Cancer Immunology

Uptodate: Immunology 9

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University of London Audio-Visual Centre, 1974.
Made for British Postgraduate Medical Federation.

Produced by Peter Bowen and David Sharp.

Black-and-white
Duration: 00:28:21:21

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<Opening titles>

<Professor Fairley to camera>

For there to be an immunological reaction in malignant disease, it is quite clear that the malignant cell must possess antigens which are not normally present in the adult host. Now, if we look at the first slide, […]

<Fairley narrates over slide>

[…] we know from animal experiments that basically there are two different sorts of antigens. First, in the chemically induced tumours, the important antigen is individually specific for that tumour. This means that even if you produce tumours in identical animals using the same chemical compound, nevertheless, in order to immunise an animal against that tumour, you would have to use the cells from that tumour, and that tumour only. With the virally induced tumours, the situation is quite different. Here, one has a group-specific antigen, the neoantigen of the virus, and all

the tumours produced by any one virus carry this antigen. This means that one can immunise an animal against a particular virally induced tumour by using the cells from any tumour produced by that virus. In terms of human malignant disease, the significance of this, of course, is that if one is dealing with tumours such as carcinoma of the lung and the bladder, which may well be chemically induced, then any immunisation procedure, that is any immunotherapy, would have to be done with the tumour from the individual patient.

<Fairley to camera>

Whereas if you are dealing with virally induced tumours, and in tumour malignant disease one would think perhaps of leukaemia, then it will be possible to use the leukaemic cells from other people.

<Fairley refers to series of charts on display board beside him and narrates over them, interspersed with talk to camera>

Now, if we look at the first chart, probably the easiest way to show that a tumour immunises an animal is by this type of simple experiment. Here, one has a chemically induced tumour, and if it is removed and a cell suspension is made and 2 million of these cells are injected into this animal's identical twin brothers and sisters i.e. syngeneic animals, then in every case a tumour forms. But if you now implant the same number of cells back into the original animal, no tumours grow. In other words, this tumour has immunised this animal, but despite that the tumour will continue to grow and kill that animal; in other words, the immunological effect has been very small.

<*Next chart*> Now, the next chart shows that if one takes a chemically induced tumour and this is transplanted into genetically identical animals so that it is growing, it is very difficult to show that there are cytotoxic lymphocytes against the tumour while the tumour is still present. For example, if the tumour is removed and the spleen is removed at the same time, then the spleen cells have no effect either in vitro or in vivo against the tumour. But if, on the other hand, the tumour is removed

and the spleen is then removed 14 days later, one can show that the spleen cells have now become cytotoxic; they will kill the malignant cells in vitro and they will also, when mixed with the malignant cells, prevent them from growing when injected into animals.

<*To camera*> The next chart shows that it is also difficult to demonstrate the presence of antibodies frequently in the presence of malignant disease. In fact, with chemically induced tumours, it was at one time thought that antibodies did not occur. We now know this is not true. <*Next chart*> And this quite simple experiment, which was done at the Chester Beatty, shows that here you are measuring the level of antibody against a tumour, but the tumour is still in the animal. If the tumour is removed, some time later the antibody appears. <*To camera*> Now, this is very important because it means that it is difficult to find evidence of an immunological reaction in malignant disease while there is still a great deal of malignant disease in either the animal or in man. It is much easier to show this effect when most of the malignant disease has been removed.

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Now, if we look at the next slide, […]

<Fairley narrates over slides which illustrate clinical signs of malignant melanoma>

[…] I would like to discuss a particular human malignant disease, malignant melanoma. This comes from an article by Mr Bodenham, a plastic surgeon in Bristol, and this is the picture of a leg of a patient taken in March 1966 at the top and 1967 at the bottom. A cursory glance at this leg would suggest there has been no change, but, in fact, if you look carefully in the region of the ankle, you will see that there are more lesions in 1967 than in 1966. But if you look at the calf, there are, in fact, less. In other words, although the disease in total terms is slowly progressing, nevertheless, regressions are occurring at the same time that new lesions form. <*Next slide*> And the next slide shows this quite clearly, there is an arrow at the

bottom pointing to a new lesion. On the top left is a lesion which is beginning to disappear, and one at the top which has virtually regressed.

<Fairley to camera>

Now this suggests that there might be some host mechanisms; they needn't, of course, be immunological in this disease – however, we now know that we can find antibodies in malignant melanoma and cytotoxic lymphocytes as well.

<Fairley narrates over slides>

Now, the next slide shows that if you group the patients with melanoma into three grades, grades I and II being when the tumour has spread no further than the regional lymph nodes, and stage III when it has gone far beyond that, you find that antibodies really only occur in the grade I and grade II patients, as we see on the next slide. <*Next slide*> You will see that there were 59 patients with clinical grades I and II, and 33 of these had autoantibodies, that is antibodies directed against their own melanoma cells, but by the time the disease had spread, 60 patients only 2 had autoantibodies.

<Fairley to camera>

Now, if one looks at the next chart, one can also see some interesting things about lymphocytes in malignant melanoma. It has been known for some time that one can get lymphocytes from patients with melanoma, and if these are placed in special chambers, they will kill the melanoma cells. However, the degree to which they are capable of killing the cells depends very much upon how many times they are washed.

<Fairley narrates over chart>

If you look at this experiment here, these lymphocytes had to be washed up to 6 times to get the maximum cytotoxic effect. In fact, if you just take the lymphocytes,

they only killed 20% of the melanoma cells but here 80% of the melanoma cells <*indicates 6 washes*>. What has been happening during this process is that something has been washed off the surface of the melanoma cells and one can, in fact, put this back again; if you take these cells that have been washed and add the initial serum to the cells, you will find that the cytotoxic effect of those lymphocytes has been greatly reduced.

<Fairley to camera>

This work has been carried out at the Chester Beatty by Dr Graham Currie working with Professor Alexander, and they now have very good evidence that what, in fact, they are washing off these cells is either antigen or antigen-antibody complexes. And, in fact, from the results in melanoma, one can build up a pattern of what may be happening in malignant disease, and in particular what may be happening in the serum which may prevent the immunological reactions from being effective. Now, we know from animal experiments that lymphocytes can kill tumour cells. We know that under certain circumstances antibodies can also do so, although under other circumstances, there is some evidence that antibodies may actually enhance tumours. I think that it is simplest to look at it in this way.

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<Fairley sticks illustrated diagrams onto board and narrates over display, interspersed with talk to camera>

If we take here a lymphocyte and here a tumour cell, there are receptors on the tumour cell, the antigen, which will react with receptors on the lymphocyte, and the lymphocyte can destroy the tumour cell. If there is excess antibody then it is possible that the antibody can sit on the receptors, as it were, of the tumour cell and block the action of the lymphocyte. This is certainly quite clearly shown in animal experiments but it is very doubtful, I think, if the situation really applies in man, that is to say, there is no direct evidence that there are enhancing antibodies in man. The other possibility is that if one has excess antigen, this may then combine with the receptors

on the lymphocytes and block the lymphocytes from attacking the tumour cell. And I think it is the general consensus of opinion now that this is probably a much more important mechanism in interfering with lymphocyte cytotoxicity than is the effect of antibodies on the surface of tumour cells.

<Fairley to camera>

Now, I would like to leave the question of melanoma and this for a moment and come to something very practical. There have been a lot of suggestions lately that if there is an immunological reaction against tumours, and this is likely to occur chiefly in the drainage lymph nodes, particularly with carcinomas, then perhaps one should leave the lymph nodes alone. And, in fact, one might actually be doing harm by removing drainage lymph nodes where an immunological reaction is in progress.

<Fairley narrates over slides, interspersed with talk to camera>

Now, we see on the next slide, which is concerned with breast cancer, the results – and these are pooled results from the literature – of a radical mastectomy versus a simple mastectomy. Radical mastectomy means removal of the breast and all the lymph nodes, of course; simple mastectomy – no interference with the lymph nodes. And you will see that the percentage of patients alive at five years is the same in both groups. Now, five years is a short time for carcinoma of the breast, but even if these patients are followed longer, there is no evidence, one way or the other, that interference with the lymph nodes is actually beneficial.

<*To camera*> However, it is very dangerous to argue from this example to all tumours. <*Next slide*> And if we look at the next slide which shows the results of testicular seminoma, the situation is totally reversed. If all one does is to remove the tumour then the 5 year survival rate is 50%. But if the tumour is removed and the drainage lymph nodes are irradiated then the 5 year survival rate is increased to 90%.

<*To camera*> And this really illustrates the very important point that different tumours behave in different ways, and while it may or it may not be right to interfere with lymph nodes in carcinoma of the breast, it certainly would be disastrous not to interfere with them in seminoma. With other cancers, for example, melanoma and with, say, carcinomas of the colon, the situation is far from clear. But in general, malignant disease should be removed and one should not rely upon any theoretical immunological response.

If there is then the possibility of an immunological reaction by a patient against his own tumour, one has to consider what can be done to enhance this and whether this, in fact, is a practical proposition at the present time.

<*Next slide*> Now, the next slide shows what one can do in malignant disease to attempt to stimulate the immunological reaction. First, in a totally non-specific way, if one gives either BCG or an organism *Corynebacterium parvum*, this has a general effect on the immunological system so that grafts are rejected faster, antibodies are formed more readily etc. As far as non-specific lymphoid cells are concerned, I think that these can be ignored at the present time.

Now, if we continue on to the next slide, this shows what can be done in a specific manner <*next slide*>. One can, of course, give the antigen, and in this case this is irradiated tumour cells. One can, theoretically, give antibodies, but because of the dangers of immunological enhancement, these, in fact, are not used and have never, in man at any rate, been shown to be effective. To use specifically stimulated lymphoid cells is an attractive idea, but for reasons of quantitation, one cannot do them at the present time. One needs too many lymphoid cells to be able to affect a tumour.

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<*To camera*> So, the two practical things one can do are first to give non-specific stimulation using BCG and, secondly, to give irradiated tumour cells. Now, there are two ways of assessing what happens if you do this. The first example I shall use will

be from the work at the Chester Beatty with malignant melanoma. The patients were immunised with this combination: BCG and irradiated tumour cells.

<Fairley refers to charts and narrates over them, interspersed with talk to camera>

Now, this chart shows that the inhibitory substance in the serum of these patients, which I have already suggested is either antigen or antigen-antibody complexes, in fact, goes down following immunisation but rises again. <*To camera*> It may seem a paradox that with a patient who has, in fact, a lot of tumour, and presumably therefore excess antigen, that giving more antigen should remove it from the circulation. I think the probable explanation for this is that the antigen, when injected, particularly if it is given into numerous sites, fires off a number of lymph nodes which are not normally reacting against this antigen, and in this way, possibly by the creation of circulating antibody, the excess circulating antigen is cleared from the blood.

<*Next chart*> The next chart shows that it is necessary to go on immunising if one wants to keep this antigen at a low level. In other words, this is only a temporary effect and particularly in the presence of advanced disease, the antigen will return. <*Next chart*> Now the next chart, if I can, shows a combination of things that may happen. The first is that you can measure both antigen and antibody in the circulation, and if one looks at the situation of circulation antigen, this is this inhibitory factor, you will see that in 5 patients immunised with their own irradiated cells, the amount of antigen fell on each occasion. The second thing – the level of antibody – shows that the level of antibody rose. <*To camera*> And we think that this is probably what will be required for successful immunotherapy: the disappearance of excess antigen, which may be blocking lymphocytes, possibly by the creation of more antibody to neutralise that antigen.

So much for what one may measure, what, in fact, is the effect in animals and in human tumours? This next chart shows the work from the same laboratory but done by Dr Parr: the effect of immunising animals that are experimentally injected with

1000 living tumour cells of a particular lymphoma. <*Next chart*> If nothing is done to these animals they all die within 25 days. But if after the living tumour cells have been injected, the animals are then immunised with the irradiated tumour cells and BCG, there are a number who are alive at this point <*indicates 60 days*>, in fact, two thirds of them, and free from disease. <*To camera*> It's very important though to realise that this experiment is purely quantitative, that is to say, if one injects many more living tumour cells, this effect can be abolished. It takes a powerful immune response to deal with even this small number of malignant cells. And I think it is probably for this reason that when immunotherapy was first used in acute leukaemia by George Mathé in Paris that he was successful because he chose the situation, which is shown on this next chart, where immunotherapy was most likely to work.

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<*Next chart*> Now, this particular chart represents the results of treatment of a number of patients with acute leukaemia of childhood. Each of these squares or dots represents a patient. Now, all the patients had been given 2 years of chemotherapy, so they arrive at this point in time already having had very intensive chemotherapy, and they are all in complete remission. That is to say, there is no evidence of leukaemia whatsoever. The patients were then divided into 2 groups. The top group had no further treatment, the bottom group had immunotherapy. The closed areas, the black areas, represent relapses, and the open circles represent continuing remission. The numbers here are the numbers of days from the beginning of immunotherapy. Now, you'll see that all the controls, that is the patients that had no further treatment, relapsed within 130 days. Half the patients on immunotherapy did as well, but the other half had long remissions and some of these patients are still in remission and it is now 3 or 4 years since this particular piece of work was published.

<*To camera*> He had obviously chosen an ideal situation where there was a very small number of residual malignant cells. It is not certain, however, that this is necessarily the best form of treatment at the moment for the acute leukaemia of childhood because recently some very good results have also been obtained using combination chemotherapy together with treatment of the central nervous system to

eradicate the tumour cells. But, undoubtedly, something quite dramatic happened in the Mathé series.

The next chart shows a trial which has been conducted at Bart's and the Royal Marsden attempting to evaluate the role of immunotherapy, this time in the management of acute myelogenous leukaemia of adults. Now, the reason this disease was chosen was because the prognosis is very much worse, and chemotherapy in maintaining remissions is really very disappointing indeed. So we had two specific reasons: first, the treatment we were giving was not particularly effective and, secondly, one would obviously find out in a relatively short period of time whether immunotherapy had anything to offer or not. And the trial was planned in this way.

<*Next chart*> Patients were given courses of chemotherapy and came into complete remission. They were then divided into two groups. One group had chemotherapy 5 days each month like this, and the other group had the same chemotherapy but, in fact, had immunotherapy in addition once a week. <*To camera*> The immunotherapy we used was very similar to the immunotherapy which was used by Mathé, that is to say, we used BCG and irradiated leukaemic cells from other patients. Now, the results of this are shown on the next slide.

<Fairley narrates over slide>

There are two ways in which one can, in fact, assess the value of any treatment with patients who are in remission in acute leukaemia. The first is to measure the duration of the remission and the second is to measure the duration of life. Now, this slide shows that in the group that received chemotherapy only, the median length of first remission – the time for 50% of the patients to relapse – was 26 weeks. And the median life expectancy from achieving the initial remission, 31 weeks. When immunotherapy was added, 51 weeks for the median length of first remission, and 77 for the median life expectancy.

<Fairley to camera>

In other words, the situation had been improved with the duration of each being just over doubled.

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When we come to look at the breakdown of these figures, it is very interesting.

<Fairley narrates over chart>

And the next chart shows in diagrammatic form the relapses of these patients, the black line are the patients treated only with chemotherapy. The white line shows the chemotherapy plus immunotherapy group. Now, the first striking thing is that there is, in fact, no difference between the relapse rate in the first 150 days, but after a 150 days these lines part company very rapidly.

<Fairley to camera>

The probable explanation for this is that if one considers that relapses occur from a small number of residual tumour cells, then obviously the time at which the relapse occurs will depend upon how many tumour cells are left behind. If there are a considerable number then the relapse will occur earlier. We think that the late relapses come from patients who have very few leukaemic cells left in the body, and the early relapses from those who have many. And knowing that the immunological mechanisms are really only capable of dealing with a small number of malignant cells, one would expect, in fact, that the early relapses would not be affected by immunotherapy, whereas the late relapses would. And this, in fact, is what is shown here.

<Fairley narrates briefly over chart and then to camera>

Now, the next slide shows the, the next chart shows the survival of these patients. And this is interesting because right from the very beginning, these lines part

company. I think the reason for this is that if patients have been treated with immunotherapy as well as chemotherapy, it is very much easier to get a second remission and, in fact, they are generally very much fitter than the people that are maintained on chemotherapy alone. Exactly why this should be so, we don't know at the present time.

What these results show is that if you take a malignant disease in which apparently all disease has disappeared and yet you know that relapse is inevitable, that is, the patient is well but has a small number of residual tumour cells, then immunotherapy added to chemotherapy might play a beneficial part in the management of such patients.

And this brings me really to the final point which is: what is the role of immunotherapy today in human malignant disease? I think it's absolutely essential to realise that immunotherapy in no way replaces any of the orthodox medical treatment. In fact, if patients have large amounts of malignant disease, immunotherapy is very unlikely to do anything at all. The standard methods of reducing malignant cell populations to as near zero as possible – that is surgery, radiotherapy and chemotherapy – should be used, and immunotherapy should only be given as an adjunct in an attempt to rid the body of minimal residual disease.

<End credits>