detect 0·04% of codeine in the morphine sample and rule out the possibility that the norcodeine could originate from the injected codeine.

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The formation of norcodeine from morphine in man

In answer to the views expressed by Yeh (1975) we affirm that codeine impurities were not detected by mass spectrometry in the morphine used in our studies (Boerner, Roe & Becker, 1974).

We appear to differ over the interpretation of the work of Oguri, Yoshimura & Taukamoto (1970) and Brunk & Delle (1974). Our understanding is that both groups did not administer morphine chronically. Oguri & others administered 10 mg of morphine hydrochloride three times into one patient over a 23 h period and Brunk & Delle administered only one dose of 10 mg radioactive morphine sulphate to their volunteers. Oguri & others determined morphine, normorphine, morphine-3-glucuronide, and morphine-6-glucuronide in the 35 h pooled urine collection; presence or absence of codeine was not reported. Brunk & Delle determined morphine, morphine-3-glucuronide, and morphine ethereal sulphate in the urine of their volunteers. No statements are made of any attempt to determine the presence or absence of codeine or norcodeine.

We agree, however, that animal studies may sometimes serve as useful models in suggesting possible metabolic pathways in man. The study of rats by Abrams & Elliott (1974), which was cited as a recent example of possible metabolic differences between jaundiced Gunn rats and Long Evans rats during prolonged chronic morphine administration and did not show occurrence of codeine as a urinary metabolite, prompts some comments. Even though the investigators of this study claimed a high sensitivity for the detection of codeine, morphine, normorphine, and morphine-glucuronide, the only morphine metabolites found in their analysis of urine were morphine-3-glucuronide and free morphine. These workers specifically stated that they were unable to detect either normorphine or codeine. However, because normorphine is a long-established and generally accepted urinary morphine metabolite in rat studies and is also present in significant quantities, these findings must be

viewed at best as equivocal for their detection method of normorphine and codeine.

In summary, we believe that the references cited do not support the contention that codeine impurities in the morphine used in our study gave rise to the norcodeine detected in urine reported in our study. It is possible that formation of norcodeine as a metabolite of morphine is enhanced in certain pathologic conditions. The metabolic fate of approximately 20% or $\frac{1}{5}$ of any morphine dose administered to man, however, still remains unknown.

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An improvement in the use of the L-transformation

In a recent paper (Mackay & Wheeler, 1974) a method was presented for deriving useful information from comparison of pairs of sets of dose-response data. The method suggested involved the use of a transformation, the L-transformation, to describe each set of data in terms of three adjustable constants, and each pair of sets of data in terms of five adjustable constants. By combining this transformation with equations derived from the occupation theory of drug action it was shown that affinity constants of agonists or antagonists, and other theoretical quantities, could be estimated from these adjustable constants. The standard errors of the various derived quantities could also be obtained from the variances and covariances of the adjustable constants. Potency ratios of agonists, with fiducial limits, could also be calculated. These calculations were facilitated by the use of several computer programs.

Since Fieller's theorem can be applied to the ratio of any two quantities that are linear functions of a set of observations with normally distributed errors (Fieller, 1944; Finney, 1964) this theorem has now been used to derive fiducial limits for all of the quantities that are of practical or theoretical interest (Mackay & Wheeler, 1974, Tables 1 and 2). The program FINCALC has therefore been modified to provide estimates of such fiducial limits as well as the information previously provided.

Since there have been many requests for reprints of the original paper it will be necessary to limit the supply of copies of the various computer programs to those who *specifically* request them.

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