

Now, we've just had the T-cells very briefly and these B-cells very briefly; tell me a little bit about the macrophages and how and under what circumstances, they appear to be able to kill tumour cells.

<Alexander>

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Well, if I can just backtrack for a little while. Of course, to many people dealing with bacterial infections, it was little surprising that, in fact, the macrophage has only been considered seriously relatively recently because we know that, I think that B- and T-cells don't have much of a role in controlling bacterial infections, whereas the intercellular parasites are controlled, of course, by macrophages, and the word 'cell-mediated immunity' was invented for macrophages. And so it's really no surprise that they also come into the tumour field and it's now quite clear that macrophages can kill tumours by cell to cell contact, not only by phagocytes. And phagocytosis is a late event. Again, I think it can come into the same situation as those funny B-cells we were talking about, which might, in fact, be early monocytes; it's that the macrophage is probably coated with the cytophilic antibody-like material, the exact nature of which remains to be resolved, that brings it to the target and the macrophage has all the killing mechanisms in it then to kill the target cell. So, probably, the specificity lies in some cytophilic antibody coating the macrophage…

<Davies>

Which is probably, the antibody's probably produced by a B-cell?

<Alexander>

It's probably produced by a B-cell, but there clearly is a – and this, of course, is your main interest – it probably requires T-cell cooperation because one doesn't get these killing macrophages in T-deprived animals. So the cytophilic antibody that coats them, although it probably is made by B-cell, although it could be made by T-cells, I think there's no, there have been some suggestions to that, but one certainly need T-cell cooperation.

<Davies>

So that, all in all, this mechanism of anti-tumour immunity is a sort of tridentate attack with interactions between the component cells.

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<Alexander>

Absolutely and, of course, the macrophage will also enter in the initial arm of the immune response, in the initiation, because processing of tumour antigens to get an immune response will bring in the macrophage, so I think you have to think of the macrophage at both arms of, at both ends of the immune…

<Davies>

Well, that's fine. So far it's been a little euphoric in a way, so far as we've got tumour antigens, we can detect them and describe them in different ways in man and in experimental animals, and we've got some various mechanisms by which we can demonstrate immunity, the involvement of various of these lymphoids and reticuloendothelial cells in anti-tumour immunity. Now, it's all very well to say this, but when one looks at the human situation, it's perfectly clear that people do die with tumours; why do they die if this defence mechanism, if such it be, is in operation? Why does it fail?

<Alexander>

Well, again, this isn't unique to tumours. I don't want to overplay the antigenicity of tumours, but even if they were very antigenic, escape from immune defences is quite common. I mean tuberculosis, before there were suitable chemotherapeutic agents, killed a considerable portion of people who had the disease. They had active immunity, the patient who, with advancing tuberculosis, had a perfectly active tuberculin response until very close to death. Other bacterial diseases similarly escape. A very old one, childbed fever – the body's full of antibodies to streptococcus, but in the disorganised uterus after birth, they don't get in and they can escape, so there are many escape mechanisms from immunity which we know from infectious diseases and from parasitic diseases, no doubt.

<Davies>

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But, I mean, could one summarise this by saying that at least under some circumstances, the parasite can grow faster than it can be killed, or perhaps a tumour can grow faster than it can be killed?

<Alexander>

Yes, but that, of course, would only, I think we've got to think of escape at two levels: the initial escape when there are relatively few cells, and then, I think, once there is a large mass of tumour, I think these purely quantitative considerations which you've advanced are quite adequate to explain…

<Davies>

Is there any possibility of specific immunological tolerance under these circumstances?

<Alexander>

I don't think so because if there were we, of course, wouldn't recognise the tumours as being antigenic. I mean the whole proof in man certainly that they're antigenic is that one finds antibody in cytotoxic cells. If there were specific tolerance, we would, in fact, then have to say that human tumours weren't antigenic.

00:26:57:09

<Davies>

There's still a bit of a paradox: you've got a situation where you've got antibodies produced, where you've got cytotoxic cells; why don't these antibodies act on the tumour cells? Why don't the cytotoxic cells act on the tumour cells?

<Alexander>

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Well, this is the escape problem and, as I've tried to indicate, it doesn't operate only with tumours, it operates with bacteria. There are anatomical reasons why they escape. I mentioned the childbed fever type of thing, but there may be even some more, and there are lots of escape mechanisms which, in fact, infectious disease people have outlined over the whole of this century. But there is quite an interesting one, namely that there is, in fact, a circulating factor which specifically antagonises the effector arms[?], be they antibodies or cell-mediated. This was discovered by a group of Swedish workers, now working in the States, called the Hellströms, man and wife. They found that when they were doing these in vitro tests of taking patients' or animals' mononuclear blood cells and putting them against tumour cells in tissue culture that when they took serum from tumour-bearing animals or men that they would antagonise the cytotoxicity, and they called this…

<Davies>

Actively antagonise or just simply passively block?

<Alexander>

Passively, yes, passively, well, it's a circulating thing, so it's passively blocking…

<Davies off camera>

Right.

<Alexander>

… and that they would interfere with the, that they would inhibit the reaction of the cytotoxic cells in a specific way. It was immunologically specific. If you took the wrong tumour, if you took the serum from the animal with the wrong tumour, it didn't work. And so they unfortunately made, they made this very interesting and, I think,

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very important discovery, but then, unfortunately, they made a great mistake. They made a mistake which many people…

<Davies off camera>

Can scientists make mistakes?

<Alexander>

Oh yes, all the time. They equated serum with antibody and, of course, there are many other things in serum besides antibody. So at first they said that this was blocking antibody, but there was a specific type of antibody made which coated the cell, which however did not bind complement, so it wasn't cytotoxic but it prevented the action with the cytotoxic cells. A very attractive hypothesis but, unfortunately, it wasn't true.

<Davies off camera>

<Laughs>

<Alexander>

And as they looked at it more closely, they found that the actual blocking material, or I rather like to call it now, inhibiting material, but that's just a bit of faddism, that that was either antigen-antibody complexes or antigen itself. Now, there's still a bit of dispute whether antigen-antibody complexes are at all important in this, i.e. the antibody part, or whether it is only the antigen that blocks, because we know from in vitro experiments now by isolating antigens from both human and animal tumours that adding antigen, containing no immunoglobulin at all, will combine with the cytotoxic cells and thereby pre-empt the immune response. The whole attack is now thwarted, the antigen is met in a specific way, the aggressor cell, it, so to speak, neutralised it. And therefore, they no longer combine with the tumour cell, via some specific interaction, hence the killing doesn't occur. Now, antigen-antibody

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complexes also enter into it, but my own feeling is that they are not very important because experiments have now been done in birds where one can, by removing the bursa – well, you know this much better than I do – one can totally suppress antibody reaction. And birds bearing tumours, their sera, the sera from birds bearing tumours, which has no antigen-antibody complexes but only circulating tumour antigen, blocks perfectly well.

<Davies>

These are completely agammaglobulinaemic birds?

<Alexander>

That's right. And so, but this remains to be solved, this is all reasonably new. One thing is certain: antigens can inhibit cytotoxic cells. Whether antigen-antibody complexes do anything more than just provide antigen will be sorted out in a relatively short time.

00:31:20:05

<Davies>

OK. So what we've, we've taken a little bit of the pressure out of the thing because in the human situation, particularly also in experimental animals, although there are immunological mechanisms active, which one can demonstrate, nevertheless, for some reasons which are not yet clear, these immunological mechanisms seem to be self-effacing, perhaps if antibody is involved or, alternatively, the tumours are producing antigenic material which goes out and spikes the guns which would otherwise be trained against it. So what is being done, what can be done in this rather blocked situation, if I can put it like that, by virtue of immunotherapy because this is a big and emotive word these days?

<Alexander>

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Yes, well, there are two general approaches. One can, in fact, provide more effector mechanisms. One could provide more antibody and more cytotoxic cells…

<Davies>

By stimulating the capacity of the organism to respond?

<Alexander>

Well, no, I was thinking of it passively. First, you could have some donor animal, say, immunised to make antibody or from whom you can collect cytotoxic cells, mononuclear cells, and then inject those into the tumour-bearing animal or eventually patient. Now, that has been shown to work in experimental animal systems but is not, I think, at the present time anything which one can begin to take seriously clinically because: a) it's very difficult to induce these and there's a great deal of toxicity…

<Davies>

But not only that but transfer of cells between two human people is obviously a difficult matter because of the rejection problem.

<Alexander>

That's right, I mean there are endless problems and I don't think... So the other one then is to indicate, as you indicate, is to boost the patient's own immune reactivity or to ablate in some way the escape mechanisms. Now, so far we really don't know the escape mechanisms in detail and some are quite difficult to think of and so one's thought about boosting the immune response and that's been done in two ways: either non-specifically by giving so-called agents that stimulate the reticuloendothelial system; it really doesn't tell us anything about their mechanism, it really is that one injects usually bacterial cell walls which make, which cause tremendous macrophage proliferation, increased spleen size, lung weight, liver weight. And animals treated in

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this way are more resistant to bacterial attack – that was shown 20 years ago – and they are also slightly more resistant to injected tumours and so one thinks that that may be a way in, and BCG is one of those agents.

<Davies off camera>

BCG, what's this?

<Alexander>

This, of course, it isn't really an attenuated tubercle bacilli, it's an organism which cross-reacts with tubercle, was developed at the turn of the century in France and has this property, is used widely for protection against tuberculosis and has this additional property of stimulating the RE system.

<Davies>

Stimulate the macrophages, it's a rather old concept, isn't it?

<Alexander>

Well, yes. Well, of course, some people would maintain that it also stimulates T-cells and B-cells, but I think everything's so integrated and you probably can't do one without t'other. And so that's one approach; the other one is a more specific stimulation, which at first sight seems rather paradoxical, that is, in fact, to inoculate at sites distant from the tumour which you wish to treat, kill tumour cells so as to stimulate distant lymphoid organs to respond. And that has sort of, has been called a vaccine-type of treatment. This works in some animal situations quite well and can also be tried in man and does work. I would say the mechanisms are not really fully understood.

<Davies>

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OK, good. Well, we've covered quite a lot of ground, Peter. We've considered tumour antigens, we've considered the methods of detection of these tumour antigens. We've considered almost entirely the immunological interactions between tumour and host. Of course, there are others. There are the hormonal components of this tumour-host interaction which may well be important, but I hope the students have got some better idea of tumour immunology now than perhaps they had when they started.

<End credits>

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