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

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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

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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

hollow screws and allow the brain potentials to be recorded on a Grass Model 7 polygraph. Reference and bipolar recordings have been made on each animal twice weekly so that the development of a firing focus could be monitored.

Using this technique, we have investigated the effects of implanting cobalt into either frontal or parietal cortex. Differences in the time of onset, duration and location of the spike discharges and in the associated motor disturbance have been observed and will be described. Preliminary observations of the effects of a few anticonvulsant drugs will also be reported.

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Influence of pH on absorption of thymoxamine through buccal mucosa in man

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The influence of concentration, contact time and pH on buccal absorption (Beckett & Triggs, 1967) of thymoxamine hydrochloride has been studied using an assay pro-

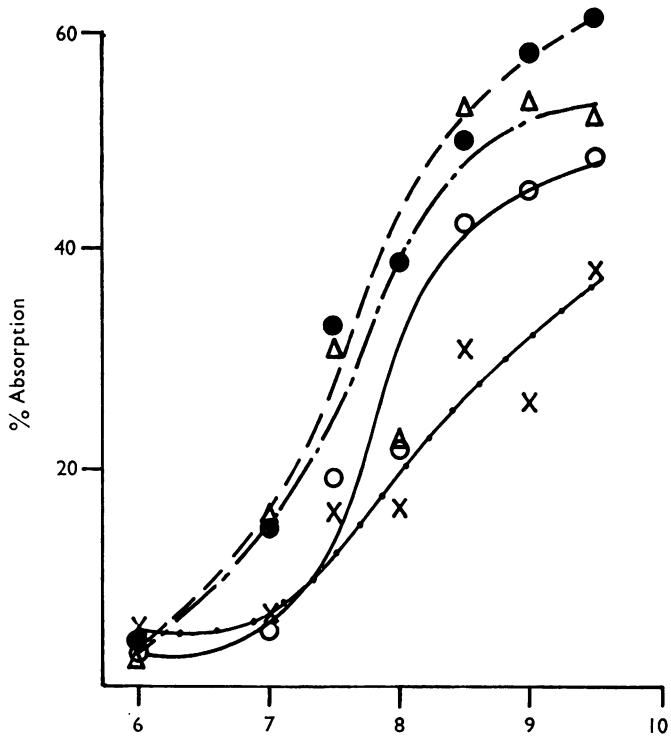

FIG. 1. Influence of pH on the percentage absorption of thymoxamine hydrochloride (2 mg/25 ml) through the buccal mucosa in four subjects. Contact time was 4 minutes. Values were corrected to allow for loss by swallowing.