Discussion

Sections on Rejection and Donor Treatment

The final session of this meeting was introduced by the comprehensive review of the immunologic aspects of pancreatic transplantation by Barker and co-workers. More specifically, the discussion dealt with the influence of in vitro islet cell culture conditions on the ultimate outcome of the allograft survival. Central to the theme of the discussion was the concept of donor-passenger leukocytes (preferably called stimulator cells, SC; Lafferty) and the role of these cells in allograft rejection. In general, culture conditions were designed for optimum islet cell survival and evidence for the concomitant elimination of donor stimulator cells from diminution of rejection. There was uniform agreement that a high oxygen concentration (as opposed to air) was injurious for isolated islet cell cultures and, at the same time, probably cytotoxic for the stimulator cells. In this regard, the evidence presented by Lafferty and co-workers, that clustered islet cells were protected from oxygen toxicity, was considered very encouraging. Observations presented by Morris et al., showing the failure of allogeneic fetal rat islet cells, cultured for 21 days in air, to correct hyperglycemia in vivo, suggested, inter alia, that low tissue oxygen tension may not be adequate for eliminating those cells responsible for the rejection of the islet cell allografts. Parenthetically, fetal rat islets cultured under the same conditions were capable of restoring normoglycemia to syngeneic recipients.

The idiosyncrasies of the culture conditions were further complicated by evidence highlighting the importance of ambient temperature on islet cell growth in vitro.

The influence of physiologic (37°C) versus room temperature (22–24°C) on islet cell growth was compared. With isolated islet cells from newborn or fetal mice (Talmage) or adult rats (Lacy), lower culture temperatures were more protective of the islets in an environment of oxygen than higher (37°C) temperatures. In similar fashion, thyroid allografts, cultured at low (22–24°C) temperatures, show improved survival over those cultures exposed to physiologic temperatures. Although culture in air appeared to result in the best fetal islet survival (Talmage et al.), such conditions were not judged adequate for the elimination of SC. Additional data regarding the effect of culture temperatures on the SC population is awaited.

On an immunologic level, the SC contaminating the islet cell populations were considered more important than parenchymal elements in triggering allograft rejection. Unlike islet or parenchymal cells, donor SC are presumed to stimulate the recipient immune system through the release of soluble mediator(s) (Lafferty et al.). Characteristics of the SC place it among the lymphocyte-macrophage cell lineage. In this regard, the presence of lymphoid tissue interspersed within the pancreatic parenchyma was emphasized. Furthermore, the likelihood that islets may contain integral fixed mononuclear histocytes (similar to the concept of Langerhans cells in the epidermis) was mentioned. The possibility that endothelial (or other) cell types, contaminating islet cell cultures, may trigger a host-immune response by simulating SC or by acting as targets for immune destruction remains to be elucidated. Based on the above discussion, it was concluded that histologically "pure" preparations of islet cells would be most likely to result in an optimum transplant outcome.

Recent reports that mouse islet cells lack surface histocompatibility (H-2) antigens, as determined by immunoferritin staining (E. Parr: J. Exp. Med. *150*:1–9, 1979), raises the future possibility of immune selection of pure islet cell preparations. Whether SC present in fetal transplantation tissue are immunologically mature and contribute to the allograft rejection process remains conjectural at this time. The suggestion was made that islet-cell cell lines (which would theoretically lack SC) be established as a means of elucidating the mechanisms of allograft rejection. Transplantation of such islet cell lines may provide a good model for nonimmune mechanisms of graft rejection. The possibility that stimulatory mediators released from SC may elicit nonspecific inflammatory responses capable of damaging the integrity of the sensitive islet cell elements was raised.

A number of in vivo animal studies was discussed and is relevant to the mechanisms of transplantation rejection and the possible role of SC. Of interest was the pertinent obser-

vation by Mullen that viable fetal rat pancreas transplants were still capable of eliciting an immune response when transplanted into a nonimmunosuppressed allogeneic host after 300 days of survival in the original host. One of many possible explanations for this observation was that fixed islet cell histiocytes in the transplanted organ survive despite prolonged in vivo existence in the original host. In contradistinction to the above experiment, Barker reported preliminary findings that, in tolerant rat recipients, allogeneic fetal pancreas grafts were resistant to immune rejection upon restoration of immune competence with host lymphocytes. Further, the same group mentioned that transplant recipients tolerant of allogeneic donor lymph node cells were still capable of rejecting isolated islet cells from the same donor. It was agreed that these apparently discrepant findings highlight the need for further understanding the pathogenesis of pancreas transplantation rejection and the specific role of SC in this immune process.

Numerous methods of suppressing the recipient immune system and prolonging allograft survival were discussed. In general, rejection characterized the transplantation of allogeneic adult islets, fetal pancreas (cultured and noncultured) and vascularized grafts in nonimmunosuppressed rat recipients. Vascularized grafts were considered less prone to the rejection process than isolated islets (Barker). Of the agents used for immunosuppression of the recipient, antilymphocyte serum was the most successful in the rat. Immunologic enhancement by the use of antidonor serum or immunoglobulin failed to produce encouraging results. The use of newer agents, such as Cyclosporin, was found to be beneficial in vascularized grafts and adult islet cell grafts only if continuous immunosuppression was undertaken posttransplantation (Sutherland). Preliminary evidence in dogs suggests that Cyclosporin may be valuable in segmental pancreas transplants. The potential use of total lymphoid irradiation as an immunosuppressive modality in pancreas transplantation awaits further investigation (Slavin). The ability of streptozotocin-treated recipients to regenerate their own islet cells emphasizes the necessity for built-in controls in allograft transplant protocols. Finally, the critical mass of allograft tissue required to permit engraftment and function remains to be established.