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Crawhall J C, Scowen E F & Watts R W E. Effect of penicillamine on cystinuria. *Brit. Med. J.* 1:588-90, 1963.

[Medical Professorial Unit, St. Bartholomew's Hospital, London, and Department of Medicine, University of London, England]

Urinary cystine excretion of two patients with cystinuria was reduced following oral administration of D-penicillamine by a mechanism of thiol-disulfide exchange. Penicillamine-cysteine disulfide and penicillamine disulfide were identified in the urine. [The *SCI*® indicates that this paper has been cited in over 220 publications.]

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The Medical Professorial Unit of St. Bartholomew's Hospital in London was established by Sir Archibald Garrod whose particular interest was in hereditary disorders of metabolism. E.F. Scowen was director of the unit when I was a house officer (intern) there. Around that time an 11-year-old girl was admitted for evaluation by Richard Watts, who was a senior lecturer in medicine. The patient had bilateral renal calculi because of cystinuria. We visited her on ward rounds, and as we were leaving Scowen said to me, "There must be some way of stopping the cystine excretion of these patients." This was not just another provocative statement from a professor of medicine to his house officer.

Earlier in my career I studied chemistry and obtained my PhD as a graduate student of D.F. Elliott at the National Institute for Medical Research, where I had worked on the subject of chemical interactions of amino acids and peptides. I then came to the Medical School of St. Bartholomew's Hospital, which is part of the University of London Medical School system.

As a lecturer in biochemistry, I quickly started my research association with Watts and Scowen with an investigation of another stone-forming disease, hyperoxaluria. I remember that I reviewed in my mind all sorts of chemical reagents that would alter cystine excretion, but only one reaction occurred rapidly and readily and that was thiol-disulfide exchange. Of course, most thiols are too unpleasant or toxic to use, but John Walshe had already shown that D-penicillamine could be used successfully in the treatment of Wilson's disease. The group accepted this proposal, but the analytical procedure presented a problem. We did not have an amino acid analyser available so, with the help of H.E. Archer, we established a gravimetric assay for cystine. Two patients were brought into the hospital and their cystine excretion measured by this procedure. Penicillamine was then administered in descending dosages. At the highest dosage, no cystine at all could be found in the urine, and a simple dose-response curve was obtained using isotope dilution techniques.

The work was readily accepted for publication and was confirmed in other medical centres around the world.[1-3] It was not until later that examples of the adverse effects of penicillamine began to appear.[4] I feel sure it was that one remark of Scowen that set this whole process in motion, coupled with the fact that we were already a team in place with a variety of different skills.

1. **Bartter F C, Lotz M, Thier S, Rosenberg L E & Potts J T.** Cystinuria—combined clinical staff conference at the National Institutes of Health. *Ann. Intern. Med.* 62:796-822, 1965.
2. **Dahlberg P J, Van Den Berg C J, Kurtz S B & Smith L H.** Clinical features and management of cystinuria. *Mayo Clin. Proc.* 52:533-42, 1977.
3. **Crawhall J C.** Cystinuria—diagnosis and treatment. (Nyhan W L, ed.) *Heritable disorders of amino acid metabolism: patterns of clinical expression and genetic variation.* New York: Wiley, 1974. p. 593-617.
4. **Halperin E C, Thier S O & Rosenberg L E.** The use of D-penicillamine in cystinuria: efficacy and untoward reactions. *Yale J. Biol. Med.* 54:439-66, 1981.

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