The field of transplantation has come a long way since the first successful kidney transplant performed by Murray and colleagues in 1954. Kidney, heart, lung, and liver transplantation, among other organs, is now routine, and short-term (1 yr) outcomes have steadily improved to rates of >90 to 95% graft survival (http://www.unos.org). Despite these successes, the major shortfall of our current therapy, which requires potent immunosuppression for life, is that long-term graft survival rates are unacceptable. Fifty percent of kidney transplants are lost by the 10- to 13-yr mark, and survival of heart and lung transplants is significantly worse. The clinical, emotional, and economic consequences of kidney graft failure to the patient, including reinstitution of dialysis, retransplantation, and death, are enormous. Because newer therapies have not had an impact on long-term outcomes, many clinicians and scientists believe that the only way to improve significantly these less-than-optimal long-term results is to eliminate immunosuppression while somehow training the recipient’s immune system to be nonresponsive to the donor organ—that is, to induce immunologic tolerance.

The initial description and “proof of principle” that acquired immune tolerance could be achieved came from the now classic studies by Sir Peter Medawar and colleagues,2 for which he was awarded the Nobel Prize in 1960. Since then, we have learned a vast amount regarding underlying mechanisms of tolerance and how to induce immune tolerance successfully in animals. This large body of work has shown that central and peripheral deletion of autoreactive T and B cells, anergy (unresponsiveness), ignorance, and active regulation/suppression are the predominant mechanisms through which an organism’s immune system differentiates nondangerous self-tissues from foreign invaders that must be destroyed. Applying these concepts to animal models of transplantation, numerous research groups have shown that it is possible to exploit the same mechanisms to achieve indefinite graft survival associated with an absence of pathologic immune reactivity to the donor organ while maintaining an otherwise intact immune system—true immunologic tolerance. The accomplishments have included approaches that use “re-educating” the immune system (immunoablation and bone marrow transplantation), blocking co-stimulatory molecules that are involved in activation and differentiation of pathogenic T and B cells, and inducing active immune regulation. Translation of the successes seen in small animal models to human transplant recipients has been difficult, but we now realize that transplant tolerance can be achieved in humans, and we are beginning to understand the barriers that need to be overcome to facilitate its induction. The goal of this month’s Frontiers in Nephrology is to provide an update on this topic, including an analysis of clinical transplant tolerance in humans, as well as several articles that discuss newly recognized mechanisms of and barriers to achieving the tolerant state.

In the initial clinical contribution, Girlanda and Kirk3 review the current state of the art of human transplantation tolerance and offer several take-home messages. First, operational tolerance, prolonged graft survival without allograft injury in the absence of immunosuppression, does indeed occur spontaneously in humans, albeit rarely (<1% of transplants). Ongoing work through the National Institutes of Health–funded Immune Tolerance Network, among other sources, is studying spontaneously tolerant kidney transplant recipients, and emerging data are beginning to provide some clues as to underlying mechanisms. The article emphasizes that although tolerance is often recognized because of nonadherence to medical regimens, the vast majority of patients who stop taking their medications develop rejection and graft loss. Girlanda and Kirk also outline our current understanding of tolerance mechanism. They review the current experience in tolerance induction protocols in humans, including nonmyeloablative bone marrow transplantation and co-stimulatory blockade and provide potential explanations for why it is more difficult to induce tolerance in humans versus animals. Lastly, the review emphasizes the important concept that tolerance is a dynamic pro-
cess influenced by the host’s environmental exposures, thus necessitating the development and implementation of novel approaches to define and detect the tolerant state.

One such environmental force is the constant exposure to infectious organisms that the immune system must effectively respond to and that could have an impact on the tenuous nature of acquired tolerance. The article by Selin and Brehm addresses this issue through discussing the complexities of cross-reactive/heterologous T cell immunity. The authors outline the data supporting the concept that immune responses that are induced to one infectious organism often cross-react with, and subsequently influence, immunity that is reactive to antigens from a different pathogen. Depending on the specific effect of the initial insult on the immune repertoire, the result can aid the host in eradicating another infection or occasionally can prevent the host’s immune system from responding appropriately to a different, second insult. The authors then discuss the highly relevant concept than an antiviral immune response can cross-react with, and thereby have an impact on, the immune response to a transplanted organ, potentially accelerating rejection and preventing tolerance induction. The constant exposure to viral antigens is one of many differences between humans and animals in controlled laboratory environments (in which tolerance is routinely induced), providing one explanation for why tolerance may be more difficult to achieve in humans.

This theme is explored in further depth by Valujskikh and Li in their contribution on T cell memory as a barrier to transplantation. In practice, T cell memory results from exposure to pathogens, immunizations, blood transfusions, pregnancies, and previous transplants, among other stimuli. Immunologic memory evolved to respond rapidly and effectively to infectious organisms already encountered by the host, thereby limiting the clinical impact of the secondary infection. When compared with naïve T cells, memory T cells are more frequent, have higher functional avidity, and can respond faster to their specific cognate antigen. Although these features are clearly protective in the context of preventing re-infection, such features could have a negative impact on transplant outcome. It turns out that human immune repertoires often contain alloreactive memory T cells, likely as a result of previous environmental exposures that cross-react with alloantigens. With this as a background, Valujskikh and Li then outline the data that T cell memory functions as a barrier to transplant tolerance, explain how memory cells prevent tolerance, and describe how new therapeutic approaches specifically targeting memory T cells may be effective in circumventing this important barrier.

In the final contribution of the series, Bielke and Gill describe a recently discovered and unanticipated novel paradigm in transplant tolerance: That natural killer (NK) cells can be protolerogenic. NK cells are considered a component of the innate immune system. They express germline-encoded activating and inhibitory receptors and are thought to respond rapidly after an immune stimulus by killing infected cells and shaping the subsequent proinflammatory adaptive immune repertoire. Despite these known effects and an established role in preventing bone marrow engraftment, it has been difficult to delineate a clear function for NK cells as mediators of solid-organ transplant injury (limited evidence suggests that NK cells contribute to chronic allograft failure). The surprise outlined by Beilke and Gill is that NK cells can be essential mediators of transplant tolerance; that is, tolerance cannot be induced in their absence. These authors outline the data to support this conclusion and provide insight into how the NK cell may function to facilitate the tolerant state. An understanding of this novel paradigm has the potential to provide new targets for inducing and maintaining tolerance in humans.

Despite more than 50 yr of progress in the clinical care of transplant patients and in the science underlying transplant tolerance, we know that allograft tolerance is achievable in humans but that many barriers prevent routine induction and maintenance of the allograft-tolerant state. It is hoped that the recent findings described in this Frontiers in Nephrology will spawn new research and will help guide the design of novel approaches to implement, maintain, and monitor transplant tolerance in humans.

DISCLOSURES
None.

REFERENCES
1. Meier-Kriesche HU, Schold JD, Kaplan B: Long-term renal allograft survival: Have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant 4: 1289–1295, 2004