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Discussion

Dr. Watts R. Webb (Dallas): I think Dr. Williams and his coworkers have presented some very important studies. Histocompatibility, however, is far from the total answer in the rejection phenomenon and just as important is the presence of preformed antibodies directed specifically against the organ that is being transplanted.

We have had two patients with heart transplants that have undergone hyperacute rejection and [slide] with immunofluorescent technics. The papillary muscle when stained with antiglobulin, as you see, takes on the green fluorescent stain indicating gamma globulin is deposited there.

[Slide] The next slide shows a similar response when the papillary muscle is stained with beta I complement. Complement is utilized in this re-

action indicating that it is truly an antigen-antibody reaction.

[Slide] The next slide shows the precipitation of the fibrin along the capillaries, again indicating the hallmark of the Schwartzman reaction on the hyperacute rejection.

[Slide] And the final slide shows the precipitation of gamma globulin in the immunocytes which are present within the heart itself.

Now this is not dependent at all on histocompatibility. This is dependent on the preformed circulating antibodies to the heart itself.

Drs. Hess and Ziff at The University of Texas Southwestern Medical School at Dallas some years ago demonstrated that in at least two-thirds of the patients who have acute rheumatic myocarditis, and about one-third of patients with myocardial infarctions—one can demonstrate circulating antibodies to the heart itself.

Preformed antibodies are not demonstrable by histocompatibility technics such as cross-matching the lymphocytes but can be picked up only by checking the reaction of the serum of the potential recipient against normal heart tissue.

Since this hyperacute reaction with preformed antibodies is very poorly controlled, if at all, by immunosuppression, it is most important that this be detected prior to a graft. For this we perform not only routine histocompatibility studies, but we believe that it is very important that the circulating antibodies against the heart or against the kidney be specifically looked for in the recipient prior to the time of the transplant.

DR. LLOYD MACLEAN (Montreal): Over the past 3 years in a clinical, renal transplant program we have routinely done the crossmatch; that is, matching recipient serum against specific donor cells and have not done the transplant if this was positive in about 80 patients, even though in one patient this required screening almost 200 possible donors and other staff people.

We have not encountered hyperacute rejection or accelerated rejection or immediate rejection as it is sometimes called over this 3-year period. This is in marked contrast to our experience prior to this time which is illustrated on this slide.

[Slide] About the time we became aware of this problem, there were three patients in whom we clearly demonstrated acute rejection by finding the antibody against the donor, but going ahead with the transplant and having the patient reject on the table or within 24 hours and then finding acute fibrinoid necrosis in the graft after after it had been removed.

These three patients are marked with an asterisk.

I am sure we had it in others because the commonest way to become sensitized is through pregnancy. We should look at the patients we have done up until that time, 3 years ago, and if this was a factor, we should expect a difference in propensity to rejection in pregnant women as compared to nulliparous women or men. This, in fact, was the case as illustrated on the rest of this slide. You see at the top 11 nulliparous women. They had a low rejection rate in the first three months in 82 per cent of the cases and males, 22 in number at that time, also had the same low rejection index.

In the pregnant females, of those who had had one to six children, there was a low rejection index in only one-third. This has been changed in the last three years so that pregnant women have the same outlook as men or nulliparous women.

I would like to ask the authors two questions; One: Could they comment on how important the rare red cell antigens might be? Those are the antigens outside the ABO system. We became worried about that recently.

And the second question: Would there be any rationale to leaving in the patient's own kidneys, when feasible, to mop up circulating anti-kidney antibodies in contrast to the ones detected on the lymphotoxic cross-hatch and thereby project the graft? I ask this because we have been rather dilatory about removing the patient's own kidneys unless the patient had pyelonephritis or a kidney with a tumor or some reason where one just must remove both kidneys, and actually, we have had only one patient out of about 130 transplants in whom we have demonstrated development of glomerulonephritis in the patient.

DR. FRANCIS D. MOORE (Boston): I would like to congratulate Dr. Williams and Dr. Hume and their group on their, as usual, very sophisticated and beautiful study. I am not competent to discuss the question of whether or not there are antigens on kidney cells that are not shared by lymphocytes.

I would like to make just two points. The first is that increasing sophistication in immunology and donor-recipient matching sharply limits the number of acceptable donors.

In the case of the kidney, this is not too severe a problem because of recipient maintenance by dialysis. In Boston, for example, in the Boston Interhospital Organ Bank (organized by Dr. Murray, Dr. Russell and Dr. Barnes) a large panel of potential recipients is maintained so that when a donor comes along, we can match him up with the best recipient out of a panel of 20 to 40 individuals.

In many cases we have had a cadaver in whom one kidney was used in one hospital and the other in another.

This is going to be very difficult for the heart on any such local basis.

As regards the liver, there is now a list of waiting recipients throughout the country and it is a big list, waiting for proper donors. Even as recently as a year ago, a number of donors might

have been used that we now avoid because of a poor Terasaki match or the presence of preformed antibodies many recipients die while awaiting donors. So we are in a fix because we are getting so much better at matching that the availability of acceptable donors is very sharply restricted.

My second point is that the solution to this problem is a classic logistic organization and bioengineering endeavor. It must be a regional or national matching procurement and transportation system.

One such has been set up in Europe under Van Rood that Professor Woodruff may tell us something about. He must be able to ship these organs around the country in an adequate state of preservation. Then, when there is a proper donor the appropriate recipient can be found, even if he is a couple of thousand miles away, and the organ put to good use.

SIR MICHAEL WOODRUFF (Edinburgh): May I take the opportunity of saying how much I value the opportunity of being an Honorary Member of this Association, and may I also say, sir, how delighted your very many friends and admirers in Britain, of whom there are a very large number, were when you were elected president of this Association.

I think Dr. Williams and his colleagues have directed attention to a most important phenomenon which, indeed, threatens to put kidney transplanters out of business.

Dr. MacLean said that the commonest cause of sensitization is pregnancy. In our experience the commonest cause of sensitization as judged by an unsatisfactory direct, cross-matching test in the context of renal transplantation is long-continued, preceding hemodialysis. I think the important lesson to be learned from this is that we have got to get away from thinking or letting our colleagues think that the initial treatment of somebody with irreversible renal failure is to go on dialyzing them either until they run out of shunt sites or get tired of being machine dependent.

We still get many patients referred to us under these circumstances who have been dialyzed for a year or more.

I should suggest that renal transplantation should be used very much earlier and then I think the number of patients who come along with preformed antibodies will be very much smaller.

Dr. Moore mentioned an organization known on the other side of the Atlantic as Eurotransplant. We, in Britain, are not in this because it has been run essentially by Common Market Countries. We are, however, very interested in this organization and I think it is of great importance.

Many of the countries of Western Europe have joined together under the leadership of Dr. Van Rood of Holland, and they have a pool, I think, of between 200 and 300 renal transplant recipients. Cadaver organs are sent not only from one city to another but from one country to another, if this is necessary to achieve good matching.

Similar developments are occurring in the U. S. A. Thus when I was visiting Cleveland recently, two kidneys arrived from Ann Arbor by helicopter and were duly transplanted. This is certainly important, but the main thing I got up to emphasize—and I would be very interested to know—if Dr. Williams and Dr. Hume agree about this, is the desirability of early transplantation in the patient with renal failure.

DR. EDWARD B. STINSON (Palo Alto): Upon initial evaluation of the relationship between apparent histocompatibility and clinical outcome, there is no clear correlation with early survival, number of rejection episodes, or myocardian function.

In contrast, many other factors at this point seem to have determined the outcome in most of the cases; in particular, factors such as preoperative pulmonary hypertension in the recipient can seriously affect graft function both immediately and in a delayed fashion. The complication of irreversible pulmonary hypertension causing immediate graft failure has been reported for clinical heart transplantation.

In addition, following operation, the continuing effects of pulmonary hypertension can be observed in the evolution of right ventricular hypertrophy.

It is, I think, impossible at this time to either quantify or discount the importance of pre-existing, specific anti-heart antibodies in cardiac recipients.

DR. OWEN H. WANGENSTEEN (Minneapolis): I am certain we will all want to hear from Dr. Hume. Before he comes to the platform, may I say as a frank amateur, I am interested in the tissue transplantation program.

All transplanters should have for bedside reading the interesting monograph now available in English by Elie Metchnikoff on Comparative Studies on Inflammation. It has a lot of extraordinarily interesting data in it. Elie Metchnikoff wrote this, mind you, in 1891, but it has pertinence for the present scene.

DR. DAVID HUME (Richmond): I think perhaps one point might be clarified, that there seems to be a confusion between GBM antibodies; that is, antibodies directed against a specific antigen in kidneys only, and antitransplant antibodies which are directed against histocompatibility antigens which are represented on the kidney as well as the heart and other tissues. I think, therefore, the point needs to be clarified about whether or not taking out the kidney will help to either un-

mask the antibodies or perhaps would take away the organ which is absorbing the antibodies.

Now as far as anti GBM antibodies are concerned, taking the kidney out certainly makes the titer in anti GBM antibodies go up, and it does unmask such antibodies, and the kidneys which are in place do absorb these antibodies.

However, it is also true that these kidneys which are in place contain the antigen, that is the basement membrane which induces the formation of such antibodies, and we found that whether you take the kidneys out or whether you leave the kidneys in, doesn't seem to have any influence on the development of nephritis in the transplanted kidney.

Of course, taking the kidneys out doesn't have anything to do with the antibodies that Dr. Williams is talking about which are antihistocompatibility antibodies.

These are directed against the antigens of the donor and have nothing to do with the donors of the kidneys or heart of the recipient at all because they are entirely different antigens, and I think he may clarify this point more, but there is a point about which there seems to be some confusion in the discussion.

DR. G. M. WILLIAMS (Closing): I believe one slide should clarify the issues of what antigens we are talking about when we find reactions against kidney cells and not against lymphocytes, so if I could have that slide, please.

Dr. dePlanque in our laboratory typed kidney cells and lymphocytes from 14 individuals using monospecific standard typing sera obtained from the NIH.

What he was measuring was the ability of these two cells to respond to known antibodies in the typing sera.

In these 14 patients in which you could compare the reactivity of lymphocytes and kidney cells, there were 234 individual comparisons that could be made. We found that the kidney cells reacted positively while the lymphocytes reacted negatively on 57 occasions.

Conversely, the kidney cells reacted negatively, the lymphocytes positively on 25 occasions.

Two antigen groups appeared to react much more often to kidney cells than to lymphocytes from the same individual. These are HLA3 and HLA7.

Lymphocytes apparently reacted more often with antigen group 4B.

Absorption experiments were carried out with the negatively reacting cell of the individual to determine if that cell lacked the antigen or simply had it represented in a poor concentration. If the antigen were present in a low concentration, then the cell still ought to absorb out activity against the positively reacting cell, and this is what we found. Under circumstances where the kidney reacted negatively, the kidney cells were still able to absorb out all the activity against the lymphocytes of the individual. Lymphocytes absorbed some but never removed all of the activity present against kidney cells. Thus, the kidney cell appears richly endowed with histocompatibility antigens, and when you use this as a target for immunological reactions, you detect things that you simply can't detect using lymphocytotoxicity.

Now leuco-agglutination may detect some of these antigens present on lymphocytes that we don't detect by lymhpocytotoxicity, but as a method for excluding important antibodies prior to transplantation, it doesn't appear to be particularly valid because we have already experienced one case of hyperacute rejection in which the leuko-agglutination cross-match was clearly negative, so that what we need is a really sophisticated technic for excluding ahead of time the existence of preformed immunity. I have a hunch that this plays a great deal more importance in transplantation than we currently realize.

The target cell that should be selected is probably the endothelial cell. This cell, of course, is critical because if this cell is disrupted, the graft simply isn't going to perfuse well. If we could devise a nice, simple method for excluding antibodies to the endothelial cells which will be common in heart and liver and kidney grafts, then I think major improvement in results would follow.

The present stage of transplantation is analogous to giving blood transfusions matched for ABO groups and not cross-matched well. If you are dealing with a population that isn't heavily immunized you are not going to have a significant reaction giving group specific blood. But if you are dealing with a highly immunized population (and every transplant center is going to end up with this) then you have to develop a much more reliable and sensitive means for excluding the presence of preformed immunity.

With regard to some of the other comments, there is absolutely no doubt that the country needs to be organized regionally if the correct organ is to be used in the correct recipient. We have made an attempt at this in the South and are pretty well organized, or will be soon, from Baltimore to Atlanta. We have recently sutured a kidney in place that was removed in Atlanta. Two have been sent from Richmond to Washington. Two have been sent to Durham and so forth. Thus the exchange of kidneys in regions is entirely feasible. The Europeans have led the way in this regard, but it is hoped that we can catch up to them soon.