Routine assessment of drug-related induction of liver microsomal enzymes during toxicity trials in animals

J. HAYES and R. M. QUINTON
Toxicology Department, Research Division, Pfizer Ltd., Sandwich, Kent

Many drugs when given chronically to animals induce liver microsomal enzymes responsible for their own metabolism. This induction can affect the toxicity of the drug itself, and also the toxicity and efficacy of other drugs given concomitantly. During the early stages of the development of a drug, its assay and its route of metabolism are often unknown. In order to monitor drug-related induction, it is therefore necessary to establish a screening procedure whereby the activities of a number of liver microsomal enzymes are estimated.

Procaine esterase, glucose-6-phosphatase and the enzymes concerned in the O-demethylation of para-nitroanisole, N-demethylation of amidopyrine, and hydroxylation of aniline have all been estimated *in vitro* in livers from animals on toxicity trial, and hydroxylation of antipyrine and N-demethylation of amidopyrine have been estimated *in vivo*. Urinary ascorbate excretion and sulphobromophthalein elimination have also been monitored. These methods were chosen because they were simple and quick and so could serve as a routine screen. The effects of a number of novel compounds on these and certain other parameters will be demonstrated, together with their limitation and value in noting liver microsomal enzyme induction in dogs, rats and mice.

Method for the production and detection of epileptogenic lesions in rat cerebral cortex

R. C. DOW, JUDITH K. PARK, HELEN M. PRYOR and H. R. A. TOWNSEND
M.R.C. Brain Metabolism Unit, Department of Pharmacology, Edinburgh University, 1 George Square, Edinburgh, EH8 9JZ, and Department of Surgical Neurology, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU

Epileptogenic lesions produced by cobalt have been described previously (Dow, Fernandez-Guardida & Manni, 1962; Fischer, Holubař & Malik, 1967). Our technique produces discrete firing foci whose abnormal electrical activity is recorded through chronically implanted electrodes.

Male PVG rats, 200–250 g, were anaesthetized with halothane. The skull was trephined and pairs of holes located, one on either side of the sagittal suture, over the frontal, parietal and occipital areas. At the site of cobalt implantation, the dura was split with the tip of a sterile 23 gauge needle. A cube of cobalt-gelatine (1 mm^3) prepared as described by Fischer *et al.* (1967), was inserted vertically into the cortex so that its top was flush with the cortical surface. Specially constructed hollow stainless steel screws (8 BA, overall length 10 mm) inserted into the skull served as extradural recording electrodes. The collar of each screw was secured to the bone with acrylic resin. One electrode was placed directly over the cobalt implant and a total of 5 or 7 electrodes were inserted in each animal. Holes were punched in the skin flap so that this fitted neatly over the electrodes and the incision was then closed with Michel clips.

Electrocorticogram (ECoG) recordings can be made from the unrestrained, conscious rat within 24 h of the operation. Plug-type or spring connectors fit into the