

This Week's Citation Classic®

Kuntzman R. Drugs and enzyme induction. *Annu. Rev. Pharmacol.* 9:21-36, 1969.
[Wellcome Research Laboratories, Burroughs Wellcome and Co. (USA) Inc., Tuckahoe, NY]

This review describes the stimulatory effect of drugs and environmental pollutants on the metabolism of foreign chemicals as well as on the metabolism and concentration of normal body constituents such as steroids, sterols, fatty acids, microsomal hemoproteins, bilirubin, thyroxin, and melatonin. The possible therapeutic implications of liver microsomal enzyme induction are discussed. [The *SCI*® indicates that this paper has been cited in over 285 publications.]

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My research career began in the 1950s when I went to work for Bernard Brodie at the National Institutes of Health (NIH). These early days, during which I also studied toward my PhD degree in biochemistry at George Washington University, were devoted to research on biogenic amine metabolism, turnover, and mechanism of action. The guidance and encouragement I received from Brodie, along with my involvement with many renowned scientists, contributed in large part to my growth as a biochemical pharmacologist.

During my stay at the NIH, I met Allan Conney and John Burns, who were pursuing their research interests in drug metabolism and enzyme induction, also under Brodie. After receiving my degree in 1962, I had the good fortune of joining Conney and Burns at Burroughs Wellcome, where I embarked upon studies concerning the variety of factors influencing the metabolism and action of drugs, steroids, and carcinogens. With a lot of hard work, dedication, and support from my colleagues and collaborators, my research progressed to the point where I had the honor of receiving the John Jacob Abel Award for my achievements from the American Society for Pharmacology

and Experimental Therapeutics in 1969 and was asked to write this annual review that same year. The body of literature devoted to enzyme induction had grown substantially during the 1960s, and what I tried to do in writing the review was bring together those papers, including my own, that had contributed toward our understanding the pharmacological, toxicological, and therapeutic implications of this phenomenon.

The review points out the importance of enzyme induction in relation to the planning and interpretation of chronic toxicity studies, our exposure to environmental chemicals, multiple drug therapy, and the metabolism of a number of normal body constituents. An important section includes a discussion indicating the presence of multiple cytochromes P-450 in rat liver microsomes, a concept that was not readily accepted at the time the review was written. Today, more than a dozen cytochromes P-450 have been purified from rat liver microsomes, and many selective inducers of these enzymes have been identified.^{1,2} In addition, several P-450 genes have been cloned, and one of them has been inserted into yeast cells that could then synthesize catalytically active cytochrome P-450.^{3,4} It is conceivable that highly selective inducers of specific cytochrome P-450 enzymes will be found someday for the treatment of certain human diseases involving impaired or excessive expression of cytochrome P-450 genes that participate in the metabolism of endogenous substrates such as cholesterol or cortisol. Other prospects for future research include the possible use of these enzymes or their cloned genes in suitable microorganisms for the facile synthesis of organic molecules or for the inactivation of toxic chemical wastes.

I believe that my review on drugs and enzyme induction has been highly cited because it covers a wealth of fundamental information that has allowed us to gain more insight into the broad implications of microsomal enzyme induction and has served as the basis for the kind of research being done today.

1. Ryan D, Ramanathan L, Iida S, Thomas P E, Hanu M, Shively J E, Lieber C S & Levin W. Characterization of a major form of rat hepatic microsomal cytochrome P-450 induced by isoniazid. *J. Biol. Chem.* 260:6385-93, 1985.
2. Thomas P E, Bandiera S, Reik L M, Maines S L, Ryan D E & Levin W. Polyclonal and monoclonal antibodies as probes of rat hepatic cytochrome P-450 isozymes. *Fed. Proc.* (In press.)
3. Adesnik M & Atchison M. Genes for cytochrome P-450 and their regulation. *CRC Crit. Rev. Biochem.* 19:247-305, 1985.
4. Oeda K, Sakaki T & Ohkawa H. Expression of rat liver cytochrome P-450(MC) cDNA in *Saccharomyces cerevisiae*. *DNA* 4:203-10, 1985.