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Remmer H & Merker H J. Effect of drugs on the formation of smooth endoplasmic reticulum and drug-metabolizing enzymes. *Ann. NY Acad. Sci.* **123**:79-96, 1965.
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Enzyme induction by phenobarbital and other chemicals increases drug metabolism. It plays a minor role in therapy but influences toxic actions of drugs significantly and is widely used as a tool in biochemical research. Its discovery is described. [The SCI® indicates that this paper has been cited in over 415 publications.]

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For almost 100 years, pharmacologists tried to explain the phenomenon of tolerance to drug action. They believed the cause to be reduced sensitivity of the receptor site, since no experiments had shown increased drug metabolism. The *in vitro* procedures published by Axelrod and Brodie, who had first described the drug-metabolizing enzyme system, were used to investigate the system.[1,2] My finding of decreased drug metabolism in adrenalectomized animals, which could be reversed by administration of glucocorticoids,[3] led me to the theory that adrenal hormones should stimulate the drug-metabolizing enzymes. My later experiments in which I showed that phenobarbital exerts its action in rats without adrenals made me realize that this theory was not correct, but the wrong concept inspired the right experiment.

Brigitte Alsleben and I then treated rats with increasing doses of phenobarbital or morphine, and several weeks later (after vacation) we checked the hexobarbital sleeping times of these animals prior to sacrifice for preparation of liver supernatant. (In later experiments we also checked the meperidine action.) The results were so convincing that we did not need statistical analysis.

We expected phenobarbital to increase only the hexobarbital metabolism and to shorten the sleeping time and morphine to enhance the rate of oxidation of meperidine and to diminish its analgesic action. We were surprised to find that phenobarbital pretreatment increased the oxidative metabolism of both meperidine and hexobarbital and shortened the action of both. Morphine, however, had no effect on the action of the two drugs. We reported these results on a single page in *Klinische Wochenschrift*[4] after the article was rejected by Naunyn Schmiederberg's *Archiv für Pharmakologie* for lack of sufficient data. Further work revealed that we were seeing an unspecific phenomenon of increased drug metabolism favoring drug detoxification elicited by numerous lipid-soluble compounds unrelated chemically or pharmacologically.

The papers went almost unnoticed before I was invited to present my findings in 1964 at the New York Academy of Sciences. My presentation summarized all my research at the Free University of Berlin, previously published only in German. I could conclusively prove that increased drug metabolism is caused by enzyme induction and that the amount of the main enzyme responsible for drug oxidation, cytochrome P-450, rises and falls concomitantly with the drug oxidation rate. When smooth and rough microsomal particles were separated from rabbit livers, I could even view with my own eyes the induction phenomenon, as brown colored particles settled above the denser rough liver microsomes from phenobarbital-treated rabbits only. The protein and lipid contents were shown to be increased two- to threefold. This suggested to me that the augmentation of the smooth particles might be visible in the electron microscope. H.J. Merker from the Department of Anatomy at the Free University of Berlin showed that indeed there was a surprisingly well-formed latticework of tubules filling the entire cytoplasm of liver cells.[5] Even connections among the tubular network and the rough endoplasmic reticulum and the Golgi apparatus as well as the sinusoids were detectable. This seemed plausible since, with the accelerated production of more water-soluble metabolites, their excretion via the augmented tubular system must also be improved.

What tremendous progress could be achieved if engineers could imitate nature by using tubes containing similar catalysts to detoxify our waste products in sewer systems. The Achilles' heel of this system—that it can also produce more toxic metabolites—was discovered later. Nature is not really perfect!

For recent work in this area, see references 6 and 7.

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