great in the centrilobular hepatocytes as in the periportal cells. After the administration of 1mg of phenobarbitone/ml in the drinking water for 4 days, the activity in the periportal region was unaltered whereas that of the centrilobular region was increased to 2.5 times the value found in the corresponding hepatocytes of the control liver.

Brodie *et al.* (1971) have shown that single doses of chlorobenzene and of α - and β -chlorinated naphthalenes produce a massive centrilobular necrosis in the liver within 24h. This effect is markedly potentiated in rats previously treated with phenobarbitone. It would seem of significance that necrosis is produced in that region of the liver lobule with a high rate of production of type I hydrogen, and that it is intensified by phenobarbitone, which increases the rate of this pathway only in that specific region.

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Changes in the Mechanism Regulating Liver Uridine Diphosphate Glucuronyltransferase Activity during Embryonic Life

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UDP-glucuronyltransferase activity towards *o*-aminophenol appears in chick-embryo liver at 7–8 days, remains low, but then increases dramatically on hatching (Dutton & Ko, 1966). UDP-glucuronyltransferase activity develops precociously in simple embryo-liver cultures, being initiated by removal from an embryonic environment rather than by culture conditions or change in cell replication rate (Ko, Dutton & Nemeth, 1967; Skea & Nemeth, 1969). This development of UDP-glucuronyltransferase activity varies directly with protein synthesis from amino acids (Dutton, Hanson & Burchell, 1970; B. Burchell, A. M. Nemeth & G. J. Dutton, unpublished work).

Development of UDP-glucuronyltransferase activity in culture differs with embryo age. For 5-day-embryo liver it rises to a plateau 5–8 times the adult value; for 11-day-embryo liver development ceases at a plateau equal to the adult value

(Skea & Nemeth, 1969). We now report the influence of phenobarbital on this phenomenon.

Phenobarbital increases liver UDP-glucuronyltransferase activity if administered to chickens or added to liver cultures (Dutton, 1970; Dutton *et al.* 1970). With 5.5mm-phenobarbital present during culture of 5-day-embryo liver the UDP-glucuronyltransferase activity reaches the high plateau more rapidly; when phenobarbital is present with 11-day-embryo liver the lower plateau is raised to that same high value displayed by cultured 5-day-embryo liver.

Kinetic studies permit some tentative conclusions. In cultured liver from 5-day embryos phenobarbital increases, by the same factor, the rate of UDP-glucuronyltransferase synthesis from amino acids, *S*, and the rate constant of degradation, *k*; it may therefore be affecting a single control site. In cultures from 11-day embryos phenobarbital increases *S* but has no effect on *k*. In the older embryo regulation of *S* and of *k* therefore appears to have become dissociated (see Berlin & Schimke, 1965).

Moreover, phenobarbital initiates these changes in UDP-glucuronyltransferase activity in 5-day liver only during the first few hours of culture, but in 11-day-embryo liver it increases activity if added at any time during at least 5 days of culture.

Chick-embryo livers cultured at different ages thus exhibit control mechanisms for UDP-glucuronyltransferase activity that are established sequentially long before hatching; the embryonic environment may therefore not inhibit development of this enzyme in the same way throughout embryonic life.

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