# Discussion

*Dr. Strober:* Dr. Rynasiewicz, the data about the lymphocyte reactivity outside of autologous plasma and the diurnal changes in autologous plasma, is that a general finding that other people have reported or have they not looked at it?

*Dr. Rynasiewicz:* Yes. The diurnal variation following an oral dose has been reported during maintenance therapy at least by the Canadian group.

*Dr. Mandel:* Has anybody got any idea about why CsA has marked species differences in effect?

*Dr. Rynasiewicz:* No. Most of you work with the mouse. The mouse is the most resistant strain. CsA works well in the rat, the dog, the monkey, and the pig.

*Dr. Mandel:* Why is the mouse so resistant?

*Dr. Rynasiewicz:* I don't know.

*Dr. Strober:* What about suppressor cells for cyclosporin in the blood of these patients? I'm not talking about the MLR, but about spontaneous suppressors.

*Dr. Rynasiewicz:* We've not found that in our lab. In clinical transplantation I am not familiar with anybody who has reported convincingly that there is a specific or nonspecific suppressor.

*Dr. Strober:* In conventional immunosuppressed patients MLR reactivity being present after taking the cells out of the autologous process would be very unusual.

*Dr. Rynasiewicz:* Right. Such cells usually function abnormally in nonautologous plasma as well.

*Dr. Strober:* Conventionally treated patients have diminished MLR reactivity.

*Dr. Rynasiewicz:* Right.

*Dr. Strober:* The pattern of responsiveness in CsA compared to conventional immunosuppression is very different.

*Dr. Sutherland:* Permanent unresponsiveness does not occur even when CsA is stopped in most models, so the thought that one can induce some organ-specific unresponsiveness with CsA is not correct. Basically CsA is just another general immunosuppresent. It is not the ultimate answer to transplantation, but maybe it is a little better than what we used in the past.

*Dr. Danilovs:* Did you transfuse the CsA patients?

*Dr. Rynasiewicz:* Yes. They were all transfused with donor nonspecific blood. The other thing I didn't mention is that we used DR typing as an aid in matching.

*Dr. Danilovs:* I thought they were mismatched.

*Dr. Sutherland:* All grafts were mismatched. Some were more mismatched than others. We try to match at least two of six antigens of the A, B and DR loci.

*Dr. Strober:* You didn't randomize before matching.

*Dr. Sutherland:* No. When we have a cadaver donor we look at our list and we see who matches at least two antigens, and then we call in a recipient from that pool. Then we randomize CsA to azathioprine after we have selected a recipient on the basis of being matched for at least two HLA antigens.

Most of the related recipients are one-haplotype matches, although some of them are zero-haplotype matches. All parent-to-child or child-to-parent grafts are one haplotype matches. I would say about 90% of the siblings grafts were one-haplotype matches and the other 10% were completely mismatched. All our cadaver transplants were matched for at least two antigens of the A, B and DR series.

At Cambridge matching is not the practice. I think their graft survival rates are lower because they do things differently that we think are important. We can't show a big difference with CsA. Our CsA patients receive small doses of prednisone. In conventional patients, 10 years after transplant, if they have been treated for rejection some have aseptic necrosis of the hip. Prednisone takes its toll over the long term even at low dose. With CsA we may get down to a very low dose.

The one thing we would have to do differently to really show a difference between CsA and conventional treatment is use a fixed dose of steroids, the same dose of steroids on both groups. We chose not to do that. We don't really know for sure how much steroids to use in either group. The conventional regimen is an empirically derived immunosuppression that surgeons who started transplantation back in the 50's and early 60's decided was appropriate.

We don't know if we have to give that much prednisone. We know that certain transplant groups give a lot less steroids in AZA patients than we do.