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Discussion

DR. JOHN A. MANNICK (Boston, Massachusetts): I would like to thank Dr. Foglia for presenting me with a copy of the manuscript, which I enjoyed reading. I must say that with the current legal climate in the United States, I am a little skeptical that fetal organ donation is likely to become a clinical reality very soon. This paper nevertheless addresses an important point in transplantation biology.

Earlier work in this field has clearly shown that some fetal tissues are easier to transplant than others, and there has been the general impression that the earlier the tissues are harvested in gestation, the better the chance they had for survival. This work very nicely shows that there is a marked difference in rejection response to liver *versus* kidney *versus* gonad, and that the earlier the organ is harvested in the gestational period, the longer the tissue survives.

My question for the authors is: Why did they choose to use an outbred set of rats? With the use of outbred rats, differences in survival can sometimes be altered by chance compatibilities of donors and recipients. I wonder if they would consider repeating their work using two inbred rat strains that differ in the major histocompatibility complex so that in each experiment there will be a similar transplant rejection response elicited by the foreign histocompatibility antigens that are present on the transplanted tissue. They also would have the monoclonal antibody tools available to dissect the very important question in this whole issue, and that is, what is the representation of the transplant antigens on the tissues that are transplanted? I think they should particularly look for the representation of the Class II antigens that trigger the transplant rejection response.

DR. CHARLES A. HUFNAGEL (Washington, D.C.): I rise to congratulate Dr. Foglia and his group for a very nice presentation of a complex problem.

It has been well demonstrated that different organs develop their immunological maturity at different times during gestation, but in general one can say that the period of immunity from the maturity of the immunosystem is basically the first half of gestation. The differentiation of organs is also very poor in many organs during that period. The fact that the kidney cells showed some maturity after transplantation is a very helpful contribution by the authors.

The basic issue, however, which Dr. Mannick expressed, is that it has been demonstrated that fetal tissue can be transplanted to an adult. The endocrine tissues, which secrete directly into the blood stream, require no organoid representation, and organs like the kidney have to be fully mature and have all the right connections to make urine. Its endocrine function is a different matter. I have five adult patients, two with Addison's disease and three with other endocrine deficiencies, all of whom have shown that physiologically they require no support for up to a year. Reports on some of those patients have been lost to follow-up.

The real problem is organ procurement. Meadowar demonstrated very well that a fetus is an available recipient for organs from the mother, which does not help anybody very much. On the other hand, what we need is a reverse Meadowar, to make animal donor chimera. That could be done by making a strong antibody to the organ and then injecting the fetus with the antibody. Can we really make this species step across that barrier? In amphibia subspecies, bridges have already been demonstrated, and cloning of amphibia and mice has been demonstrated with nucleus transplantation. This cannot yet be done after the gastrulation stage of development. This again is not a very practical matter except in animal species.

The real challenge still remains that the major source of donors for transplantation must ultimately be from an animal source probably by manipulation of the fetus or germ plasm. That will certainly be a fertile field when we start making that step.

DR. DAVID E. R. SUTHERLAND (Minneapolis, Minnesota): This paper is an interesting addition to an extensive literature on fetal allotransplantation. A group in Australia has consistently been able to engraft 12-day-old fetal mouse pancreases in diabetic mice and cure the diabetes if they do manipulations to prevent rejection, which includes tissue culture. However, fresh allografts invariably fail and do not cure the diabetes. Thus, at least 12-day-old fetal mouse pancreas retains its immunogenicity. They have also done work showing that there is expression of histocompatibility antigens in that stage of development, and I wonder if the authors have looked at their tissue for expression of histocompatibility antigens by the immunocytochemical techniques.

Also, as far as the human work is concerned, there have been about 100 or so fetal pancreas transplants performed in China in diabetic patients and about 50 in Russia that have been reported to the International Pancreas and Islet Transplant Registry, with some claims of function in the absence of immunosuppression. However, in Australia, of 20 or so clinical fetal pancreas transplants, there have been no cures of diabetes with or without immunosuppression.

DR. ELTON WATKINS, JR. (Burlington, Massachusetts): Twenty years ago, before I had a Human Studies Committee, I did vascularized fetal

parathyroid transplants in eight patients with postthyroidectomy hypoparathyroidism. Reduction of calcium requirement was dramatic, but two late complete biopsies showed classical patterns of transplant rejection.

I am interested in this report because I have been fascinated with the thrust of Dr. Donahoe's work. I wonder if the transfer of fetal tissue alone does not remove one element of the entire biological structure, and that is the placental interrelationship between the fetus and the host. After all, acquired tolerance does depend on placentation, and there is evidence that possibly some of the hormones produced by the placenta show a disappearance curve quite similar to your rejection pattern. I wonder if there might be some relationship between placental hormones that are carried within your transplants and the prolongation of time that the tissues persist in the transplanted position.

DR. ACHILLES A. DEMETRIOU (Bronx, New York): I have enjoyed this paper very much. I have a question about your conclusion that the difference in survival between liver and renal tissue is due to differences in the degree of antigenic maturity or in the expression of transplantation antigens. Is it possible that the difference in survival is due to inherent tissue differences like the ability of various tissues to become vascularized and survive in the host? Have you carried out any experiments in which these tissues are transplanted into syngeneic recipients?

DR. ROBERT P. FOGLIA (Closing discussion): Dr. Mannick, in regard to the question about syngeneic recipients, we wanted basically to stack the cards against the grafts growing. That is why we went to an outbred model. We mean to do studies now with syngeneics.

In regard to Dr. Hufnagel's comments, we certainly feel that putting 1 mm fragments in is not the answer to whole organ transplantation. But in certain types of endocrine function, pancreatic cells, parathyroid, and adrenal, we think this might work. We have done some other studies with implanting fetal adrenal grafts, and we find that the growth is quite comparable to that of the gonadal tissue, a bit less than what we see with the kidney.

When I heard the talk yesterday about hepatocytes and superfusion, the thought crossed my mind that liver cells are rejected very easily. It might be that with a single cell suspension you could alter the antigenicity of the liver tissue. Thus, although it has early antigenic expression, you might be able to turn that off in much the same way that you turn off pancreatic islet cells.

Dr. Sutherland, we have not looked yet at using histocompatibility antigen probes.

Dr. Watkins, in regard to your comment about hormonal factors, we think the growth factors are very important for the growth of these tissues. We are beginning now to look at growth factors such as alpha-beta TGF and EGF in our model.