

## A History of Transplant Nephrology at UCSF

By William Amend

### 1962-1974 Background

Clinical renal transplantation was initiated in 1962 by the Department of Surgery – Dr. J. Englebert Dunphy, chairman. He appointed a young faculty member, Dr. John Najarian, to learn the surgical techniques from Thomas Starzl, then in Denver. Dr. Najarian performed the first UCSF living donor transplant in 1964 assisted by Dr. Folkert Belzer, another young Dunphy-trainee. Because of the scarcity of hemodialysis, a Selection Committee (consisting of MDs, social workers and nurses along with religious/psychiatry input) rigorously chose persons with chronic renal failure – only approving a patient to receive dialysis if he/she was a transplant candidate. At the time, both life-saving treatments were on a self-pay basis.

Besides having few possible living-donors, there were similar barriers to the use of deceased donors – procurement and recipient surgeries had daunting logistical problems. To address this obstacle, Dr. Belzer did landmark research utilizing cold storage and pulsatile perfusion in cadaver procurement and preservation.

During this time, immunosuppressants included only corticosteroids, azathioprine and the occasional use of crude antilymphocyte preparations. Since there was not a good clinical alternative (chronic dialysis was often unavailable), over-immunosuppression often resulted. Sometimes transplants (two or more) were serially performed in desperate attempts to save the patient following graft failure. It is not surprising that Infectious Disease consults provided the brunt of posttransplant medical care. The nephrologists at that time were simply utilized to take care of any kidney transplant-failure.

When Dr. Najarian went to the University of Minnesota (1967), the new chief of the UCSF transplant service was Dr. Samuel Koontz, a PhD who was not only a surgeon but a clinical immunologist as well. He and Dr. Belzer enjoyed great success with their complementary research interests.

Beginning in 1967, UCSF received a 10-year NIH center grant: “Clinical Utility of Kidney Transplantation,” the purpose of which was to explore how various renal disease-states might affect clinical outcomes. Since the surgical procedure had no insurance coverage and was self-pay, the research funding allowed for the rapid growth

of the program. Although UCSF soon became one of the largest kidney transplant programs in the world, nephrology participation remained limited.

Dr. Kent Cochrum, DVM, of the Immunology Laboratory developed the three-day mixed lymphocyte culture (MLC). It was only useful prospectively with living donors but provided retrospective information in the cases of deceased-donor transplantation. This test turned out to be the in-vitro biologic correlate of what later became known as Class II HL-A (DR-locus) compatibility.

Dr. Koontz was also a consummate activist. While at UCSF (and subsequently at Downstate SUNY as chairman of surgery), he: 1. Functionally defined the term “End-stage renal disease” (ESRD) = when a person is chronically so uremic that he needs dialysis or a transplant to remain alive; 2. Helped develop the Uniform Anatomic Gift Act which led to developing criteria of brain death; 3. Served as a major advocate to get Congressional approval of Medicare coverage for persons with ESRD (1972). This last advance catalyzed the proliferation of chronic dialysis programs and kidney transplant services throughout the U.S.

Dr. Koontz departed in 1972, Dr. Belzer to U. Wisconsin in 1974 and the surgical directorship was assumed by Dr. Oscar Salvatierra, a highly respected urologist.

Dr. Salvatierra was a trainee of Drs. Koontz and Belzer. His initial contributions included making kidney transplant available to a wide variety of “high risk” disease-states (e.g. diabetes); developing techniques for very young pediatric patients (en-bloc procedures); and formulating the principle of limiting immunosuppression – a truly unique philosophy at the time. This strategy, coupled with an increased access to dialysis, allowed the kidney transplant patient to have substantially lower morbidity and mortality without any effect on overall graft success rates.

#### 1974-1983 Nephrology Association with the Kidney Transplant Service

By 1974, the UCSF program had grown from 20/year to 100 surgeries/year and the pre- and post transplant clinic had burgeoned. Dr. Salvatierra, Chief of Surgery (Dr. Paul Ebert), Chief of Medicine (Dr. L.H. Smith) and the Division of Nephrology Director (Dr. Floyd Rector) recognized the need for a nephrologist who would be assigned full time to this important university program.

Dr. William Amend was recruited after completing a nephrology fellowship with Dr. John Merrill in Boston, and soon joined by a second surgeon, Dr. Nicholas Feduska (1975) and a second nephrologist, Dr. Flavio Vincenti (1976). With a growing collegiality between the four, the clinical experience was enriched. Given the limited types of immunosuppression, the unit's numerous publications included descriptions (and management) of infections, aseptic necrosis, cancer, gastrointestinal problems, cataracts and the many other complications, which affected the patients. Since 1974, renal fellows at UCSF have rotated through the kidney transplant service.

The surgeons and two nephrologists developed a unique (for UCSF and other academic centers at the time) team-approach . . . each providing a particular expertise to each patient. Since it was such an unusually closely-knit arrangement, it was of little surprise that a concern was raised during a Medicare-audit looking at billing practices (1978). The auditor asked one of the nephrologists: "How many surgeries did you do last year?" ('None'); then: "Well, do you split the surgical fees?" ('No'); followed by: "What do you do, then, on a surgical service?" ('I do nephrology consultation at the request of the surgeons on kidney transplant. '); then: "What does this mean?" ('I assess dialysis need, manage hypertension, treat diabetes, diagnose infections, etc.' before adding, 'I guess I am doing transplant nephrology. ') The interchange ended with the auditor concluding: "Then you're not a surgeon?" ('Sometime I wish I were but no, no, no! I'm a nephrologist. '). Satisfied, the auditor sat back and stated: "Then I'll write down here that you are a 'transplant nephrologist' ." (The term stuck).

During this time, Amend and collaborators in the School of Pharmacy published studies of prednisone and azathioprine in attempts to improve their use. Dr. Vincenti published the large UCSF experience (1978-NEJM) – it was sobering: <70-85% living donor 2year graft success and <47% cadaver donor graft success. In addition, the initial hospitalization was 30 days with frequent readmissions.

Dr. Juliet Melzer joined the surgical faculty in 1983 to assist handling the surgical load that had increased to nearly 200 kidney transplants per year.

Immunologic advances included the use of a more potent, less toxic polyclonal rabbit-ATG, collaboration with Drs. Terasaki and Opelz (UCLA) regarding overall benefits of blood transfusions and importantly, a unique, surprisingly successful series of

living (mismatched) donor transplants following pretransplant donor- specific transfusions (the DST-story). The protocol, devised by Drs. Salvatierra and Cochrum, had the downside risk, however, of potential recipient sensitization.

In the early 1980s, clinical management advances took hold. The widespread use of certain antimicrobials and newer antivirals in the first month post transplant markedly reduced the incidences of CMV, PCP, Candidiasis and postoperative infections. Collaboration with the Department of Radiology led to the increased use of sonographically guided transplant renal biopsies.

Dr. Marvin Garovoy was recruited from the Peter Bent Brigham to run a newly formed UCSF Histocompatibility Lab. Under his direction, the flow-activated cell sorting technique (FACS) was invented for precise cross matching. The two nephrologists and Garovoy became founding members of the American Society of Transplant Physicians, in 1982, which initially numbered 30; the successor AST now has nearly 3,000. In 2003, Dr. Vincenti served as the President of the American Society of Transplantation.

### 1983-1988

The biggest paradigm shift in clinical immunosuppression followed the discovery of cyclosporine A. The agent was extremely effective in clinical trials but had frequent nephrotoxicity. Within one month of the drug's approval (1983), the UCSF staff noted striking differences in outcomes – patients had earlier discharges and the rejection rate was halved. The task now was to differentiate rejection from acute CSA toxicity. Biopsies were increasingly utilized along with studies of non-invasive surveillance.

Dr. Stephen Tomlanovich joined the UCSF Transplant Nephrology faculty in 1985. His renal fellowship research at Stanford with Dr. Bryan Myers included several investigations in the nephrotoxicity of cyclosporine. His expertise and clinical skills would prove invaluable. Drug levels using an immunoassay were performed at Stanford before an HPLC assay was developed at UCSF. In 1986, Drs. Melzer and Tomlanovich published the large UCSF CSA-treated transplant outcomes. Their analysis showed a doubled success rate and lowered morbidities compared to only a decade previously. The pre- and post-CSA eras were thereafter referenced as such.

These CSA-associated kidney transplant successes kindled an enthusiasm for the development of ‘nephew’ programs at UCSF in the areas of liver, pancreas, pulmonary and heart transplants – all as treatments of various “end-stage organ failures.” The UCSF kidney transplant program served as a model for the formation of combined surgical-medical programs with similar cross-disciplinary participation (including pods of other committed specialists and researchers). As an example, Dr. Melzer began the pancreas-kidney transplant service in (1988) with assistance of diabetologists and the nephrologists.

### 1988-2005

Drs. Nancy Ascher and John Roberts from the U.Minnesota joined the faculty in 1988. Dr. Ascher initiated the surgical transplant fellowship program with 5 subsequent trainees becoming surgical faculty – Drs. Peter Stock, Chris Friese, Sandy Feng, Ryo Hirose, Sang-Mo Kang and Andrew Posselt. As well, Drs. Tomlanovich and Vincenti developed an intensive kidney transplant fellowship for board-qualified nephrologists interested in this career-track.

Dr. Ascher and Roberts formed the UCSF Liver Transplant Service as a combined service with interested hepatologists (soon known as ‘transplant hepatologists’). The UCSF transplant nephrologists have routinely consulted on this and other solid organ transplant services and continue to coauthor many conjoint publications.

Following Drs. Salvatierra’s and Feduska’s departures in the late ‘80’s, the heads of the UCSF surgical services became: Dr. Ascher – chair of Surgery and Dr. Roberts – head of the Renal & Liver Transplant Program. Dr. Tomlanovich was appointed as the Kidney Transplant Program’s Medical Director in 1995. Dr. Garovoy moved to a biotechnology firm and Dr. Lee-Anne Baxter was subsequently appointed head of the UCSF Immunogenetics Lab.

Dr. Deborah Adey joined the transplant nephrology section in 1997 and was instrumental in the education of medical students, residents and fellows. Dr. Adey’s research interest focused on approaches to highly sensitized recipients and on the detection of polyoma (BK) virus infections. She left in 2005 and currently is on faculty at UC Davis.

Dr. Amend retired in 2005.

### 2005-present

During the previous decade, and continuing since, Dr. Vincenti, Tomlanovich and other colleagues initiated many clinical drug trials involving a variety of unique immunosuppressants: OKT3 (a murine antibody), tacrolimus, mycophenolate, rapamycin, and costimulatory signal blockers (belatacept and daclizumab). All of these studies led to the approval of important immunosuppressive therapies. As an offshoot, Dr. Vincenti has retained a special interest in studying the pathogenesis of (and treatments for) FSGS because of the condition's propensity to recur in allografts. Dr. Vincenti has held the Faiman Chair of Medicine & Surgery since 2007.

Dr. Tomlanovich has spearheaded the development of a referral network within Northern California. This has allowed better access to clinical care and participation in many of UCSF's ongoing transplant research studies. He and Dr. Roberts have helped create a national network-system to deal with incompatible living donor-recipient pairs.

For the past 35 years, residents and general nephrology fellows have rotated through the Kidney Transplant Service. This involves experiences in kidney transplant inpatient-care (15 pts./day), nephrology consultation on non-renal solid organ recipients (5-6/day) and rotation through the kidney transplant clinic (1-2 half-day/week). As mentioned, there has also been an AST-certified fellowship trainee(s) for the past fifteen years.

In 2010, the transplant clinic and offices were relocated to a new, state-of-the-art facility at the UCSF Parnassus Campus – the Connie Frank Transplant Center.

The transplant nephrology faculty (with their research interests) now includes: Sindhu Chandran (serial analyses of transplant biopsy phenotypes and their predictive value on long term outcomes), Brian Lee (studies involving renal donors and posttransplant development of diabetes), Allison Webber (newer techniques of immune monitoring), and David Wojciechowski (studies of more effective diagnosis and management of posttransplant infections).

Current and comparative data of the UCSF clinical program (case loads and outcomes) may be best obtained by accessing the Scientific Registry of Transplant Recipients website: [SRTR.org](http://SRTR.org).

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