Early studies on bacteria demonstrated that many organisms were capable of growth and survival in a variety of different media. In modern terms, these studies showed that genomic function could be altered by environmental factors. It was discovered that various microorganisms were capable of growth at different temperatures, at different pH values, and in different salt solutions. Furthermore, they could often adapt to changes of nutrients in their media. For example, bacteria were found to synthesize the amino acid, arginine, when arginine was not present in the culture medium. When present, arginine acted as a repressive factor toward synthesis of the enzymes required to produce the amino acid. Conversely, it was found that the fungus, *Aspergillus niger*, only produced the sucrose-hydrolyzing enzyme, invertase, when there is sucrose in the medium. Microbiologists considered this an adaptive response; today, we describe it as enzyme induction. We can clearly describe two types of enzyme systems in microorganisms: those related to enzymes that are constitutive and necessary for basic life functions, and those related to enzymes that are synthesized or repressed in response to genomically active chemicals in the environment (Brock and Madigan, 1991).

In 1950, Knox and Mehler reported that livers from rabbits treated with tryptophan demonstrated an increase in the rate of conversion of tryptophan to kynurenine by tryptophan peroxidase (pyrrolase). Gros *et al.* (1954) showed that tryptophan treatment resulted in increased incorporation of radioactive valine into purified tryptophan peroxidase, suggesting enzyme induction. A series of studies, which had a dramatic effect on the field of toxicology, was initiated at the laboratory of J. A. and E. C. Miller at the University of Wisconsin. Brown *et al.* (1954) reported that liver homogenates from rats or mice fed different diets for several weeks metabolized 3-methyl-4-monomethylaminoazobenzene at different rates. Enrichment of the diet with any of several compounds—including 20-methylcholanthrene, pyrene, 1,2-benzanthracene, and phenanthrene—increased the rate of 3-methyl-4-monomethylaminoazobenzene metabolism. Evidence that the increased rate was caused by induction of the synthesis of the xenobiotic-metabolizing enzyme system came from the studies led by Allan A. Conney (*Conney et al.*, 1956). These studies showed that the increase in metabolism produced by polycyclic aromatic hydrocarbons could be antagonized by ethionine or puromycin (*Conney and Gilman, 1963*), either of which inhibits protein synthesis. [One of the more interesting coincidences in the literature of toxicology is that the first page of the paper by *Conney et al.* (1956) was p. 450.]

*Conney et al.* (1957) also demonstrated that treatment of rats with benzo[a]pyrene caused an increase in hepatic microsomal benzo[a]pyrene hydroxylase, the induction of which was also inhibited by ethionine. Conney and Burns (1959) showed that demethylase activity could be induced by chloretone, barbital, phenobarbital, thiopental, aminopyrine, phenylbutazone, orphenadrine, and 3-methylcholanthrene. *Conney et al.* (1960) then reported that phenobarbital also induced 3-methyl-4-monomethylaminoazobenzene demethylation and that the induction was accompanied by an increase in liver weight, liver protein, and microsomal protein. These observations indicated that the increases in enzyme activity were the result of an amplified production of the enzyme which metabolized 3-methyl-4-monomethylaminoazobenzene.

Herbert Remmer, a junior faculty member in the Institute of Pharmacology at the Free University of Berlin, undertook the study of the mechanism by which tolerance to barbiturates and opioids developed. Remmer’s familiarity with B. B. Brodie’s work on drug metabolism led him to suspect that altered metabolism played a role in tolerance. Remmer demonstrated that microsomes from rats pretreated with phenobarbital metabolized hexobarbital (*Remmer, 1958; Remmer and Albleben, 1958*) and methylaminooantipyrine (*Remmer, 1959a,b*) more rapidly than controls. Electron microscopic analysis by Remmer and Merker (1963, 1965) demonstrated that phenobarbital treatment caused proliferation of the hepatic smooth endoplasmic reticulum, which is the intracellular location of the drug.

1 For correspondence via fax: (732) 445-0119. E-mail: rsnyder@eohsi.rutgers.edu.
metabolizing enzymes. Treatment with phenobarbital increased CYP450 (Reichert and Remmer, 1964) at a rate parallel with increases in the metabolism of hexobarbital and Eunarcon. Orrenius and Ernster (1964) made a comparable observation for the demethylation of aminopyrine. Remmer and Merker (1964) and Alvares et al. (1967) reported similar increases in CYP450 after treating rats with benzo[a]pyrene and 3-methylcholanthrene, respectively. Gelboin and Sokoloff (1961) found that both treatments led to increases in amino acid incorporation into hepatic protein.

Together, these observations indicated that mammalian hepatic enzyme induction resulted in the synthesis of new CYP450. The recognition that xenobiotic chemicals could stimulate the synthesis of new protein suggested an effect on the genome. The utilization of enzyme induction studies to explore the polygenomic and polymorphic nature of CYP450 has been an area of major interest in toxicology over the past few decades.

Barbiturates are therapeutic agents and, as a result, a considerable amount of literature has been dedicated to the implications of enzyme induction during drug therapy. In a similar vein, the reports of enzyme induction by polycyclic aromatic hydrocarbons led to a considerable effort to explore the implications of enzyme induction in carcinogenesis. A third independent report came from environmental toxicologists’ research on enzyme induction by pesticides.

Legend has it that in Dr. James Fouts’s laboratory at the University of Iowa, a series of studies was underway which required the measurement of sleeping time in rats following the administration of hexobarbital. When one group of rats was found to be resistant to the hypnotic effects of hexobarbital, the resulting investigation led to an interesting revelation. Eight days prior to the study, the quarters in which these animals were housed had been sprayed with chlordane (Fouts, 1963). Hart and Fouts (1963) and Fouts and Rogers (1965) went on to demonstrate that chlordane and several other chlorinated pesticides reduced hexobarbital sleeping time and increased the rate of metabolism of several substrates for the microsomal enzyme system. Fouts’s discovery laid the foundation for subsequent research on the metabolic effects of other pesticides and environmental pollutants such as halogenated dioxins, furans, PCBs, and PBBs.

Studies on enzyme induction provided an explanation for the mechanism of tolerance to barbiturates, but more importantly demonstrated a model for understanding many types of drug interactions, as well as interactions between environmentally active chemicals. Furthermore, the actions of various inducers led to an understanding of the many forms of CYP450.

**REFERENCES**


