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This Week's Citation Classic®

Axelrod J. An enzyme for the deamination of sympathomimetic amines: properties and distribution. *J. Pharmacol. Exp. Ther.* 110(1), 1954 (abstract); The enzymatic deamination of amphetamine (Benzedrine). *J. Biol. Chem.* 214:753-63, 1955; Enzymatic demethylation of sympathomimetic amines. *Fed. Proc.* 13:332, 1954 (abstract); and, The enzymatic demethylation of ephedrine. *J. Pharmacol. Exp. Ther.* 114:430-8, 1955.
[Lab. Chemical Pharmacology, Natl. Heart Inst., Natl. Insts. Health, Bethesda, MD]

These abstracts and the papers that followed were the first description of a new class of enzymes localized in liver microsomes, requiring NADPH and O_2, that can metabolize drugs and foreign compounds. These publications also showed that microsomal enzymes having the same cofactor requirements can metabolize drugs by different pathways. [Taken together, the two abstracts and two papers have been cited in more than 300 publications.]

Microsomal Enzymes That Metabolize Drugs

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Although I consider this *Journal of Biological Chemistry* paper one of two or three of my most important contributions during the last 45 years in research, there were more than 50 papers that I published that received more citations. The abstracts clearly described the intracellular localization of enzymes and cofactors required to metabolize drugs by different pathways. In these abstracts, the experimental details showing how the body metabolizes drugs were obvious. The full papers were delayed and published two years after I completed this work. Several papers on the microsomal enzymes that metabolize drugs were published at the same time or soon after my full papers were published. Abstracts are rarely cited, and my discovery of the microsomal enzymes that metabolize drugs was lost in the shuffle.

The body has the remarkable capacity to metabolize almost any drug and foreign organic compound by a variety of metabolic pathways. For the most part, these compounds are transformed to less pharmacologically active metabolites and excreted. Depending on the chemical structure, some drugs are metabolized to more pharmacologically active, toxic, or carcinogenic compounds. How the body can recognize and transform drugs and foreign compounds was a mystery for more than a century.

In 1952, while working in the laboratory of B.B. Brodie in the National Heart Institute, I was allowed to choose and carry out my own research projects, although I did not have a doctorate. I was intrigued by the behavioral and the cardiovascular actions of the sympathomimetic amines, amphetamine and ephedrine, since little was known about their fate in the body. I soon found that amphetamine and methylamphetamine were transformed in several mammalian species by a variety of pathways. When amphetamine was administered to rabbits, it disappeared without a trace.

I thought that it might be easier to identify the metabolic products of amphetamine in rabbits by using an in vitro approach. In a series of experiments using rabbit liver slices, homogenates, and various subcellular fractions, I found that amphetamine was metabolized by deamination when the microsomes and the cytosolic fraction were combined and when NADP was added. I soon found that the enzyme that deaminated amphetamine was localized in the microsomes and that glucose-6-phosphate dehydrogenase in the cytosol was generating NADPH. Adding NADPH to rabbit liver microsomes in the presence of O_2 resulted in the deamination of amphetamine.

By June 1953, I knew I had discovered an enzyme that metabolized drugs. I reported these findings at the 1953 fall meeting of the American Society of Pharmacology and Experimental Therapeutics, and an abstract was published in January 1954. About the same time, I also found that rabbit liver microsomes in the presence of NADPH and O_2 can N-demethylate ephedrine, O-demethylate codeine,[1] and cleave aromatic ethers.[2] In studies on the N-demethylation of narcotic drugs,[3] it became apparent that there were multiple microsomal enzymes that required NADPH and O_2, that they could be induced by testosterone, and that there were marked sex differences in enzyme activity in the rat liver.

The work on the microsomal enzymes that metabolize amphetamines and ephedrine was part of my dissertation for a PhD degree at George Washington University. At the age of 42, I received my union card, a PhD. In 1955, I joined the National Institute of Mental Health and started a new career in neuroscience research.

Since my original report of the microsomal enzymes (also known as cytochrome P_{450} enzymes, monoxygenases, or mixed function oxidases), many advances have been made and thousands of papers published. A multitude of microsomal enzymes that require NADPH and O_2 and utilize cytochrome P_{450} have been described. Microsomal enzymes with similar properties also were shown to metabolize normally occurring compounds such as steroids, fatty acids, and eicosinoids. A recent review on these enzymes has been published.[4]

[Editor's note: Julius Axelrod received the 1970 Nobel Prize in physiology or medicine for discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release, and inactivation.]

1. **Axelrod J.** The enzymatic conversion of codeine to morphine. *J. Pharmacol. Exp. Ther.* 115:259-67, 1955. (Cited 65 times.)
2. ----------. The enzymic cleavage of aromatic ethers. *Biochem. J.* 63:634-9, 1956. (Cited 220 times.)
3. ----------. The enzymatic N-demethylation of narcotic drugs. *J. Pharmacol. Exp. Ther.* 117:322-30, 1956. (Cited 300 times.)
4. **Nebert D W & Gonzalez F J.** P_{450} genes—structure, evolution, and regulation. *Annu. Rev. Biochem.* 56:945-93, 1987. (Cited 210 times.)

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