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

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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

data which do not go beyond the half response point. If the multiplier which standardizes y is l, then:

$$\sum\left[\frac{-\ln\left(\frac{1}{y_i l}-1\right)}{\ln x_i}\right]-\frac{n}{\Sigma(\ln x_i)}\sum\left[-\ln\left(\frac{1}{y_i l}-1\right)\right]=0$$

can be used to find the best estimate of l. It can be shown that this function is applicable whether 'rate' or 'occupancy' theories of drug action describe the data, using the formulae given by Paton (1961).

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Use of a digital computer programme as a guide to the prescribing of kanamycin in patients with renal insufficiency

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The antibiotic kanamycin may induce serious and permanent adverse effects expecially if high serum concentrations of kanamycin develop and are sustained. The elimination of kanamycin is dependent on renal function and patients with renal insufficiency are particularly prone to cumulative toxicity.

In view of this risk a computer programme written in 1900 Fortran for operation on the ICL 1901A computer has been devised to recommend kanamycin dosage schedules for individual patients with renal insufficiency.

The programme is based upon published studies of kanamycin absorption, distribution and excretion (Welch, Wright, Weinstein & Staffa, 1958; Orme & Cutler, 1969).

Estimates of distribution volume and serum kanamycin clearance are derived from clinical and laboratory measurements which are made routinely on each hospital inpatient with renal insufficiency. Safeguards have been incorporated in an attempt to minimize the effects of accidental loss of a part of a 24 h urine collection.

The input data includes the patients' age, sex, body weight, estimated net protein intake, blood and urine urea concentration, serum and urine creatinine concentration and 24 h urine volume. The input also includes the amounts, times and dates of kanamycin doses already administered to the patient.

The output includes the hypothetical serum concentrations of kanamycin at 2 and 12 h after each dose already given. The computer then proceeds to recommend a series of the largest doses of kanamycin which may be given at 12 h intervals without the 2 h hypothetical serum concentrations exceeding an arbitrary upper limit of 30 μg/ml.

In a prospective study the validity of the programme is being tested by comparing the results of serum kanamycin assay by a diffusion method (Garrod & O'Grady, 1971) with the concentrations predicted by the computer (Table 1) in hospital patients