

DISCUSSION

The CHAIRMAN (Walsh, Dublin): Ladies and Gentlemen, I am sure you have many questions for Dr. Van Rood, but I think we can assure him that we have no idea that increasing immuno-suppression would replace histocompatibility testing because it is the ambition of every surgeon doing transplant work to diminish the amount of the immuno-suppression because this causes all sorts of problems. I will straightaway open this to discussion.

HAMBURGER (Paris): Four short remarks: first, I think the work of Dr. Van Rood as well as that of Dausset is one of the most wonderful achievements of recent years.

Secondly, we now have evidence that in living donors late clinical results, if not early ones, are correlated with leucocyte-typing, but—thirdly—we now have a fair knowledge of the so-called 'chronic rejection' in transplanted kidneys, and we know that this rejection is not uniform in all transplants. There are several possibilities—sometimes it is glomerular lesions, in other cases an arterial rejection, and in others an interstitial one. This, many factors suggest, is probably due to localised antigens and it is difficult to understand how any kind of typing based on one single cell, such as the leucocyte, may predict such local differences, that is, the possibility of local antigenic structure.

Finally, we have recently compared this leucocyte-typing with another fascinating technique: the mixed lymphocyte culture between donor and recipient. We have found an overall correlation between the two types, but, if you take 140 donor/recipient pairs and separate related pairs and unrelated pairs, you find that, with the same leucocyte-typings—e.g. no difference, or one difference of such and such a type—the mixed lymphocyte culture does not give, in the same leucocyte-typing situation, the same results in related vs. unrelated people. The percentage of transformed cells is 50 per cent higher in unrelated than in related people even with the same leucocyte-typing position.

That means that some extra factors exist, some extra antigen exists in unrelated people. There is a possibility that these extra factors in unrelated people will be discovered, one of these days, by leucocyte-typing; there is also a possibility that they will never be detectable by leucocyte-typing because there is no evidence that these extra factors are induced serological factors, circulating antibodies.

Anyhow, I think that we know now that the usefulness of leucocyte-typing is demonstrated for related donors; we do not know if it will be demonstrated for unrelated, cadaver donors, and to know this is a matter of urgency because, at the moment, I do not think that there is any evidence that typing will really be of first-class use in cadaver kidney transplant.

VAN ROOD (Leyden): I quite agree with most of Professor Hamburger's points and I am grateful to him for stressing some very important points which I did not perhaps emphasise enough, in order to avoid making my story more complicated than I thought was absolutely essential.

As to his first main point, the question whether, apart from transplantation antigens which will be present in all tissues, as apparently the HLA antigens are, you also have antigens which are transplantation antigens and present only in one special kind of tissue, the antigens which we call 'tissue-specific iso-antigens'. There are, of course, examples of this; we know of antigens which are only present in the erythrocyte—the Rhesus antigens being probably a good example; we know of antigens which are only present in the granulocytes—we think of the antigens which have been described by Laragari in New York for the granulocyte, A1 and B1, and our 9A—and a similar antigen has been described for the lymphocyte and also the platelets. There is, *a priori*, no reason why the kidney should be an exception.

We have thought about this, and we have also analysed our data taking this into account.

Our first impression is that these antigens are generally speaking not so important if the recipient is not pre-immunised; only where pre-immunisation against these antigens exists do they apparently become quite important. Now, this pre-immunisation could be due to a kidney graft that the patient had received before; it could also be due to a process of auto-immunisation, and I think this is a very important point which certainly warrants further study.

As to the mixed lymphocyte culture test, the second point raised by Prof. Hamburger who pointed out the difference between related and unrelated people, I quite agree with him. However, I would like to emphasise again an extremely important point about identity between sibs and identity between parental types. Professor Hamburger said 'between related people and unrelated people', but I think we must sub-divide this, and make a division between 'related' and 'unrelated' in general, and then between 'sibs' and 'parents' and 'unrelated'. The interesting and important point which is often missed is that parents are more like unrelated people in this respect, however curious that may sound, than related. Let me explain this.

Two children can be identical when they have received the same alleles from the parents, e.g. there could be two children who both have received the A-C alleles from the parents, and these two would be really and truly identical. That is what Professor Hamburger was referring to when speaking about this m.l.c. test. There you will really have instances of no stimulation. What is the situation with the parents? Here you can also have identity but the identity will be slightly different; it will be the two alleles A. Really this is an oversimplification because I should say 'A and A'—they are not really completely identical, but for our serological and kidney-transplantation purposes, they are identical enough. This form of 'identity' is different from the identity in which two children get an A-C allele from the parents, and I think you will find also that in these combinations, if you do enough m.l.c. tests and take account of the number of reacting cells, etc. (work which has been done by Bach in Wisconsin), you will find that these have a significantly lower stimulation than the non-identical pairs.

I quite agree with Professor Hamburger that one would expect to find between unrelated people also very low stimulation; there is some indication that this might be the case, but I quite agree with him that in many of these cases the stimulation is still higher than one would expect if these were the only antigens which were really of importance, and this implies, of course, that we are still looking, that our insight into these antigens is still not complete.

Finally, on the third point that Professor Hamburger was making, the point that we still did not have data to show that leucocyte-grouping can improve kidney-transplant prognosis: I did show the data of the spleen-absorptions from which the conclusion could be drawn that leucocyte-grouping in unrelated people can also improve the prognosis for the graft. I have not seen the data myself, but apparently also a number of centres in the United States have found the same thing, using the typing of Terasaki.

PRECENT (Paris): One simple question: in the case where two sibs had identical groups would you consider stopping drugs at some time in the evolution?

VAN ROOD (Leyden): Not before a lot of experimental work, for instance in dogs, had been done. Actually, the work done on dogs suggests strongly that you could do this. The typing has not been done, but it is interesting that if you stop immuno-suppression in dogs after different periods of time—6–8 weeks—a quarter of the dogs, exactly the percentage you would expect, completely and normally survive.

PRECENT (Paris): But in human cases do you have any way at the present time of finding out if two sibs are exactly identical according to these typings? You say it is suggested that it might be possible in dogs. I was trying to find out whether, using the usual typing that is known now, you can say that one sib is identical to another.

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VAN ROOD (Leyden): I think that if you are able to recognise, say, between 10–15 of the antigens of the HLA system you can make a pretty good guess whether or not two sibs are identical, yes. This has been tested not only in retrospective studies for kidney transplants but also in prospective, both by us and by other people, for skin transplants and also for the correlation with the m.l.c. test.

SEINFELD (Munich): What is the relationship between those circulating tissue-bound antigens and the cell-bound antibodies?

VAN ROOD (Leyden): That is a big question! I confess I do not know the answer, but our guess at the moment is that in general both forms of immunity, cell-bound and circulating, are important; that in the first situation in which the recipient is not pre-immunised, the cell-bound antibody is the more important; while in the second situation, in which the recipient has been immunised, circulating antibodies might cause many of the symptoms we see. I agree that this is a very rough and schematic answer, and I would like to stress again that I do not know the real answer to your question.