Bibliography

1. Atkinson, W. B.: The Physicians and Surgeons of the United States. Chas. Robinson, Phila., 1878.
2. Bauer, E. L.: Doctors Made in America. J. B. Lippincott Co., Phila., 1963.
3. Book for Constitution and By-Laws of Philadelphia Academy of Surgery.
4. Bordley, J. and Harvey, A. M.: Two Centuries of American Medicine. W. B. Saunders Co., Phila., 1976.
5. Brinton, J. H.: Personal Memoirs. Neale Co., N.Y., 1914.
6. Complimentary Dinner Given to Professor S. D. Gross, April 10, 1879. Lindsay and Blakiston Co., Phila.
7. Garrison, F. H.: An Introduction to the History of Medicine. 4th Ed., W. B. Saunders Co., Phila., 1929.
8. Gibbon, J. H.: Memoir of John Hooker Packard, M.D. Trans. Coll. Phys. Phila., Vol. XXXI, 1909, p. lv-lx.
9. Gould, G. N.: History of the Jefferson Medical College. Lewis Co., N.Y., 1904.
10. Gross, S. D.: Autobiography of Samuel D. Gross, M.D., with Sketches of His Contemporaries. Vol. I and II. Arno Press and The New York Times, N.Y., 1972.
11. Harte, R. H.: Memoir of J. Ewing Mears, M.D. Trans. Coll. Phys. Phila., Vol. XLIII, 1921, p. lxi-lxviii.
12. Hays, I. M.: Memoir of Samuel D. Gross. Trans. Coll. Phys. Phila., Vol. VII, 1884, p. xcv-cxxi.
13. Konkle, B. H. and Henry, F. P.: Standard History of the Medical Profession of Philadelphia. 2nd Ed., AMS Press, New York City, 1977.
14. Lewis, M. J. Memoir of Thomas G. Morton, M.D. Trans. Coll. Phys. Phila., Vol. XXXVI, 1914, p. lxviii-lxxii.
15. Minutes of the Philadelphia Academy of Surgery, 1879-1909 (442 pages).
16. Morris, M. C.: Memoir of Addinell Hewson. Trans. Coll. Phys. Phila., Vol. XII, 1890, p. xxxiii-xliv.
17. Obituary of Samuel W. Gross, M.D. Medical News, 1889, p. 474-476.
18. Pancoast, W. H.: Report on the Surgical Considerations in Regard to the Propriety of an Operation for the Separation of Eng and Chang Bunker, Commonly Known as the Siamese Twins. Trans. Coll. Surg. Phila., Vol. I, 1875, P. 149-169.
19. Report of Committee on Necrology: Samuel Weissel Gross, M.D. Trans. Am. Surg. Assoc., Vol. VII, 1889, p. xxi-xxiii.
20. Report of the Committee on Necrology: Richard J. Levis, M.D. Trans. Am. Surg. Assoc., Vol. IX, 1891, p. xxiv-xxv.
21. Transactions of the Philadelphia Academy of Surgery, Vol. I (1899) to Vol. XXXII (1976).
22. White, J. W.: Memoir of D. Hays Agnew, M.D., LL.D. Trans. Coll. Phys. Phila., Vol. XV, 1893, p. xxix-lxv.

Annual Oration for 1980

The Role of Immunology and Pancreatic Transplantation in Diabetes

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The role of immunology in diabetes might seem an unusual subject for consideration at a surgical meeting. Yet there is good precedent for the interest of surgeons in the pathogenesis and treatment of this disease. The Canadian surgeon Frederick Banting was, of course, the first to isolate insulin and use it to maintain life in pancreatectomized animals, an accomplishment which could hardly have been expected from investigators lacking surgical skills. It is ironic that this landmark experiment, which must surely be considered one of the greatest in all of medical history, although allowing prolongation of life in juvenile diabetics, has not led to "cure" of the disease, as initially hoped.[1] Instead the incidence of diabetes has continued to increase so that 20% of the population are soon expected to be stricken by a malady which is already the fourth ranking cause of death in Americans. It is also the third most common cause of renal disease and the most common cause of blindness occurring in adults. As surgeons we are confronted daily with the peripheral vascular complications of the disease, leading so commonly to requirement for amputation.

Despite the failure of present insulin regimens to prevent the disease there is new evidence that if insulin could be delivered more effectively—in such a way as to really normalize blood glucose concentration—complications would be diminished or prevented.[2] Unfortunately, the practical aspects of such perfect insulin delivery are not easy and could be accomplished only in two ways. One would be continuous monitoring of blood glucose, the use of a computer to determine the proper insulin dose and its delivery intravenously by a mechanical device (artificial pancreas). The other method is replacement of normal pancreatic tissue, which although presenting formidable biological problems, is likely to be a more practical method. Thus, the rationale for transplantation as a treatment for diabetes is not avoidance of the inconvenience of insulin injection, but complete normalization of blood glucose, which probably is the only method by which vascular sequelae of the disease can be avoided. Experimental evidence in animals supports the contention that this treatment would be effective, since vascular lesions characteristic of experimental diabetes in inbred rats are prevented, and even reversed if treated early, by replacement of normal islets.[3] In outbred species such as man, in which histocompatible donors are unlikely to be available, the most serious

problem associated with islet replacement will undoubtedly be immunologic rejection.

Rejection Problem

The rejection problem (common to transplantation of foreign tissue by any method), will no doubt frustrate to some degree efforts to replace pancreatic islets, whether this be accomplished by transplanting the entire pancreas with vascular anastomoses, or by isolating the islets of Langerhans and transplanting them by simple injection, a non operative technique which would be easier and safer for the patient. There is, however, considerable evidence that the rejection process may be particularly severe in the case of isolated islet allografts.[4]

Initially it was hoped that the opposite might be true since pancreatic islets might share the immunologically privileged status of other endocrine tissues. However, the initial report of successfully transplanted islet allografts by Reckard and Barker indicated that their rejection was disappointingly rapid, sometimes occurring as early as 1-2 days after transplantation to strongly histoincompatible recipients, while syngeneic (histocompatible) islets transplanted in inbred animals by identical techniques enjoyed permanent survival.[5] Many other workers have now confirmed the finding that allogeneic islet survival is short lived in a number of species.[4] In the rat, median survival times of islet allografts transplanted across a major histocompatibility barrier have been variously reported as 3.2 days, 5.2 days and 4 days. Survival times of skin, kidney and heart allografts are, however, consistently longer, 8-12 days.[6] The reason for discrepancy in survival of islets as compared with other tissues is unknown, but one simple possibility is that the method of transplantation of isolated islets as a dispersed cell preparation renders them more susceptible to immune destruction than vascularized organ allografts. In fact, a number of studies in which result of transplantation of isolated islets was compared with that of various vascularized organs, suggest that transplantation of the dispersed islet tissue may place it at a disadvantage as compared with other types of allografts which are immediately revascularized. Most of these studies, however, compared islet allografts in the rat with kidney or heart allografts in this species, or with whole pancreas allografts in other species such as the dog. To clarify whether islets and vascularized pancreas allografts in the same species would have a different likelihood of success, Perloff et al. recently compared the outcome of these two methods of transplanting beta cells in the same strains of inbred rats.[7] Isolated BN islets were rejected by major histocompatibility complex (MHC) incompatible diabetic Lewis rats in 4.4 + 1.8 days, while vascularized whole pancreas grafts consistently survived longer, 7.6 + 1.1 days. When histocompatibility was minimized, a greater difference in functional survival was seen, as Lewis islets survived in MHC compatible Fischer rates for only 4.4 + 1.8 days, while vascularized pancreas survived for 16.5 + 3.9 days (occasionally for as long as 75 days). Histological examination of allografts at various intervals revealed earlier and more extensive damage of the

isolated islet allografts than of islets within vascularized pancreas. Perloff also found that he was unable to prolong islet allograft survival by an enhancement protocol which proved effective in prolonging heart and kidney allograft survival. A similar result has been reported by Reckard et al.,[8] and by Morris et al.,[9] who had only minor success in enhancement of islet allograft survival. Morris also found that prolongation of survival of pancreas grafts is more easily achieved by immunosuppressive drugs than is the case with isolated islet allografts. Thus, it seems clear that when isolated islet survival is compared to that of vascularized pancreas, islets fare worse either in normal or immunosuppressed animals.

The rather dismal results of clinical trials in man lend support to the concept that transplanted isolated islet tissue is especially vulnerable to rejection (although technical problems in separating islets from the fibrous human pancreas could also play a role). Indeed only 4 of 68 isolated islet allografts in humans appear to have had even transient function.[10] These results are so poor that at this time isolated islet transplantation in man probably has only one indication, this being replacement of a patient's own pancreatic islets in instances when pancreatectomy is being performed for benign disease. Najarian et al. recently reported ten instances of islet autotransplantation to prevent diabetes in patients undergoing near total pancreatectomy for pancreatitis.[11] In three of these patients the autograft apparently succeeded, thus avoiding diabetes and the necessity for insulin therapy.

Allografts

The possibility of successful transplantation of allografts of isolated islets as a treatment for human diabetes in the future should not, however, be discounted. Despite the seemingly great vulnerability of transplanted islets to rejection documented above, islet cells may paradoxically in themselves be only weakly immunogenic. Until recently, there has been no direct evidence regarding the makeup of cell surface antigens of islets cells. It now appears that rather than being especially immunogenic, they may actually be *deficient* with regard to histocompatibility antigens. Parr recently reported that with an immunoferatin labeling technique he was unable to demonstrate H-2 antigens on the surface of beta cells of dissociated islets, though H-2 antigens were present on acinar, ductal and capillary endothelial cells.[12] He postulated that beta cell failure after islet transplantation occurs only as a result of their proximity to other pancreatic cells, which provoke an immune response and subsequently come under its direct attack.

More recently, Faustman et al. studied islet cells by cytotoxicity and absorption assays, using 20 antisera directed against different portions of the MHC (H2) locus.[13] They reported that H-2K and H-2D antigens were present on islet cells in mice, but found no evidence that Ia antigens were present. Since Ia antigens appear to be necessary for stimulation of immune responses, although H-2K and H-2D antigens can serve as targets for immune reactivity, this finding could explain the success of Bower et al.[14] and of Lacy et al.[15] in

preventing islet allograft rejection by a pretransplant period of tissue culture. Considerable evidence has now been accumulated by Talmage that passenger leukocytes, especially those of the macrophage series, which are known to express the Ia antigens necessary for stimulating an immune response, are destroyed by prolonged culture under high 02 tension.[16] This may also be true of other cell types, such as vascular or ductal endothelium, which may express Ia antigens, while pancreatic beta cells could survive these conditions. "Pure" cultured islet cells might then be transplanted to allogeneic hosts, presenting only H-2D and H-2K histocompatibility antigens on islet cells, and not the Ia determinants necessary to initiate the immune response (but which may be present only on the non endocrine cells). Thus, islet cells might survive without immunosuppression. However, they would remain vulnerable to rejection if the recipient was later confronted with Ia antigen bearing cells of the donor type. This has, in fact, been the finding of Lacy et al.[15]

Until these theoretical and experimental results are shown to have clinical application, islet tissue appears more likely to function in humans without being rejected if it is transplanted as a portion of a vascularized pancreas allograft. Since 1977, 64 patients have received pancreas allografts and of these, 10 presently retain their grafts, 4 for more than 1 year.[16] Although these results are much superior to those achieved so far with isolated islet allografts in man, it is of interest that they are worse than those of transplanting any other organ, i.e., kidney, heart, liver. This may be due to the complications arising from manipulating the exocrine portion of the pancreas (e.g., pancreatic fistulas), but could suggest another reason. The original disease process may recur in the transplanted tissue, causing destruction of the new islets. If human diabetes is an autoimmune disease (as seems likely), this possibility would be a real one. Recurrence of another autoimmune disease (glomerulonephritis) is known to occur in a significant fraction of kidney transplants, even of identical twin donors (11/17).[17]

Another likely etiological mechanism of human diabetes is that islet destruction is mediated by viral infection. These two etiological possibilities (autoimmune and viral), rather than being mutually exclusive are likely to work in combination, the hypothesis being that viral infection modifies islet cell surface antigens so that their autoimmune destruction is brought about. If this is indeed the case, the possibility must be seriously considered that an ongoing autoimmune state or recurrence of autoimmunity triggered by reinfection with a viral agent could bring about destruction of transplanted islets. A theoretical possibility of more optimistic implication is that islet destruction on an autoimmune basis might be prevented (or even reversed), by immunosuppression alone. Several animal models have recently been examined by us with regard to these possibilities.

Infection (EMC)

Infection with the encephalomyocarditis virus (EMC) induces a short lived hyperglycemic syndrome in some, but not all strains of mice. Susceptibility has been attributed to viral receptors in the islet cells, although an extrapancreatic host factor is another possibility.[18] Dafoe et al. demonstrated that immunosuppression with ALS was usually able to prevent the induction of EMC diabetes.[19] Dafoe et al. also showed that pancreata from either EMC susceptible or non susceptible strains were equally vulnerable to EMC induced damage when transplanted to F1 hybrids.[20] Thus, susceptibility to the virus seemed likely to be attributable to the immunological responsiveness of the host, rather than the intrinsic susceptibility of the pancreas. With regard to possible adverse effects that EMC virus-induced autoimmunity might have on transplanted islets, both Naji et al.[21] and Howard et al.[22] showed that syngeneic isolated islet transplantation could be carried out successfully in EMC diabetic mice. Thus, it seems unlikely that this autoimmune state will damage islets transplanted late in its course.

Another animal model in which autoimmunity appears to play a role is the "BB" rat. These animals spontaneously and abruptly develop hyperglycemia and insulin dependence.[23] The histological appearance of the islets in newly diabetic rats is one of mononuclear infiltration, strongly suggesting autoimmunity. Like et al.[24] and Naji et al.[25] have demonstrated that immunosuppression may prevent or even reverse early stages of diabetes in these animals. Naji et al.[21] also demonstrated that transplanted allogeneic islets from Wistar Furth donors survive and function normally in immunosuppressed diabetic "BB" rats, even reversing hyperglycemia of long standing in animals in which the native islets were irreversibly damaged. Immunosuppression was necessary for islet transplant survival in these animals, since the outbred status of the "BB" stock provided no opportunity for transplantation of (truly histocompatible) syngeneic islets. Thus, these experiments did not allow assessment of whether the unmodified immune state would preclude successful islet transplantation in nonimmunosuppressed diabetic hosts. In order to answer this, Naji[25] has recently used donor islets from a second "BB" stock not susceptible diabetes, but rather closely histocompatible with the diabetic recipients (routinely allowing skin allograft survival of >30 days). When such islets were transplanted to *artificially* diabetic streptozotocin treated "BB" rats, 60% remained normoglycemic for 4 months, showing that rejection was very indolent because of the close histocompatibility. However, when "BB" islets were transplanted to *spontaneous* (and non-immunosuppressed) diabetics, 9 of 10 rats remained normoglycemic for less than 5 days and the other for only 18 days. In these rats, the transplanted islets were found to be heavily infiltrated with mononuclear cells, suggesting that they had been destroyed by an autoimmune reaction. The rapid failure of islet grafts in the non-immunosuppressed spontaneous "BB" diabetics (but not in chemically induced "BB" diabetics), indicates that transplanted islets may remain vulnerable to the same ongoing autoimmune factors that caused failure of the native islets. These findings merit consideration with regard to possible recurrence of diabetes in humans who might receive a pancreas transplant from a closely histocompatible related donor.

Recently Naji et al.[26] considered the possibility that since susceptibility of

the "BB" rat appears to be based on both genetic and immune factors, alteration of the make-up of the immune system of these rats might alter their predisposition to diabetes. Members of some "BB" litters were inoculated at birth with bone marrow cells from a nondiabetes prone strain of rats. Preliminary results indicate that these chimeric "BB" rats have about a fourfold lessening in the expected incidence of diabetes.

Conclusion

Thus, one hope for future therapy or prevention of diabetes might be the identification of potentially susceptible individuals and protection from an autoimmune reaction by immunosuppression, or conceivably by changing the make-up of some cellular elements of the immune system. These possibilities for future immunotherapy of diabetes, along with hopes for improving results of pancreatic transplantation seem likely to be the best hope for a real "cure" of this disease.

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References

1. Report of the National Conference on Diabetes: Current Status and Future Directions. Appendix to the Third Annual Report of the National Diabetes Advisory Board. U.S. Dept. of Health and Human Service Public Health Service. NIH Publication No. 80-2073, April 1980.
2. Tamborlane, W. V., Sherwin, R. S., Genel, M. and Felig, P.: Lancet 1: 1258 (1979).
3. Mauer, S. M., Sutherland, D. E. R., Steffes, M. W., Leonard, A. J., Najarian, J. S., Michael, A. F., and Brown, D. M.: Diabetes 23:748 (1974).
4. Barker, C. F., Naji, A., and Silvers, W. K.: Diabetes 29:86 (1980).
5. Reckard, C. R. and Barker, C. F.: Transplant. Proc. 5:761 (1973).
6. Barker, C. F., Silvers, W. K., and Lubaroff, D. M.: Science 172:1050 (1971).
7. Perloff, L. J., Naji, A., Silvers, W. K., and Barker, C. F.: Surg. 88:222 (1980).
8. Reckard, C. R., Shulack, J., and Stuart, F.: Transplant. Proc. (In Press).
9. Morris, P. J., Finch, D. R., Garvey, J. F., Poole, M.D., and Millard, P. R.: Diabetes 29:107 (1980).
10. Sutherland, D. E. R., Goetz, F. C., and Najarian, J. S.: Hormone and Metabolic Research (In Press).
11. Najarian, J. S., Sutherland, D. E. R., Baumgartner, D., Burke, B., Rynasiewicz, J. J., Matas, A. J., and Goetz, F. C.: Ann. of Surg. 192:526 (1980).
12. Paar, E. L.: J. Exp. Med. 150:1 (1979).
13. Faustman, D., Hauptfield, V., Davie, J. M., Lacy, P. E., and Schreffler, D. C.: J. Exp. Med. 151:1563 (1980).
14. Bower, K. M., Andrus, L., and Lafferty, K. J.: Diabetes 29:98 (1980).
15. Lacy, P. E., Davie, J. J., Finke, E. H.: Science 204:312 (1979).
16. Talmage, D. W.: Diabetes 29:105 (1980).

17. Glassock, R. J., Feldman, E. S., Reynolds, G. J., and Dammin, G. J.: Med. 47: 411 (1968).
18. Yoon, J. W. and Notkins, A. L.: J. Exp. Med. 143:1170 (1976).
19. Dafoe, D. C., Naji, A., Kirby, W., and Barker, C. F.: Surg. Forum 31:51 (1980).
20. Dafoe, D. C., Naji, A., and Barker, C. F.: J. Surg. Res. 28:338 (1980).
21. Naji, A., Silvers, W. K., Plotkin, S. A., and Dafoe, D. C.: Surg. 86:218 (1979).
22. Howard, R. J., Sutherland, D. E. R., Matas, A. J., and Najarian, J. S.: Surg. Forum 29:343 (1978).
23. Nakhooda, A. F., Like, A. A., Chappel, C. I., Murray, F. T., and Marliss, E. B.: Diabetes 26:100 (1977).
24. Like, A. A., Rossini, A. A., Guberski, D. L., Appel, M. C., and Williams, M. W. Science 206:1421 (1979).
25. Naji, A., Silvers, W. K., and Barker, C. F.: Transplant. Proc. (In Press).
26. Naji, A., Silvers, W. K., Bellgrau, D., and Barker, C. F. (Unpublished).