bile-duct exploration was necessary. Taloximine, 150 mg, was given as a resuscitant procedure and samples of bile were collected over the following 48 h. 31·4% of the taloximine injected was recovered over this period, mainly as glucuronated derivatives.

Respiratory effects

Peak plasma levels of taloximine after 2·0 g orally coincided with hyperventilation accompanied by a respiratory alkalosis, a fall in mixed venous pCO_2 and a rise in plasma and urinary pH (Prime, Griffin, Turner, Ben-Dyke & Pickering, 1970).

We gratefully acknowledge the help of our colleagues in these studies.

REFERENCES

COUPAR, I. M. & TURNER, P. (1969). Relative potencies of sympathetic amines in human smooth muscle. *Br. J. Pharmac.*, **36**, 213–214*P*.

DALY, M., LIGHTOWLER, J. E. & PICKERING, R. W. (1969). Taloximine, a new respiratory stimulant with bronchodilator properties. *Br. J. Pharmac.*, **35**, 283–294.

PEARSON, J. A. & GRIFFIN, J. P. (1969). Investigations into the site of action of taloximine: a new respiratory stimulant molecule. *Experientia*, **25**, 716–717.

PRIME, F., GRIFFIN, J. P., TURNER, P., BEN-DYKE, R. & PICKERING, R. W. (1970). Metabolic studies of taloximine and its effects on the respiratory response to carbon dioxide. *Pharmacologia Clinica*, in the Press.

Isotope dilution in drug analysis

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There is a constant need for sensitive and specific methods for determination of drug concentrations in biological fluids. An additional problem, especially prominent in the field of clinical pharmacology, is the frequent need for a general technique that can be applied at short notice to the analysis of a new compound. Isotope dilution techniques may be useful in overcoming some of these problems.

Isotope dilution techniques are widely used in chemistry, and in pharmacological investigations of endogenous materials, but they are rarely used for the measurement of concentrations of foreign compounds in the body. In an isotope dilution method, a known quantity of radioactively labelled compound is added to a sample containing an unknown quantity of unlabelled compound, and labelled and unlabelled compound are then extracted into an organic solvent. A distribution property of combined labelled and unlabelled material in the concentrated extract is used to display a ratio of radioactivity. This ratio changes with total concentration, so that by reference to standards it indicates the concentration of total material present. The original concentration of unlabelled compound is then calculated.

There are three ways in which a usable ratio for drug analysis might occur. First, for a number of drugs in plasma, the fraction bound to protein varies with overall concentration; in using this property, the extraction step could possibly be omitted. Second, in place of protein, an insoluble binding agent such as charcoal might be used. Third, a complexing agent could be used under substoichiometric conditions.

Complex formation under substoichiometric conditions has been used in preliminary experiments with fluphenazine and morphine. Both of these compounds readily

react with heptafluorobutyric anhydride (HFBA) to form derivatives which are preferentially extractable into organic solvents. The extent of reaction is related to the amount of fluphenazine or morphine when excess HFBA is present, and to the amount of HFBA when excess drug is present. Thus for each compound, when varied quantities of unlabelled drug are added to a constant quantity of labelled drug, and an amount of HFBA is added sufficient to form the derivative of the quantity of drug added to the sample in labelled form, a varied proportion of the radioactive drug is converted to the derivative. Each derivative can be preferentially extracted into an organic solvent, and the proportion of radioactivity extracted is related to the total amount of drug present. Standard curves have been plotted of proportion extracted against overall concentration. These curves provide the basis for isotope dilution methods for the analysis of fluphenazine and morphine in the nanogram range. They could also be used as models for general application of the, technique in drug analysis. The sensitivity of the technique would be limited only by the specific activity of the labelled drug.

This work was supported (in part) by contract number PH 43-66-1167 with the United States National Institute of General Medical Sciences. A gift of radioactive fluphenazine from E. R. Squibb and Sons Ltd. is gratefully acknowledged.

Quantitative infrared studies of inflammation in rheumatoid arthritis

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The human skin is a highly efficient radiator of infrared energy (Hardy, 1934). Recent developments have produced mechanisms for scanning and recording skin temperatures by the detection of emitted infrared radiation. Point temperature measurements or two dimensional maps (thermograms) may be made, without regard to skin pigmentation and as a passive method, it avoids errors caused by contact of thermistors with the skin.

The skin temperature over an inflamed arthritic joint is raised, and displays a characteristic thermal pattern (Cosh, 1966; Cosh & Ring, 1967). This pattern can be altered by surgery, simple aspiration of joint fluid or more dramatically by the inter-articular injection of drugs. Scanning techniques, when standardized and used with isotherms, giving quantitative pictorial records of the course of the disease and its modification by drug therapy.

Close relationships between the biochemical events associated with inflammation in the joint fluid and the thermographic pattern over the joint have been demonstrated. We have found this method provides a harmless, reproducible, and accurate means of quantitating the course of inflammatory disease and the effect of anti-inflammatory drug therapy.

Four infrared detecting systems have been evaluated. Currently in use is a scanning system which allows good standardization, and has the following specifications:

Camera

Focusing	1 m$\rightarrow\infty$
Field of view	width 25°
	height 12·5°