

This Week's Citation Classic®

Slater T F. Necroaenic action of carbon tetrachloride in the rat: a speculative mechanism based on activation. *Nature* 209:36-10. 1966; and **Slater T F.** *Free radical mechanisms in tissue injury*. London: Pion. 1972. 283 p. [Dept. Chemical Pathol. Univ. College Hospital Medical School, London; and Dept. Biochem., Brunel Univ., Uxbridge, Middlesex, England]

The paper addresses a number of fundamental questions concerning liver necrosis caused by carbon tetrachloride, and seeks to explain the intracellular localization of the initial damage to hepatocytes. The book deals with free radicals in relation to pathological processes. [The SC[®] indicates that the paper and the book have been cited in more than 455 and 420 publications, respectively.]

Free Radical Processes in Pathology

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When Trevor Frank Slater (TFS as he was known in the lab) was invited by Claude Rimington to join the Department of Chemical Pathology at University College Hospital Medical School (now University College London Medical School), he was already an authority on the then-burgeoning field of lysosomes. He was to work on the complexities of disease processes at the cellular level, particularly in relation to cell death, which was being tackled by a team of biochemists assembled under the aegis of the eminent pathologist Sir Roy Cameron. One of the models of necrosis espoused by Cameron was carbon-tetrachloride-induced hepatotoxicity in rats. The animals exhibited liver damage, which was thought at the time to be the result of membrane derangement caused by the lipid solvent properties of carbon tetrachloride. Slater became interested in the problem when it was shown by M.J.R. Dawkins¹ that newborn rats did not exhibit the characteristic centrilobular liver necrosis on exposure to carbon tetrachloride. Moreover, there was evidence from the work of A.E.M. McLean and E.K. McLean² suggesting that carbon tetrachloride was metabolized by the endoplasmic reticulum.

Slater was, at that time, ensconced in a small dingy office with one frosted window giving onto a dark and airless well between buildings. He spent a lot of time plotting the data obtained from the laboratory. In those precomputer days, the fitting of regression data was a time-con-

suming task; but TFS was a dab hand with a slide rule, and he investigated many possible models of metabolic conversion of carbon tetrachloride by rat liver microsomal preparations. The data suggested that carbon tetrachloride was acting as an initiator of a lipid-peroxidation chain reaction and that microsomal metabolism converted it to the trichloromethyl radical. The indirect evidence of free-radical generation was obtained by TFS with Barbara C. Sawyer,^{3,4} and the scientific evidence was sufficiently convincing by 1965 for TFS to pen the *Classic* paper. He showed a draft of it to Cameron and was delighted to obtain the great man's approval—though it was somewhat tentative since Cameron, while a respected histopathologist, was no chemist.

The wide-ranging studies that this spawned were reviewed by Slater at a Royal Society discussion meeting.⁵ The most important of these later studies was the demonstration⁶ that CCl₃ rapidly reacts with molecular oxygen⁶ and that the species-initiating lipid peroxidation is the CCl₃O₂ radical.⁷

One of the attractive features of TFS's lipid-peroxidation hypothesis was that it indicated a path whereby a limited metabolic derangement could result in widespread cellular damage. Slater felt that many aspects of pathology might, in this manner, entail free-radical mediation. As he was being pressed at the time to write a book, he began setting out some of his ideas in this direction. He worked on the draft at home in the evenings and would dictate new sections when he arrived in the morning. Since he shared the office, this often resulted in ad hoc discussions; and much interest and amusement were generated by inventing free-radical mechanisms to account for a wide range of disease states, though only a handful of these survived in the book.

The studies were highly cited because they marked the beginning of a new era of free-radical pathology. Slater's contributions to this field were widely recognized, and he was the recipient of three honorary degrees and many other awards and distinctions. His death in April 1992 was a great loss to chemical pathology.

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- Slater T F & Sawyer B C.** The effects of carbon tetrachloride on rat liver microsomes during the first hour of poisoning in vivo, and the modifying actions of promethazine. *Biochem. J.* 111:317-24. 1969.
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- Packer J E, Slater T F & Willson R L.** Reactions of the carbon tetrachloride-related peroxy free radical (CCl₃O₂) with amino acids: pulse radiolysis evidence. *Life Sci.* 23:2617-20. 1978.
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