

# This Week's Citation Classic®

Myers B D, Ross J, Newton L, Luetscher J & Perlroth M. Cyclosporine-associated chronic nephropathy. *N. Engl. J. Med.* 311:699-705, 1984.

[Division of Nephrology, Department of Medicine, and Department of Pathology, Stanford University School of Medicine. Stanford University Medical Center, CA]

The key observation in this paper was that cardiac transplant recipients treated with cyclosporine exhibited a chronic lowering of their glomerular filtration rate, a phenomenon not observed in recipients treated with other forms of immunosuppression. This led to serendipitous discovery and subsequent description of a chronic renal injury caused by cyclosporine. [The *SCF*<sup>®</sup> indicates that this paper has been cited in more than 635 publications.]

## Chronic Cyclosporine Nephrotoxicity

Bryan D. Myers

Division of Nephrology  
Department of Medicine

Stanford University School of Medicine  
Stanford University Medical Center  
Stanford, CA 94305-5114

My laboratory is devoted to the study of glomerular filtration, the first step in the process of urine formation. This process and the way that the kidney maintains sodium balance are strongly influenced by sympathetic nervous influences. Our cardiac surgeons, who had pioneered the technique of cardiac transplantation at Stanford, had shown that the transplanted heart was permanently denervated. Since many of the signals reaching the kidney via the sympathetic nervous system derive from pressure sensors in the heart, this provided us with an opportunity to examine glomerular filtration and sodium handling by the kidney in the absence of appropriate sympathetic nervous input.<sup>1</sup>

During the course of a study designed to address this issue, we noticed that some patients had a normal glomerular filtration rate (GFR), but that this quantity was severely depressed in others. On examining the patients' charts, we no-

ticed that those with low GFR were all being treated with cyclosporine. Those who received their allografts before the advent of cyclosporine all had a normal GFR. We went on to complete our study using only the latter patients.<sup>1</sup> However, the serendipitous finding that a low GFR was characteristic of cyclosporine-treated patients provided a unique opportunity to elucidate the cause and consequences of this phenomenon. The opportunity was unique because at that time the most widespread use of cyclosporine was in kidney transplant recipients. Since the transplanted kidney is damaged by rejection episodes it was, and has remained to this day, difficult to isolate any contribution to kidney damage by the cyclosporine treatment.

Heart transplant recipients, on the other hand, were shown by us to have normal kidney function in the absence of cyclosporine treatment.<sup>1</sup> The noncyclosporine-treated patients thus provided us with an ideal control group against which to compare the kidney injury in those treated with cyclosporine. This "clean look" at the kidney subjected to chronic cyclosporine administration led to this *Citation Classic*?-. We subsequently went on to elucidate the injury in more detail.<sup>2,3,4</sup>

Our most recent publication<sup>4</sup> summarizes our observations over a decade. It suggests that the primary abnormality of cyclosporine-induced nephropathy is an occlusive afferent arteriopathy which leads to downstream ischemic damage to the kidney. At least in heart transplant recipients (and also in liver transplant recipients), this damage can progress to end-stage renal failure, an event which occurs with an incidence of approximately 10 percent after a decade of continuous cyclosporine therapy.

1. Myers B D, Peterson C, Molina C R, Tomlanovich S J, Newton L D, Nitkin K, Sandier H & Murad F. Role of cardiac atria in the human renal response to changing plasma volume. *Amer. J. Physiol.* 23:F562-F573, 1988.
2. Myers B D, Sibley R, Newton L D, Tomlanovich S J, Boshkos C, Slinson E, Luetscher J A, Whitney D J, Krasny D, Coplon N S & Perlroth M G. The long-term course of cyclosporine-associated chronic nephropathy. *Kidney International.* 33:590-600, 1988. (Cited 175 times.)
3. Myers B D, Newton L, Boshkos C, Macoviak J A, Frist W H, Derby G C, Perlroth M G & Sibley R K. Chrome injury of human renal microvessels with "low-dose" cyclosporine therapy. *Transplantation* 46:694-703, 1988.
4. Myers B D & Newton L D. Cyclosporine-induced chronic nephropathy: an obliterative microvascular renal injury. *J. Amer. Soc. Nephrol.* 2:S45-S52, 1991.

Received July 27, 1993