Transplantation Immunity
Uptodate: Immunology, 8
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<**Opening titles**>

< **Brent to camera**>

In this talk I shall describe the mechanisms of graft rejection and the difficulties we still encounter clinically in manipulating the immunological response so as to ensure good graft survival and good graft function.

But I want to start by emphasising that however perfect our present-day methods of immunosuppression may be, organ transplantation is now giving a new lease of life to many hundreds of people the world over.

<**Narrated by Brent over still image of a male patient**>

This young man received a cadaveric kidney transplant at St. Mary's Hospital eleven years ago and he's been living very happily on this ever since.

<**Narrated by Brent over still image of three male patients**>

These three men have lived on a second cadaveric kidney after the failure of their first graft for a number of years. The bearded gentleman in the middle has lived on a combined first and second allograft for a total of ten years.

<**Narrated by Brent over still image of a lymph node**>

This section of a lymph node taken from a young child suffering from De Georges Syndrome, a form of thymic aplasia causing severe deficiencies in the cell-mediated responses, as in allograft rejection and delayed-type hypersensitivities, shows the very great paucity of small lymphocytes in the so-called thymus-dependent areas or periportal areas as they are sometimes called.

<**Narrated by Brent over a further still image of a lymph node**>

Another biopsy is shown here taken about three weeks after the implantation into this young patient of a foetal thymus gland which was well-matched for HLA antigens. Now you will see that the thymus-dependent areas look much more normal and have a very much greater number of small lymphocytes. The child became responsive soon after thymus implantation through skin testing with several kinds of antigens which provoke delayed-type hypersensitivity responses and the child's lymphocytes too became reactive to stimulation with phytohaemaglutinin in vitro.

<**Narrated by Brent to camera**>

Here then we have some dramatic examples of conspicuous successes in the field of transplantation. What I want to do now is to explain why we continue to have failures and what might be done in the future to improve the situation. Perhaps the best way of showing you the fundamental nature of the response to allografts is to illustrate the allograft reaction in a few species including man.

<**Table**>

Allograft/Allogeneic Graft:

Donor & recipient belong to the same species

Xenograft/Xenogeneic Graft:
Donor & recipient belong to different species

Autograft:
Donor and recipient identical

<**Brent narrates over above table**>

Allografts incidentally are defined as tissues or organs transplanted to another individual belonging to the same species whereas xenografts are inter-specific transplants, transplanted from a donor of one species to a recipient belonging to a different species. And autografts are of course transplants in which tissues are taken from one part of the body of an individual and simply transplanted to another part of that same individual and as such they do not raise any immunological problems.

<**Brent narrates over a still image of transplanted tissue**>

Here then we have an example of a human skin allograft five days after transplantation and you will see at this stage that the skin graft is clearly surviving, clearly viable. The picture however is very different ten days after transplantation when the typical scar formation occurs – the graft is now dark black and necrotic and if sectioned would show a very considerable infiltration of the dermis by small lymphocytes.

<**Brent narrates over a further still image of transplanted tissue**>

In the rabbit, the situation is very analogous. Here we have two kinds of grafts: autografts taken from the rabbit's own ears and allografts taken from the ear of a genetically different donor. And they are shown six days after transplantation at a time when you can see very little difference between the autografts and the allografts. In other words, in tissue transplantation we have a latent period in exactly

the same way as in other immunological responses. A latent period in which the host's responses are mobilised, in which lymphocytes begin to infiltrate the tissue and in which the immunological response comes about.

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<**Brent narrates over a further still image of transplanted tissue**>

Ten days after transplantation of these skin allografts the situation is quite different. You can now see that the autografts are surviving quite healthily and are beginning to send a sheet of epithelium over the granulation tissue of the wound whereas the allografts are totally necrotic and are about to be scabbed off.

<**Brent narrates over two further still images of transplanted tissue**>

In the mouse, a very similar process – a skin allograft eleven days after transplantation shows total necrosis of the epithelium and scar formation. And finally in the chicken we have a situation again in which a Rhode Island red skin graft to your left has been fully rejected by a White Label [?] recipient within eight days of transplantation, whereas to your right you may not be able to see an autograft taken from one side of the host and transplanted to the other side and is now almost invisible because it has merged into the surrounding host skin.

<**Brent to camera**>

Now what I have just said about skin allografts is essentially true about organ allografts such as kidneys.

<**Brent narrates over a still image of human kidney**>

This photomicrograph here shows a human kidney, a section taken from a human renal allograft during the process of acute rejection in which the tissue is infiltrated by

very large numbers of small lymphocytes which are in this case the main agent of tissue destruction.

<**Brent to camera**>

Similar allograft responses have been observed in goldfish for example where you can transplant one scale at a time to recipient animals and you can also show, very nicely, that the allograft response is temperature dependent and has been shown to exist in the most lowly of vertebrate species. In other words, we are dealing here with an extraordinarily basic response which has its origin way back in evolutionary history.

<**Brent, seated, points to a diagrammatic chart to his left with an indication stick**>

This chart gives you some indication of how this primitive response has been evolved over millions of years.

<**Brent narrates over above diagrammatic chart, uses indication stick**>

You can see that the more recently evolved species such as the birds and the mammals and the reptiles and, indeed, even the amphibia which go further back already show this capacity to reject tissue grafts very acutely. Further back in evolutionary history on the whole the more primitive species can indeed recognise foreign allografts but their responses are very incomplete and you get a type of chronic rejection in these species, in these groups of animals. Though here in the holostei there is a capacity to completely reject skin allografts though rather more slowly than in the more advanced and the more recently evolved groups.

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<**Brent to camera**>

What do we know about the antigens that incite this kind of response? What are they? Where do they occur? And how are they inherited? Well, the antigens are thought to be glycoproteins, proteins with carbohydrate moyetes in which the amino acid sequence largely determines the antigenic specificity. They are present on the internal as well as the external membranes of nearly all tissue cells with the exception in man of red cells which of course carry their own special blood group substances, their own special cellular antigens. In other words the histocompatibility or transplantation antigens are quite distinct from the blood groups and certainly under quite separate genetic control, at least in man.

So each individual has a set of transplantation antigens and these are represented in most tissues to a greater or lesser extent in the body of one individual. But this does not mean that some tissues may not have antigens that are peculiar to them and to them only and which are absent in other tissues. Such tissue-specific antigens may occur for example in the glomerular basement membrane, they may occur in some lymphocytes for example in the thymus derived T-lymphocytes which have the theta antigen and they may occur in some strains in the skin epithelial cells.

Because the transplantation antigens are present in virtually all tissues of the body, we can of course use blood leukocytes for typing individuals for the presence or absence of tissue antigens and this happens to be a very fortunate possibility. We don't, in other words, have to biopsy the organ concerned for tissue typing.

We can now distinguish between two kinds of transplantation antigens: those which can be shown to be responsible for eliciting the formation of antibodies, the so-called serologically defined or SD antigens, and those which fail to do so and which instead cause lymphocytes to be triggered off into blast cell formation. These lymphocytes we call lymphocyte-defined or LD antigens.

<**Brent, seated, shows a further diagrammatic chart**>

Now, what happens when lymphocytes come across lymphocyte-defined, or LD, antigens?

<**Brent narrates over above diagrammatic chart, uses indication stick**>

This chart indicates what happens in tissue culture, in vitro, and represents a situation where we more or less re-enact the allograft response in vitro. We take normal CBA mice and take their prepare lymph node cell suspensions from them and we culture these cells, these CBA cells, in the presence of genetically different lymphocytes carrying foreign histocompatibility antigens; in this case the antigens are those of the A-strain and in order to make sure that we get a one-way response system we have made sure that the target cells are hybrid cells and not pure parental strain cells. So we culture these normal CBA cells in the presence of target cells carrying foreign antigens and five days later we observe that a number of these small lymphocytes have now transformed into much bigger cells, called blast cells, which in turn have the capacity to divide and to form more small lymphocytes carrying the appropriate receptors for recognising the foreign A-strain antigens. And this is essentially the way in which small lymphocytes can transform themselves into killer cells, capable of destroying the target cell.

<**Brent narrates over a still image of tissue culture**>

This is what they look like in tissue culture and in real life. You can see, above, a small lymphocyte which has not transformed and below you can see two blast cells which have arisen by transformation of two individual, small lymphocytes.

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<**Brent to camera**>

Now, the genetic loci or genes that code for these antigens are present in a fairly large region of a chromosome pair and this region is known as the major histocompatibility complex.

<**Brent, seated, shows a further diagrammatic chart**>

This rather complex chart gives you some idea of the tremendous complexity of these major histocompatibility regions.

<**Brent narrates over above diagrammatic chart, uses indication stick**>

Let us look at the top part first which applies to the H-2 region of the mouse – the H-2 region being the major histocompatibility complex of the mouse. And here we can distinguish between a number of genetic loci spread out along the backbone of the chromosome. At one end we have the H-2K locus; at the extreme end we have the H-2D locus. And both of these code for antigens which are, in fact, serologically defined antigens; antigens which will provoke the formation of antibodies when cells or tissues containing these antigens are introduced into the body of an animal which does not have those antigens.

Now, in between are a number of other loci. Here we have the immune-response loci and we have the Ss locus which controls the expression of a serum protein – they are useful markers although they may not have anything to do with allograft rejection. But more important, here, we have the locus LD-1 locus and perhaps here we have the LD-2 locus which control the expression of LD, of lymphocyte-defined antigens.

Now, let us look at the lower part of this chart which tells us the story for man and the locus here is known as the HL-A locus. Again we have two loci called Four (for historical reasons entirely) and LA, and these control the expression of serologically-defined antigenesis. And here we have two loci again – the LD-1 and the LD-2 which are thought to control the expression of lymphocyte-defined antigens which control the formation of small lymphocytes into large blast cells and which are therefore responsible for the initiation of the immunological response.

<**Brent to camera**>

At present we know very much more about the SD antigens than about the LD antigens as they are very much easier to identify thanks to the presence of these self-revealing antibodies. They occur, as I have already indicated, in two series, each controlled by an allyl operating at the SD-1 or the SD-2 locus.

Now, so far as the SD antigens, the serologically-defined antigens, are concerned, as each allyl codes for a single antigen in man and as each individual inherits one chromosome from each parent, the total number of HLA antigens which any individual may possess amounts to four.

<**Brent narrates over diagrammatic chart, uses indication stick**>

Thus the two parents indicated in this diagram here may have these four antigens in one case and these four in the other – see there's a question mark here which indicates this individual must have an antigen which has not yet been revealed by serological methods, which we know nothing about.

Now, if these two individuals produce off-spring, the off-spring may inherit blocks of these antigens from each parent. And here you get some idea of the combinations and permutations in which these antigens may occur in individual off-spring. You can see that there are four distinct possibilities here. This is of course within a family. In cadaveric transplantation, when typing randomly sorted populations, the situation is much more complex and that any number of variations may occur in the individuals that you are trying to type. And therefore the chances of finding two random individuals containing the same HLA antigens are very small indeed.

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<**Brent narrates over a further diagrammatic chart, uses indication stick**>

Now, here we are trying to explain by complete and incomplete matching. Let us take these individuals as potential organ donors and this individual as the potential recipient. Clearly we have a complete match here because the donor does not contain antigens which are absent in the recipient here, so the recipient has nothing to respond to in the donor's tissue. Taking the other extreme, here we have a complete mismatch in that all the donor's antigens are different from those of the recipient and you would expect a fairly swift immunological response by this recipient against this donor's graft. And in between we have these two possibilities here of a partial match where in each case the donor has two antigens which are not present in the recipient and where you might expect a sort of in between situation between complete and incomplete mismatching.

<**Brent to camera**>

The function of SD and LD antigens is only now becoming clearer; it rather looks as if the LD antigens are necessary for initiating the early recognition response which all lymphocytes have to undergo before they can turn themselves into killer cells and the SD antigens are almost certainly necessary for the killer cells to have something to latch onto, for the receptors of the killer cells to get to grips with on the target cells and therefore for killer cells to be fully cytotoxic to target cells, the presence of SD antigens on the target cells seems to be essential.

There has been an enormous amount of debate as to the efficacy of HLA typing in clinical kidney transplantation. Some workers have failed to find a significant correlation between good matches and good kidney graft survival so far as cadaveric kidneys are concerned. And other workers have failed to find such correlation.

<**Brent narrates over diagrammatic chart, uses indication stick**>

These curves indicate here that at least in this particular group of patients, typed by the London Hospital Medical College, there is indeed some reasonable correlation between complete mismatching and rather poor kidney function and kidney survival

and complete matching indicating much better take of kidneys. And where you have two or three mismatches, the situation seems to be, as one would hope to find it, in between these two extremes. But, as I say, not all workers have made such observations and there are still some discussions about it.

<**Brent to camera**>

Be this as it may, there is no doubt among tissue typers that HLA typing in families where you transplant a parental graft to a child or where you transplant a sibling graft to a sibling, their HLA typing is of the utmost significance, and really well matched HLA matched grafts do very much better in terms of survival and function than grafts which have not been so well matched.

It may of course well turn out that in future we have to type for both SD and LD antigens and this is something which is only just beginning to be done. The other possible explanation as to why cadaveric HLA typing has been, on the whole, somewhat disappointing may lie in the fact that there are almost certainly other genetic loci which we know nothing about at the present time and which we may yet have to get to grips with.

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Well, there are some tissues which fortunately are exempted from the laws of allograft transplantation and the cornea is one of these.

<**Brent narrates over a still image of an eye**>

In the case of the cornea we have a situation where the corneal graft survives on the surface of the eye without being vascularised and without developing lymphatic drainage and this confers protection on the cornea - the cornea has no opportunity of sensitising the host and therefore the host does not mount an immunological response against the foreign histocompatibility antigens which are undoubtedly present on the corneal tissue. In this case we have a cornea transplanted to a

genetically quite different host and not only is this an allograft but the cornea was stored for about six months at low temperatures, indicating the storage of corneal tissue is perfectly feasible.

<Brent to camera>

I now want to say a few words about the mechanism of graft rejection. But before I do I want to remind you of the two ways in which an immunological response to antigens may come about.

<**Brent narrates over diagrammatic chart, uses indication stick**>

You will probably remember from one of the earlier talks in this series that the cells from which the immunologically competent lymphocytes, whether they are T or B lymphocytes, are derived stem cells from the bone marrow. And cells from the bone marrow go either via the thymus gland to be influenced there into becoming fully-fledged T lymphocytes which are then capable of forming blast cells which in turn are then capable of forming sensitised lymphocytes. Alternatively they may go via the bursa and become B lymphocytes which can differentiate into plasma cells which in turn can make antibody. The antibody can be detected and measured in the circulation.

Now, in mammals, as you will remember, there is no analogue to the bursa, we don't know at the moment what the analogue is or indeed if there is one. It may be that the bone marrow itself may be the analogue. These are the two arms of the immunological response and both can operate in the responsiveness to allografts.

< **Brent to camera** >

I have already said that in acute rejection, infiltration of the graft with small lymphocytes is a highly significant feature. In such cases graft rejection is largely, if not exclusively, brought about by the direct action of these thymus-dependent

lymphocytes. That T cells play a role, an important role, can be shown experimentally in a number of ways.

<**Brent narrates over diagrammatic chart, uses indication stick**>

For example, we can show that if we sensitise a recipient mouse with skin, with a skin graft from a donor strain, and we harvest the serum from this sensitised animal after rejection of the skin allograft and equally we harvest the lymph node cells, we can now transfer the cells into normal CBA mice or the serum into normal CBA mice and a few days later place on these animals skin grafts from the original donor strain. With serum the skin grafts are rejected in normal fashion, indicating that antibodies in the serum did not bring about the accelerated rejection or second set rejection of the skin graft. But the lymph node cells have had a quite dramatic effect in that they have conferred on this animal a kind of sensitivity by proxy and the skin graft is rejected much more quickly than would be expected in normal animals.

So this experiment tells us that lymph node cells and we can go further than this and say that thymus-derived lymph node cells have the ability to transfer sensitivity from a sensitised mouse to a normal mouse. Whereas serum from a sensitised mouse does not have this particular problem.

<**Brent narrates over a further diagrammatic chart, uses indication stick**>

Or we can illustrate the same point by showing that T cells from normal animals can respond in a graft who has its host's assay system. Now here we have a normal CBA mouse from which lymph node cells or indeed spleen cells have been prepared. These cells are injected in the form of a single-cell suspension into a number of newborn, hybrid litter mates; hybrid between the donor strain and the recipient strain; AxCBA hybrids in this case.

Now, these CBA cells can recognise the foreign antigens, the foreign A strain antigens in the host and they will respond to them and this response can be measured in a number of ways, one of which is to examine and weigh the spleens of

these animals eight days later and one will find that the spleen is very much enlarged compared with the controls of this side which has litter mates injected with hybrid cells which are, of course, immunologically non-reactive to the A strain antigens.

So these are our controls and we find that this reactivity of the CBA lymph node cells to host antigens is the direct consequence of the activity of the transferred cells and this is a kind of allograft rejection in reverse if you like and is known as a graft-versus-host reaction.

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<**Brent narrates over a still image of two mice**>

Now, in very special circumstances where one uses strains of mice which are genetically very different at the H2 locus, this graft-versus-host reaction can take a very dramatic form. Here we have two litter mates, one of which was injected at birth with foreign spleen cells given intravenously. The other litter mate, the large mouse, was not injected and as you can see, the presence of these foreign cells in the newborn mouse and the developing mouse, has prevented this mouse from developing normally, has interfered with the maturation of the various organ systems with the growth pattern of the mouse and in this particular case it will lead to the death of this recipient.

<**Brent to camera**>

There can, nevertheless be no doubt at all that antibodies found in the serum can play a very critical role in transplantation and I think this is most vividly illustrated in the example of hyper-acute rejection, a form of rapid rejection which occurs immediately after transplantation when patients have, due to previous blood transfusions, pre-formed antibodies against the donor's HLA antigens. This used to happen, it doesn't happen any more because nowadays one is very careful to

exclude such donors as transplant donors. But certainly this is a very vivid example of serum antibodies mediating very rapid rejection in the absence of lymphocytes.

We can also illustrate this interaction of alloantigens in immunosuppressed patients.

<**Brent narrates over still image of artery**>

This is a photomicrograph of a small artery in the allografted kidney of a patient who received a cadaveric kidney at St Mary's Hospital. This patient had managed to get along very nicely with this kidney for several years. But you will see this artery looks anything but normal and that there is a very marked thickening of the arterial wall, of the integral membranes, and there is a great deal of fibrous and platelet aggregation on its interior surfaces. And this artery will soon be totally non-patent. So these changes can certainly be demonstrated to be due to humeral antibody and not due to lymphocytes.

<**Brent narrates over a further still image**>

And this is shown perhaps even more clearly in this picture, again a micrograph of a small field of an allografted kidney, many months after transplantation, and this section has been stained with antibody directed at the third component of complement which is the component which is fixed in antigen / antibody complexes. You can see that the fluorescence here indicates the aggregation of C-Prime 3 in the glomerulus as well as in the small artery here and from this we can deduce that antigen-antibody complexes have been localised both in the glomerulus and in the arterioles. So here again we have an example of the reaction of humeral antibodies to the detriment of the graft.

<**Brent to camera**>

I showed you at the beginning of my talk a few of the success stories of renal transplantation. What are the overall figures?

<**Brent narrates over diagrammatic chart, uses indication stick**>

Here we have a series of curves where the percentage of surviving grafts, renal grafts, are plotted against the number of years and months after transplantation. We have three groups of recipients: those who received sibling grafts, those who received parental grafts and a third group receiving cadaveric kidneys. And it is quite clear that the sibling grafts do best and have a high degree, more than 80% survival at about two years, the parental grafts do next best and the cadaver grafts do worst of all.

The other general conclusion we can draw from these figures is that we seem to be reaching a kind of plateau here where the results do not appear to be improving very dramatically. The continuous lines refer to grafts transplanted in 1968 and plotted over a four-year period. The interrupted lines refer to grafts transplanted in 1970 and followed-up for a two-year period but you can see that there is no very highly significant difference between grafts transplanted in 1968 and 1970. And from this I think it is reasonable to conclude that, short of some new method which is going to change the course of transplantation very dramatically, we cannot hope to see any dramatic improvement in the results in the future.

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<**Brent to camera**>

Of course present day kidney transplantation is brought about by treating the patient with very high doses of immunosuppressant drugs and these drugs are, in the main, Imuran or Azathioprine which is an alkylating agent interfering with DNA synthesis and Prednisone, a corticosteroid hormone which has an anti-lymphatic effect and which is also anti-inflammatory and these drugs are very highly toxic and have to be used very carefully in exactly the right amounts. If one gives too much of the drug, one can kill the patient very easily. If one gives too little then the kidney may escape and the immunosuppressive properties of the drugs may not be adequate to protect it.

In addition there are some very distinct snags about these drugs as the next three slides will indicate.

<**Brent narrates over a still image of a female patient**>

Here we have a kidney recipient who was treated with Imuran and Prednisone in the usual way and who shows the distinct symptoms of Cushingoid Syndrome which is certainly an unpleasant symptom for the patient to have and to have, also, all kinds of other side effects.

<**Brent narrates over a still image of a pelvic x-ray**>

In addition patients on very strong corticosteroids very often develop this osteoporosis of the long bones which is very clearly visible in the condyles.

<**Brent narrates over a still image of a tongue**>

And finally, we have the problem of all kinds of infections which may plague the patient because his immunological system is generally immunosuppressed and therefore much less able to defend itself against bacterial infections and certainly fungal infections such as candidiasis. This patient has a very unpleasant oral infection of candidiasis which it was possible to control but which can be very troublesome and very unpleasant to the patient.

<**Brent to camera**>

For this reason, because of the problems which immunosuppressive drugs involve, it looks to me as if some new approach will eventually have to be tried and manned and that we must aim at the reduction of some kind of specific unresponsiveness, an unresponsiveness which extends to the donor antigens only but which leaves the patient free to react normally to bacterial, viral or fungal pathogens.

<**Brent narrates over diagrammatic chart, uses indication stick**>

Now there are various ways in which we can interfere with the immunological response and before I mention any of them I would like to indicate to you how one can interfere in theory at any rate and how one can manipulate the immunological response.

Here we have the graft, whatever it is, whether it's a kidney or a skin graft doesn't matter. Here we have the lymphoid organs represented symbolically, representing the spleen, the lymph nodes, the bone marrow and various other lymphoid tissues in the body. The graft of course has to sensitise the lymphoid cells and this can be done by antigen going to the immunologically competent cells via the regional lymph node, via the afferent lymphatics or possibly antigens can be picked up by lymphocytes in the graft, lymphocytes which traverse the graft via the blood stream and pick up antigen there.

So antigen has to get to the lymphoid cells, to the lymphocytes and the lymphocytes, having undergone their transformation and division, have to get back to the graft in order to cause the damage which they are known to cause. This part of the circuit is known as the afferent circuit, this part here is known as the central circuit and this is known as the efferent circuit. And we can block this in various ways either here or here or here.

One way of doing this is to prevent antigen from reaching the lymphocytes, another way would be to prevent the lymphocytes from reaching the graft, or one can produced a central block in the lymphocytes possibly by preventing the early recognition which is essential if an immunological response against alloantigens is to take place.

<**Brent to camera**>

The first phenomenon which I want to mention is immunological intolerance and this consists of the injection of viable cells, they are usually lymphoid cells merely for

convenience, into immunologically immature animals, animals which still have very few immunologically competent cells which are themselves unable to respond immunologically at the time of injection. This is the case, for example, in foetal rodents or very often in neo-natal rodents which are very poorly developed immunologically when they are born.

<**Brent narrates over still image of white mouse**>

This causes a very profound change in the development of the immunological response in these injected animals. Here we have an A-strain mouse which was injected at birth with five million hybrid CBA spleen cells. These were accepted by the animal and the animal has, in fact, become immunologically tolerant, totally unresponsive and is now unable to recognise the foreignness of the CBA donor-strain alloantigens.

<**Brent to camera**>

This phenomenon is very highly specific, it applies only to the CBA alloantigens injected. It doesn't apply to any other antigens and certainly not to bacterial or fungal antigens.

So we have here a situation which seems in many ways ideal from a clinical point of view. Unfortunately the induction of this phenomenon has been exceedingly elusive and most models of the induction of specific-unresponsiveness in adult animals have turned out to be rather different in their mechanisms, they have been due to the production of antibodies, of antigen-antibody complexes rather than due to the lack of the development of responsiveness and the complete absence of immunological response.

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Another phenomenon which is probably much more easily applicable to man, at least in theory, is that of immunological enhancement.

<**Brent narrates over diagrammatic chart, uses indication stick**>

The word enhancement was used originally because it was done on tumour grafts and it was found that alloantibodies could be used to protect tumours against the immunological response of the host and therefore to enhance tumour growth, hence the name enhancement.

But in recent years, the work of a number of people including Batchelor and French in East Grinstead has shown that this model can be applied to allotransplantation of the kidney in the rat. This is the system that French and Batchelor use in their experiments. They had an SA rat inbred recipient and this rat was grafted with an August SA F1-hybrid kidney graft. In the first week after transplantation, this recipient received a number of injections of antibodies, of anti-serum containing antibodies directed against the specificities of the donor, that is against August alloantigens.

Now, to think that this should protect the kidney is really quite paradoxical is it not, because normally antibodies are cytotoxic to grafts and can be expected to cause damage. But in this situation we have quite a different result.

<**Brent narrates over a further diagrammatic chart, uses indication stick**>

This curve here indicates the survival of these hybrid kidney grafts in rats pre-treated or treated in the first week with alloantibodies directed against graft antigens. This is the number of animals alive and the animals had their own kidneys removed so they were entirely dependent on the transplanted kidney for their survival, against the number of days after transplantation. You can see that there is virtually total survival, indefinite survival with these hybrid kidneys. If parental kidneys were transplanted, that is August kidneys to the same kinds of recipients the results were much less dramatic and much less satisfactory compared with the controls which rejected their kidneys very quickly in the absence of passively-controlled injected alloantibodies.

<**Brent to camera**>

So, here we have a situation in which alloantibodies of a special kind can be protective to the graft and they can be protective in two different ways. Firstly they probably protect the graft by coating the graft cells with alloantibody, by giving them a coating as it were of protein which the lymphocytes of the same host will not recognise as foreign and they would therefore interfere with the recognition of the lymphocytes of these alloantigens.

<**Brent refers back to previous diagrammatic chart**>

But later on at this late stage here when there seems to be a fairly stable kind of unresponsiveness it can be shown that this is due to the production of enhancing antibodies by the hosts themselves – and what is almost certainly happening here is that these antibodies complex with antigen-release from the kidney and that these antigen-antibody complexes interact with the surface of receptors on thymus-dependent lymphocytes and so prevent these lymphocytes from undergoing the usual early-recognition events which they would have to go through if they were to respond.

<**Brent to camera**>

Well, I hope to have shown that we have come a remarkably long way from the days not so long ago when allotransplantation seemed virtually impossible. But nevertheless it is also equally clear, I think, that we still have a lot of work to do before we can make clinical organ transplantation the safe, reliable procedure that we would like it to be.

<**End credits**>