

erative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2009;362:129-37.

6. Chen VK, Arguedas MR, Baron TH. Expandable metal biliary stents before pancreaticoduodenectomy for pancreatic cancer: a Monte-Carlo decision analysis. *Clin Gastroenterol Hepatol* 2005;3:1229-37.

7. Moss AC, Morris E, MacMathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. *Cochrane Database Syst Rev* 2006;1:CD004200.

8. Lawrence C, Howell DA, Conklin DE, Stefan AM, Martin RF. Delayed pancreaticoduodenectomy for cancer patients with prior ERCP-placed, nonforeshortening, self-expanding metal stents: a positive outcome. *Gastrointest Endosc* 2006;63:804-7.

9. Kahaleh M, Brock A, Conaway MR, et al. Covered self-expandable metal stents in pancreatic malignancy regardless of resectability: a new concept validated by a decision analysis. *Endoscopy* 2007;39:319-24.

10. Baron TH, Petersen BT, Mergener K, et al. Quality indicators for endoscopic retrograde cholangiopancreatography. *Am J Gastrointest* 2006;101:892-7.

11. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3487-95.

Copyright © 2010 Massachusetts Medical Society.

Immune Evasion by Chimeric Trachea

Megan Sykes, M.D.

The types of allogeneic organs and tissues that can be transplanted have expanded considerably in the past three decades. In addition to organs such as liver, heart, lungs, and pancreas, the list of allografts now includes islets of Langerhans and composite tissues such as hands and face. In this issue of the *Journal*, Delaere and colleagues report the successful transplantation of a tracheal cartilaginous allograft in which the mucosa was first replaced and revascularization established in a heterotopic location in the recipient; the graft was then implanted orthotopically and accepted without immunosuppressive therapy.¹

Allografts typically require nonspecific immunosuppressive therapy to prevent rejection. Complications of such treatment include opportunistic infections, cancer, metabolic imbalances, and end-organ damage. Therefore, a major goal of research in transplantation has been to achieve immunologic tolerance, whereby the recipient's immune system regards donor antigen as "self." Long-term immunosuppressive therapy would thus not be required to prevent rejection. Although tolerance has been observed serendipitously in a small fraction of transplant recipients who have stopped taking their immunosuppressive medications, grafts are rejected in the vast majority of such patients. Recently, several groups have reported the use of hematopoietic cell transplantation to induce renal allograft tolerance, with early reports of success in both HLA-identical^{2,3} and HLA-mismatched⁴ donor-recipient pairs. In the study by Kawai et al., robust T-cell responses to the donor that were present before

transplantation disappeared completely, whereas responses to unrelated alloantigens recovered, denoting a systemic state of tolerance.⁴

Several mechanisms, including deletion and anergy of donor-reactive T cells as well as active suppression, have been implicated in experimental models of tolerance.⁵ States of "immune ignorance" — due to either a failure of immune sensitization (the afferent arm of the immune response) or a resistance to immune-effector mechanisms (the efferent arm) — have also been reported to protect grafts from rejection.^{6,7} Both explanations may contribute to the "immune privilege" that has been reported to protect grafts in certain anatomical locations from immune attack.⁸

Delaere et al. report successful functioning of the tracheal allograft for more than a year without immunosuppressive therapy.¹ This achievement represents a new approach to tracheal reconstruction in patients with large tracheal defects that cannot otherwise be surgically repaired. However, the available data suggest that the immunogenic components of the allograft were rejected, so that the only allogeneic components of the functioning graft were the all-important cartilaginous tracheal rings. This outcome reflects the immune privilege enjoyed by chondrocytes, the living cells that produce and maintain cartilage. Although isolated chondrocytes are highly immunogenic,⁹ chondrocytes in cartilage reside in lacunae surrounded by the collagenous extracellular matrix they produce. They are nourished by diffusion from capillaries

outside the cartilage. The dense collagenous matrix may prevent antigen from passing into the recipient lymphoid tissues, where sensitization to allografts normally occurs, and may prevent lymphocytes and antibodies from gaining access to the chondrocytes.

In the case described by Delaere et al., recipient sensitization to donor alloantigens occurred, since the donor skin and noncartilaginous components of the tracheal graft were rejected. Assuming that the donor chondrocytes remain viable and are not eventually replaced by recipient chondrocytes, these results suggest that chondrocytes are resistant to attack by immune effectors, providing an example of immune ignorance due to physical isolation.

Although the immune privilege of chondrocytes in situ has previously been recognized¹⁰ and exploited to allow the transplantation of allogeneic articular-cartilage grafts,¹¹ Delaere et al. have used a unique approach to generate a tracheal allograft in which immunogenic components were replaced by autologous cells.¹ The approach was driven by the technical difficulty in achieving vascularization of a transplanted trachea, which does not have an identifiable vessel for anastomosis with a pedicle graft. These researchers wrapped the tracheal allograft in the subcutaneous fascia of the recipient's forearm, allowing neovascularization from recipient vessels to take place over a period of 9 months before implantation into the orthotopic site.

During the initial period of heterotopic implantation, rejection was prevented with an immunosuppressive triple-drug regimen similar to that used to prevent the rejection of organ allografts. The membranous posterior wall of the donor trachea underwent avascular necrosis before neovascularization had occurred and was replaced by recipient buccal mucosa sutured to recipient fascia that was wrapped around the posterior tracheal wall. Donor respiratory epithelium persisted while the patient was receiving immunosuppressive therapy, but after withdrawal of this therapy, all donor cells disappeared and the recipient's buccal mucosa grew over the cartilaginous trachea. By the time of orthotopic implantation, all mucosal tissue and blood vessels in the graft had been derived from the recipient. Although the authors did not directly demonstrate the persistence of donor chondrocytes, pre-

sumably the only allogeneic tissue in the orthotopically placed tracheal graft was the cartilage itself. The graft continued to function 1 year after orthotopic implantation, without immunosuppressive therapy.

To gauge the level of immunosuppression, the investigators transplanted a skin graft from the donor behind the recipient's ear. Immunosuppressive therapy was tapered over a period of 6 weeks and discontinued shortly before the tracheal graft was explanted from the forearm and implanted in the orthotopic site. The withdrawal of immunosuppressive therapy was associated with rejection of the donor skin graft, demonstrating a vigorous immune response to donor alloantigens. The wisdom of using highly immunogenic skin grafts as "indicator" grafts might be questioned, since rejection of less immunogenic grafts has been triggered by the transplantation of highly immunogenic skin grafts.¹² If, as is assumed, the donor chondrocytes did indeed persist in the tracheal graft in this case, the fact that rejection of the skin graft failed to trigger rejection of the donor cartilage is further evidence of the degree to which chondrocytes may be protected from the immune response. Though not evaluated in this study, donor skin-graft rejection would be expected to lead not only to T-cell sensitization but also to an alloantibody response to the donor.

This elegant approach to reconstructing an otherwise irreparable tracheal defect takes advantage of the immune privilege of the cartilaginous component while exploiting the regenerative capacity of the recipient's mucosal tissue. The success of this approach, if sustained, could provide hope for patients whose tracheal defects cannot otherwise be surgically corrected.

Dr. Sykes reports receiving consulting fees from Genzyme and Guidenz. No other potential conflict of interest relevant to this article was reported.

From Harvard Medical School and the Bone Marrow Transplantation Section, Transplantation Biology Research Center, Massachusetts General Hospital — both in Boston.

1. Delaere P, Vranckx J, Verleden G, De Leyn P, Van Raemdonck D. Tracheal allotransplantation after withdrawal of immunosuppressive therapy. *N Engl J Med* 2010;362:138-45.
2. Fudaba Y, Spitzer TR, Shaffer J, et al. Myeloma responses and tolerance following combined kidney and nonmyeloablative marrow transplantation: in vivo and in vitro analyses. *Am J Transplant* 2006;6:2121-33.
3. Scandling JD, Busque S, Dejbakhsh-Jones S, et al. Tolerance

- and chimerism after renal and hematopoietic-cell transplantation. *N Engl J Med* 2008;358:362-8.
4. Kawai T, Cosimi AB, Spitzer TR, et al. HLA-mismatched renal transplantation without maintenance immunosuppression. *N Engl J Med* 2008;358:353-61.
 5. Sykes M. Mechanisms of tolerance. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. *Thomas' hematopoietic cell transplantation*. 4th ed. Oxford, England: Blackwell, 2008:188-207.
 6. Coulombe M, Gill RG. T lymphocyte indifference to extrathymic islet allografts. *J Immunol* 1996;156:1998-2003.
 7. Lakkis FG, Arakelov A, Konieczny BT, Inoue Y. Immunologic 'ignorance' of vascularized organ transplants in the absence of secondary lymphoid tissue. *Nat Med* 2000;6:686-8.
 8. Niederkorn JY, Wang S. Immune privilege of the eye and fetus: parallel universes? *Transplantation* 2005;80:1139-44.
 9. Revell CM, Athanasiou KA. Success rates and immunologic responses of autogenic, allogenic, and xenogenic treatments to repair articular cartilage defects. *Tissue Eng Part B Rev* 2009;15:1-15.
 10. Ochi M, Ishida O, Daisaku H, Ikuta Y, Akiyama M. Immune response to fresh meniscal allografts in mice. *J Surg Res* 1995;58:478-84.
 11. Görtz S, Bugbee WD. Allografts in articular cartilage repair. *Instr Course Lect* 2007;56:469-80.
 12. Nassiri M, Viciano A, Streilein JW, Ruiz P. Donor-specific skin transplants activate alloredestructive T cells in mice resistant to neonatal H-2 tolerance induction. *Transplantation* 1993;56:1460-7.

Copyright © 2010 Massachusetts Medical Society.

ELECTRONIC ACCESS TO THE JOURNAL'S CUMULATIVE INDEX

At the *Journal's* site on the World Wide Web (**NEJM.org**), you can search an index of all articles published since January 1975 (abstracts 1975–1992, full text 1993–present). You can search by author, key word, title, type of article, and date. The results will include the citations for the articles plus links to the full text of articles published since 1993. For nonsubscribers, time-limited access to single articles and 24-hour site access can also be ordered for a fee through the Internet (**NEJM.org**).