considerations is the way in which these and other systems should be used in spontaneously breathing patients. The two subjects studied by Drs Spoerel and Bain were both provided with what must be considered, by any criteria, fresh gas flows that were not adequate to prevent the rebreathing of alveolar gas. This explains the unduly high levels of ventilation and the increases in inspired carbon dioxide concentration that are described. The response of these subjects to an imposed carbon dioxide load was to increase minute volume rather than suffer a significant increase in alveolar carbon dioxide concentration. This is a common response to the rebreathing of expired alveolar gas in lightly anaesthetized subjects. The behaviour of these two subjects is closely compatible with that seen by Byrick (1980) in the majority of his subjects who received an inadequate fresh gas flow to a coaxial T-piece system. The presence of near-normal end-tidal carbon dioxide concentrations does not necessarily mean that a breathing system is being used in a proper fashion. I do not believe that acceptable conditions can be said to exist when an anaesthetized subject is forced to hyperventilate in order to maintain normocapnia. I would strongly recommend that, with any system used during spontaneous breathing, one uses fresh gas flows large enough to ensure that the breathing system causes neither an increase in PCO₂ nor an increase in ventilation.

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PHARMACOKINETICS OF PHENOPERIDINE

Sir,—We were interested in the study of the pharmacokinetics of phenoperidine in anaesthetized patients (Fischler et al., 1985), in which the plasma concentration of the unchanged drug was measured by radioimmunoassay. Their results suggest that the elimination half-life of phenoperidine is two to three times longer than the values we previously reported in patients and volunteers, using a specific chromatographic method (Milne et al., 1980; Calvey et al., 1983). We consider that the discrepancy may be more apparent than real, and is primarily related to the different methods of analysis that were used. Although Dr. Fischler and his colleagues state that their immunoassay is specific for phenoperidine, the 1Dₐₜ values cited (40) for pethidine and norpethidine make it clear that there is some degree of cross-reactivity with these primary metabolites of phenoperidine. Within 3–6 h of administration of phenoperidine, the plasma concentration of the unchanged drug is extremely low, while that of its main metabolites may be at least 5–10 times greater. Consequently, any significant degree of cross-reactivity may result in the over-estimation of the plasma phenoperidine concentration. Since the error is likely to become progressively greater with time, it may well result in a considerable prolongation of the terminal half-life of the drug.

It is generally recognized that similar considerations may apply to the measurement of other opioid analgesics. Radioimmunoassays for morphine cross-react with its conjugates to a limited extent (usually 1–2%); nevertheless, even an apparently negligible in vitro cross-reaction with morphine glucuronides can cause significant overestimation of the unconjugated drug (Aherne, 1983; Grabiniski et al., 1983; Hanks and Aherne, 1985). Indeed, it is questionable whether any opiate can be reliably measured by radioimmunoassay as long as cross-reactivity with its metabolites can be demonstrated.

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Sir,—We have reported a mean half-life of elimination of phenoperidine (193 min) which is longer than that found in previous studies (90 min (Milne et al., 1980); 66 min (Isherwood et al., 1981)). We agree with some of the points stressed by Calvey and Williams: there is, as we had noted in our paper, some degree of cross-reaction between phenoperidine and its metabolites.

On the other hand, other points must be emphasized:

(1) The coefficient of variation and the accuracy of the chromatographic technique used by Calvey and Williams is not specified in their papers.

(2) The time of sampling was different in each paper: 120, 240, 360 min, respectively, in the studies of Isherwood and colleagues (1981), Milne and colleagues (1980) and ourselves (Fischler et al., 1985); the shorter the sampling time, the shorter the half-life of elimination.

(3) We have shown that the kinetics of phenoperidine are characterized by the possible occurrence of secondary, important concentration peaks. The magnitude of such peaks shows that they are related to phenoperidine itself, and not its metabolites. Their particular occurrence in two patients out of five is a strong argument in favour of a large individual