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

A. G. ARBAB and P. TURNER

Department of Clinical Pharmacology, St. Bartholomew's Hospital, London EC1

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

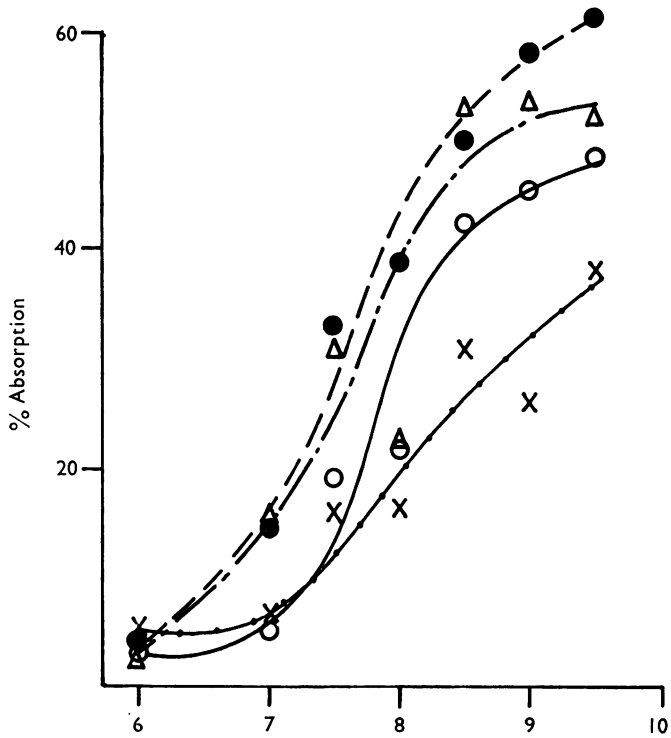

FIG. 1. Influence of pH on the percentage absorption of thymoxamine hydrochloride (2 mg/25 ml) through the buccal mucosa in four subjects. Contact time was 4 minutes. Values were corrected to allow for loss by swallowing.

cedure which depends on the fluorescence of thymoxamine and its deacetylated derivative. Polyethylene glycol (1 mg/ml) was used as a marker substance to measure loss of solution from the mouth by swallowing and was estimated spectrophotometrically (Hayden, 1955). The loss varied between 1 and 12% throughout the investigation. Thymoxamine was extracted from alkalinized buccal solution into benzene 1·5% isoamylalcohol and back extracted into 0·1 N hydrochloric acid. After boiling an aliquot of the acid phase for 30 min it was cooled and its fluorescence measured at maximum excitation 295 nm and emission 335 nm (uncorrected). This acid hydrolysis probably results in the production of desacetyl-thymoxamine which has more marked fluorescent properties than thymoxamine hydrochloride, but at the same excitation and emission wavelengths. In a series of experiments in four normal subjects contact time (1–4 min) and thymoxamine concentration (1–4 mg/25 ml) were linearly related to percentage absorption. The marked influence of pH on buccal absorption of thymoxamine is shown in Fig. 1, maximum absorption of 30–60% occurring at pH 9–9·5 compared with only 5% at pH 6. It is probable that pH has a similar influence on its absorption from the gastrointestinal tract.

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Methods to linearize the lower end of a dose-response curve

D. W. VERE

Department of Pharmacology and Therapeutics, The London Hospital Medical College, Turner Street, London E1

There are established methods for comparing drug potencies using the almost straight, central portions of log dose-response curves. When exploring new or potentially dangerous drugs in man it is necessary to use only the lower ends of these curves. A simple, accurate potency comparison is then impossible.

The logit function (Berkson, 1953; Emmens, 1940)

$$y = \frac{1}{1+e^{f(x)+f(k)}}$$

where y is the response parameter, x is dose, k is a constant,
has many useful derivatives which can be used to straighten the line which relates log dose and response, though its application has been chiefly to quantal assays. One of these derivatives compares $\frac{1}{y}$, and $\frac{1}{x}$. Though this is satisfactory for quick laboratory reference it cannot be used for least squares regression analysis, since the variance along the line is not homogeneous. Methods are demonstrated which overcome this disadvantage. They can also be used to find a statistic which approximates a maximum likelihood estimate for the line relating the standardized response to log dose from