

Lowe Syndrome Trust

**Charles Dent's probands and genetic heterogeneity in Dent's disease
Steven J. Scheinman**

**A Half-Century of Renal Tubular Disease
Symposium in honor of Professor Oliver Wrong**

**Royal Free Hampstead NHS Trust
Friday 27 March 2009**

This is a symposium organized to honor Professor Oliver Wrong on the occasion of the 50th anniversary of the publication of his classic paper on measuring how the kidney excretes acid from the body. Prof. Wrong worked closely with Professor Charles Dent, who from the 1950s until his death in 1976 made many pioneering discoveries regarding mineral metabolism and kidney function. Prof. Dent described several patients in studies subsequently augmented by Prof. Wrong, leading to the discovery of what we now call "Dent's disease". The kidney problems include loss of proteins, minerals, and other solutes in the urine, and eventual renal failure. These features resemble identically the kidney problems seen in patients with the Lowe syndrome, but patients with Dent's disease do not have the renal acidosis, mental developmental delay, or eye problems that are so characteristic of LS. It is well established that Dent's disease is associated with mutations in a gene, *CLCN5*. However, we found that about 40% of patients with Dent's disease do not have mutations in this gene, and surprisingly that about 15% of these have mutations in *OCRL1*, the gene responsible for LS. This observation has now been confirmed by laboratories in Germany and Japan as well as ours.

It is remarkable that even those patients with Dent's disease whose mutation is in *OCRL1* lack the severe eye, brain, and acidosis problems that LS patients have. A possible explanation for this mystery is now emerging. We and others have observed that the pattern of mutations in *OCRL1* in these patients differs from that in LS patients. These differences suggest that there are different forms of the *OCRL1* gene in different tissues of the body, so that mutations in one part of the gene would alter its function in the kidney but perhaps not in the eye or brain, or the cells involved in urinary acid excretion.

These observations need to be pursued in further studies, but offer the hope of understanding better the mechanisms that produce the most disabling features of the Lowe Syndrome.