NUMBER 3
JANUARY 15, 1979

This Week's Citation Classic

Conney A H. Pharmacological implications of microsomal enzyme induction. *Pharmacol. Rev.* **19**: 317-66, 1967.

This review discusses characteristics of the enzyme inducers, consequences of enzyme induction for the action of drugs, the presence of multiple monooxygenases in liver microsomes, the selective induction of microsomal monooxygenases, mechanisms of induction of microsomal enzymes, effects of drugs on electron transport systems in liver microsomes, enzyme induction in nonhepatic tissues, stimulatory effects of drugs on the metabolism of steroid hormones and other normal body constituents, enzyme induction in humans, and possible therapeutic applications of enzyme induction. [The *SCI*® indicates that this paper was cited 2019 times in the period 1967-1977.]

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June 9, 1977

Studies by H L Richardson and his associates in 1952 demonstrated that 3 methylc holanthrene–a potent skin carcinogen–inhibited the hepatocarcinogenictty of Vmethyl-4 dimethylammoazobenzene.[1] Additional research by James and Hizabeth Miller and their associates at the University of Wisconsin demonstrated that several polycyclic aromatic hydrocarbons inhibited the carcinogenicity of 3-methyl-4-dimethylaminoazobenzene and 2 acetylammofluorene.[2] While a graduate student with James and Hizabeth Miller from 1952 1956. I studied the stimulatory ettect of polycyclic hydrocarbons on liver microsomal enzymes that metabolize aminoazo dyes to none arc inogenic products. These studies helped explain why polycyclic hydrocarbons inhibited the carcinogenic action ot aminoazo dyes We also demonstrated that 3-methylcholanthrene and benzo(a)pyrene induced the synthesis of a liver microsomal enzyme system that hydroxylates benzo(a)pyrene.

"After leaving the University of Wisconsin in 1956, I entered the world of business for several months as a pharmacist in my father's drugstore. I wanted very much to return to research and to explore the possibility that microsomal enzyme induction was a broad phenomenon that could be applied to many drugs, pesticides, chemical carcinogens, and other environmental pollutants. I left the drugstore in 1957 and asked Bernard B Brodie at the National Institutes of Health if I could study the induction of microsomal drug-metabolizing enzymes in his laboratory. Brodie tried to convince me that I should work with him on other exciting aspects of drug metabolism or on aspects of the biochemistry of neurotransmitters that were already in progress in his laboratory. When he realized that I really wanted to study the possibility of the induction of drug-metabolizing enzymes, he had me work with John J Burns, who gave me the opportunity and encouragement to pursue studies on microsomal enzyme induction after the completion of my principal asignment. which was the identification of metabolites of two new drugs –zoxazolamine and chlorzoxazone.

"After demonstrating that the duration of action of zoxazolamine was 730 minutes in control rats and only 17 minutes in benzo(a)pyrenepretreated rats, we found that benzo(a)pyrene and phenobarbital decreased the action of zoxazolamine and many other drugs by stimulating their metabolism. A series of investigations on the pharmacological implications of microsomal enzyme induction then led to my 1967 review article which has become a citation classic. I tried to bring together work from my own laboratory as well as research from other laboratories that pointed out the broad implications of microsomal enzyme induction.

"I believe that my article on the pharmacological implications of microsomal enzyme induction is a citation classic because it touches on many aspects of research in the biomedical sciences and because the article has broad implications for humans who are treated with drugs or who are exposed to environmental pollutants."

1. **Richardson H L, Stier A R & Borsos-Nachlnebel E.** liver tumor inhibition and adrenal his responses in rats to which 3-methyl-4-dimethylaminoazobenzene and 20-methylehol anthrene were simulaneously administered. *Cancer Res.* **12**:365-61, 1952.
2. **Miller E C, Miller J A. Brown R R & MacDonald J C.** On the protective action ot certain polveyelic aromatic hydrocarbons against careinogenesis by aminoazo dyes and 2-acetylaminotluorene. *Cancer. Res.* **18**:469-77, 1958.