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History of Surgery Lecture

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I read with great interest and enjoyment Dr Starzl's excellent Charles Drake History of Surgery Lecture.[1] I wish to endorse strongly, on the basis of our experimental work with tolerogenesis in the baboon (*Papio ursinus*) kidney transplant model, the two principles of tolerogenic immunosuppression he derived from historical observations, namely pretreatment and the importance of limiting posttransplant immunosuppression.

In many hundreds of experiments we demonstrated consistently the ability of a modified regimen of pretransplant total lymphoid irradiation (TLI) to induce durable (greater than 10 years survival with normal graft function) and donor-specific transplantation tolerance in baboon kidney and liver transplantation, without the use of any posttransplant immunosuppressive treatment. The most effective TLI protocol obtained consisted of a total dose of 800 cGy given in 80- or 100-cGy fractions twice a week to a wide field. Tolerance occurred in one-third to one-half of many groups studied.[2-4]

In efforts to increase the tolerant fraction obtained we studied the effect of adding posttransplant immunosuppressive drug therapy to the pretransplant TLI regimen. With even limited 2-week courses of cyclosporine A, prednisone, or antilymphocyte globulin, there was either no additive effect in terms of tolerance production, or, in the case of cyclosporine A, a counterproductive effect.[3] Even more dramatic was the effect of adding only two fractions of 100 cGy each in the second and third weeks after transplantation. Graft survival was drastically shortened and tolerance induction was abrogated.[5]

We interpreted these findings as indicating that an active mechanism or mechanisms, capable of inhibition by immunosuppressive measures, were involved the process of tolerance induction. We were able to demonstrate a marked increase in activated T cells and of usually nonspecific suppressor cells in the circulation of these tolerant baboons soon after transplantation.[6,7]

These findings also probably explain why we did not achieve the same results in terms of full tolerance production with pretransplant TLI in 73 kidney transplantation patients.[8] For ethical reasons, as a result of the unpredictability of tolerance production in individual baboons, all our patients received fairly conventional doses of posttransplant immunosuppressive drugs.

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Reply

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We enthusiastically acknowledge the magnificent studies of total lymphoid irradiation (TLI) by Myburgh in baboon transplant models, beginning more than a quarter of a century ago. The radiotherapy regimen known as TLI had been developed by Henry Kaplan at Stanford for the treatment of human malignant lymphomas,[1] and was known to be immunosuppressive.[2] Because the TLI spared part of the central lymphoid organ system, it did not cause leukopenia or other overt myelotoxicity. Also

ISSN 1072-7515/03/$21.00
doi:10.1016/S1072-7515(02)01891-4

at Stanford, Slavin and Strober and colleagues[3,4] had induced specific tolerance to skin and hearts of inbred adult mice and rats using a combination of TLI and donor-specific bone marrow. Unlike the outcomes in classic experiments in which total-body irradiation was used to destroy the host immune system before bone marrow cell infusion,[5,6] the engrafted allogeneic bone marrow did not cause graft-versus-host-disease (GVHD) in the rodents.[3,4]

In their series of brilliant experiments, Myburgh and coworkers[7,8] confirmed these findings in baboons after kidney and liver allotransplantation. Eventually, five clinical trials with TLI were conducted. These were carried out at Stanford, the University of Minnesota, Louvain, and Rome Universities,[9-12] and by Myburgh at the Witwatersrand University in Johannesburg.[13-14] All except the South African patients (some of whom were liver recipients) underwent renal transplantation exclusively. The results were summarized by Myburgh at the Transplantation Society congress in August 1988.[13] His report revealed a striking change in therapeutic intention in the course of the trials. The change had been foreshadowed by new laboratory experiments showing that, on the average, TLI without bone marrow was as effective as the combined modalities.[13,15] Consequently, bone marrow was omitted altogether in the TLI-treated patients of Stanford (n = 25), Louvain (n = 20), and Rome (n = 30), and was used only occasionally in Minneapolis (5 of 22) or with decreasing frequency in Johannesburg (number unstipulated but known to include liver recipients).

TLI had become a competitor by the 1980s with the new drug, cyclosporine, as a primary immunosuppressant, rather than being viewed as a means to the end of establishing tolerance through bone marrow chimerism. Because of its inconvenience, expense, and morbidity, TLI lost the race. What was left when the smoke cleared was a group of surviving organ recipients in each of the clinical series with thoroughly documented donor-specific allogeneic tolerance. Because most of these patients did not have bone marrow infusion, organ graft acceptance was explained with different multifactorial hypotheses, all chimerism-exclusionary. With the hindsight that began to emerge with the discovery that long-surviving organ recipients did have low-level donor leukocyte chimerism,[16,17] it was possible to understand how organs transplanted under nonspecific immunosuppression could sometimes induce the same kind of drug-free tolerance as that of the cytoreduced or cytoablated bone marrow recipient. The earlier enigmatic observation made by Myburgh that immunosuppression could be tolerogenic also could be explained as in the Charles G Drake Lecture.[18]

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Postthyroidectomy Hypocalcemia

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I read with interest, in the October 2002 issue of this journal, the article by Dr Abboud and coworkers[1] concerning risk factors for postthyroidectomy hypocalcemia.

Postoperative evolution of serum calcium levels is not a response that is specific to thyroid surgery but also occurs after other noncervical operations of a similar magnitude such as herniorrhaphy.[2] Postoperative symptomatic hypocalcemia is believed to be a multifactorial phenomenon attributed to hypoparathyroidism. This phenomenon is seen only after bilateral thyroidectomies, but almost never after unilateral lobectomies unless the patient had previous thyroid operations. Although a decline in serum calcium levels will be observed, this should not be associated with hypocalcemic symptoms. Routine serum calcium monitoring should be reserved for patients who have undergone either bilateral or completion thyroidectomy and who otherwise might be at risk of symptomatic hypocalcemia. So the practice of routine postoperative calcium monitoring for patients who undergo unilateral thyroid operations, as was performed in this study, is not cost-effective and should be abandoned.

It has been suggested that a program of routine calcium supplementation should be the future basis for same-day or 1-day admission after bilateral or extensive thyroid operations.[3] But, the relatively infrequent occurrence of postoperative hypocalcemia suggests that routine treatment is probably not cost-effective, and can hinder the detection of true hypocalcemia.[4] During the risk factor analysis of the present article, the inclusion of patients who underwent unilateral thyroid lobectomy in the absence of previous thyroidectomy seems, therefore, inappropriate. There is no doubt that a bilateral thyroidectomy is readily identifiable as an independent risk factor for postthyroidectomy hypocalcemia. Recommending oral calcium supplementation for patients after bilateral thyroidectomy based on such analysis is not cost-effective and can be misleading.

This study also mentioned that patients with thyrotoxicosis were treated by a standard protocol with a combination of methimazole and propranolol until they became biochemically euthyroid. It is surprising, therefore, to observe a substantial number of patients with hyperthyroid function during the subsequent analysis, and that an elevated thyroxine level was identified as an independent risk factor for postthyroidectomy hypocalcemia. Perhaps the authors were referring to the underlying pathologies leading to thyrotoxicosis rather than the presence of an elevated thyroxine level before the operation.

We do, however, agree with the authors that patients who undergo parathyroid autotransplantations have an increased risk of developing postoperative hypocalcemia.[5] But a parathyroid autotransplantation could prevent the occurrence of permanent hypoparathyroidism for those patients who developed postoperative hypocalcemia.[5] Unfortunately, no data were shown on the follow-up status of patients in the present study to confirm either longterm outcomes or the correlation between patient outcomes and the type of hypoparathyroidism observed. Identification of parathyroid autotransplantation as an independent risk factor for postthyroidectomy hypocalcemia can be misleading without documentation of its role in preventing permanent hypoparathyroidism.

Clinical risk factors for post-thyroidectomy hypocalcemia can help the operating surgeon identify high-risk patients who warrant close monitoring of their serum calcium levels or for whom early calcium supplementation is recommended. But close monitoring of serum calcium levels is the standard practice adopted to identify postthyroidectomy hypocalcemia from parathyroid insufficiency. Concerns over the possible development of postoperative hypocalcemia secondary to hypoparathyroidism have prolonged the duration of hospitalization for patients who would otherwise be considered for early discharge. Efforts are also being made to use specific monitoring tools to identify individual patients who are at risk of developing postthyroidectomy hypocalcemia during the postoperative period. Early consecutive calcium monitoring has been used to identify patients at risk of clinically significant hypocalcemia.[4,6]