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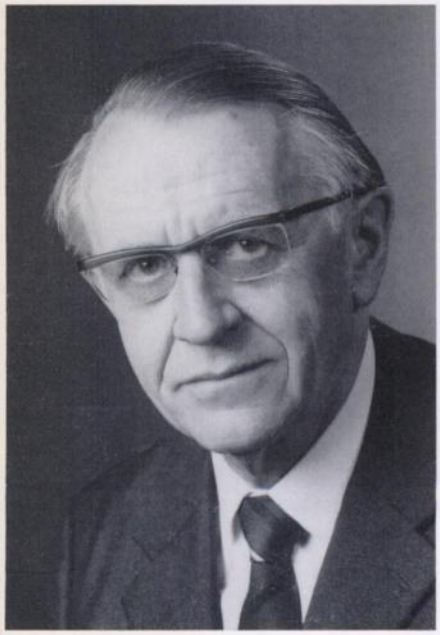
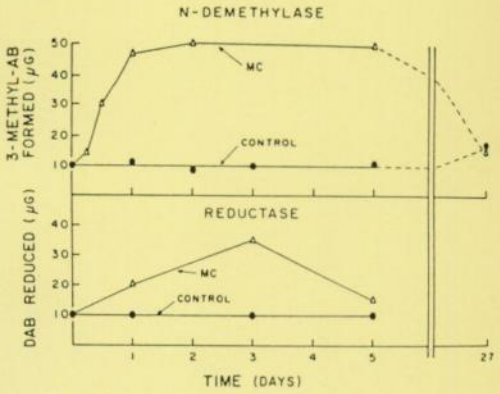
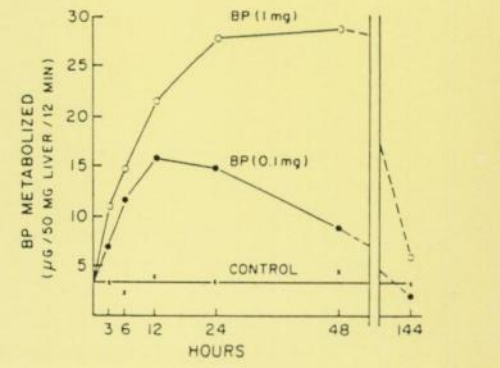
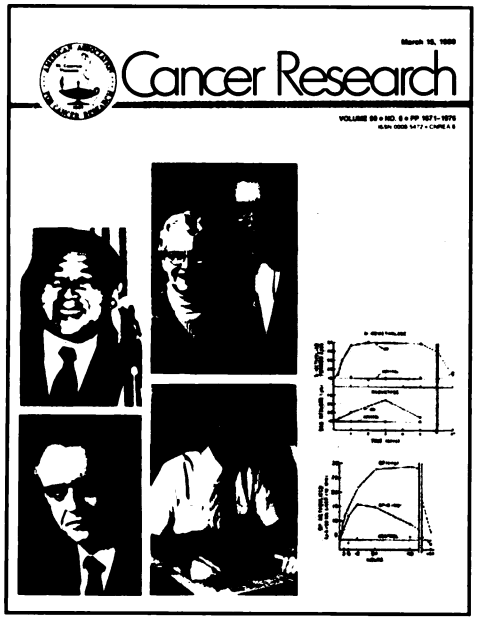




# COVER LEGEND




It is now known that most carcinogens and some drugs used in cancer therapy require host metabolism. Many chemicals and drugs are also detoxified by host metabolism. From 1956–1965, important contributions by several independent groups demonstrated that these metabolic enzyme systems have a basal constitutive level, which can be increased, often considerably, through induction of synthesis by certain chemicals. Early on, the unexpected observation was made that feeding one carcinogen, 3-methylcholanthrene, to rats inhibited the hepatocarcinogenicity of another carcinogen, an aminoazo dye (Cancer Res., *12*: 356, 1952). Conney and the Millers in the United States discovered the underlying mechanism, namely, that 3-methylcholanthrene induces the synthesis of enzymes in the liver that detoxify the dye through *N*-demethylation and azo group reduction (Cancer Res., *16*: 450, 1956). They further demonstrated that 3-methylcholanthrene or benzo(*a*)pyrene induced the synthesis of benzo(*a*)pyrene-hydroxylating enzymes in liver microsomes, essentially a substrate-induced synthesis, enhancing mammalian foreign compound metabolism (J. Biol. Chem., *228*: 753, 1957). The incidental observation was made that carbon monoxide blocked the *N*-demethylation activity (Cancer Res., *17*: 628, 1957), and others showed that the carbon monoxide-binding cytochrome P-450 enzymes were involved (J. Biol. Chem., *237*: 1375, 1962; Cancer Res. cover, December 1, 1988). Conney *et al.* also observed that phenobarbital and several unrelated drugs induced the synthesis of microsomal enzymes that metabolize both drugs and carcinogens [Science (Wash. DC), *130*: 1478, 1959; J. Pharmacol. Exp. Ther., *130*: 1, 1960]. In Germany, Remmer independently found that phenobarbital shortened the hexobarbital sleeping time of rats and showed that this was a result of an increase in the metabolism of the hexobarbital (Klin. Wochenschr., *36*: 332, 1958; Naunyn-Schmeideberg's Arch. Exp. Pathol. Pharmakol., *237*: 296, 1959; Ann. NY Acad. Sci., *123*: 79, 1965). Also, the Japanese pharmacologist, R. Kato, then working in Milan, Italy, separately observed that the activities of drugs affecting the central nervous system could be modified by other drugs that altered the rates of metabolism of the first drugs (Att. Soc. Lombarda Sci. Med. Biol., *14*: 783, 1959; Jpn. J. Pharmacol., *11*: 31, 1961; Biochem. Pharmacol., *13*: 69, 1964).

Thus, independent groups clarified the mechanisms of action of drugs in general, especially in relation to drug-drug interactions causing beneficial or adverse effects, the development of tolerance to drugs, and their addictive effects. Families of inducible drug-metabolizing enzymes have been identified (Annu. Rev. Biochem., *49*: 315, 1980; Cancer Res., *48*: 2946, 1988). The roles of these inducible enzymes include not only pathways of detoxification but also means of toxication by activation of carcinogens and drugs [Cancer (Phila.), *47*: 2327, 1981]. Many of these effects have been observed in humans, *e.g.*, altered enzyme levels from exposure to cigarette smoke or certain dietary factors (Cancer Res., *42*: 4875, 1982; Pharm. Z., *133*: 9, 1988; Jpn. J. Cancer Res., *78*: 297, 1987).

Shown are James A. Miller and the late Elizabeth Miller, Van Rensselaer Potter Emeritus Professors of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin, Madison (*top center*); Allan H. Conney, State of New Jersey Professor of Pharmacology and Chairman, Department of Chemical Biology and Pharmacognosy, College of Pharmacy, Rutgers, The State University of New Jersey (*bottom center*); Herbert K. Remmer, Professor Emeritus, Institut für Toxicologie, Eberhard-Karls-Universität Tübingen (*bottom left*); and Ryuichi Kato, Chairman, Department of Pharmacology, School of Medicine, Keio University, Tokyo (*top left*). The figures illustrate the 3-methylcholanthrene-induced azo dye *N*-demethylase and reductase (1956) and the substrate-induced benzo(*a*)pyrene metabolism (1957).

We are indebted to Professor H. Marquardt and the individuals featured for information and photographs.

John H. Weisburger