Table 2. The pharmacokinetics of i.v.[^{3}H]saccharin (100 mg kg^{-1}; 100 μCi/rat) in pentobarbitone anaesthetized normal rats by the analysis of blood samples (0·2 ml) collected at 15 min intervals. No urine was passed in the 2 h of sampling. Measurements were also made in rats with bladder cannulae in which the bladder was either left for 2 h (unrinsed) or emptied and rinsed every 15 min (rinsed).

	Normal	Bladder cannulated rinsed	unrinsed
No. of animals:	6	8	5
Half-life (min)	22·4 (3·5)	22·4 (3·2)	31·8 (8·2)*
Apparent volume of distribution (ml kg^{-1})	412 (132)	408 (141)	378 (89)
Plasma clearance (ml min^{-1} kg^{-1})	13·2 (5·3)	13·0 (5·6)	8·6 (2·8)

The results are the mean (standard deviation).
* $P<0·05$ compared with normals.

markedly increased its permeability and under such circumstances sufficient absorption to interfere with plasma pharmacokinetics may result, if the urine is not removed regularly. In this context we noted that even manipulation of the bladder with forceps or gentle palpation in an attempt to expel urine resulted in an increase in apparent permeability. Our results emphasize the care that is necessary in the interpretation of quantitative biological data obtained during experiments in which the normal physiological state of an organ is altered by the investigation.

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LETTERS TO THE EDITOR

Which pharmacological action of baclofen matters most?

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Kerwin & Pycock (1978) have shown that very high concentrations of baclofen, the β-(p-chlorphenyl) derivative of γ-aminobutyric acid (GABA), increase the radioactive content of superfusates of rat globus pallidus slices prelabelled with ^{3}H-GABA in vitro, and suggest that this compound may act as a GABA-releasing agent in vivo. While another recent study would support this view (Roberts et al 1978), earlier work has indicated that lower, and perhaps more physiologically relevant concentrations of baclofen may inhibit the release of GABA (Potashner 1978). Also, there seems to be some debate as to the pharmacological relevance of GABA-releasing effects seen with concentrations of baclofen greater than 100 μM. For example, Kerwin & Pycock (1978) find baclofen to be inactive at 100 μM and suggest that significant effects seen with 0·3–1·0 mM baclofen may be important, while Olsen et al (1978) consider that the absence of any significant effect of baclofen at 100 μM indicates the inactivity of this compound.

We feel that recent studies on the ability of baclofen to displace ^{3}H-GABA specifically bound to brain membrane preparations in vitro may be more relevant to the GABA mimetic action of this compound. Studies in this area are contentious, but both Olsen et al (1978) and ourselves (Waddington & Cross 1979) have found (±)-baclofen to displace ^{3}H-GABA binding with IC50's of 55 and 40 μM respectively. These concentrations of baclofen are considerably smaller than those reported by Kerwin & Pycock (1978) to enhance GABA release (0·3–1·0 mM). While other studies have failed to observe such low IC50's for displacement of ^{3}H-GABA binding by baclofen (Roberts et al 1978; Galli et al 1979; Lloyd & Dreksler 1979), they do not report if there was significant displacement of binding at higher concentrations. This may be important as

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Greenlee et al (1978) have reported baclofen to significantly displace ^{3}H-GABA binding at 100 μM though the IC50 was rather higher. In human post-mortem brain tissue, Iversen (1978) has reported baclofen to displace ^{3}H-GABA binding with an IC50 of 80 μM.

Baclofen has been shown to induce an increase in Cl^- influx in crayfish muscle, competition studies with GABA suggesting an action on the same receptor (Olsen et al 1978). Similarly, recent electrophysiological studies have shown baclofen to produce GABA-like, bicuculline sensitive effects (Fox et al 1978). Our own behavioural studies have indicated that baclofen may be a partial agonist or dualist at the GABA receptor, and that these effects are weakly sensitive to antagonism by picrotoxin (Waddington & Cross 1979). These studies suggest that baclofen can weakly interact directly with GABA receptors and that this effect occurs at concentrations considerably below those active on GABA release mechanisms.

However, the GABAergic activity of baclofen is substantially less than that of potent and specific GABA agonists such as muscimol. It should not be overlooked that the most potent action of baclofen may be to inhibit release of excitatory amino acid neurotransmitters (Potashner 1978; Fox et al 1978), in a manner stereospecific for the (—)-isomer (Ault & Evans 1978). At much higher concentrations of baclofen, GABA receptors may be stimulated directly and this effect does not show stereospecificity (Cross & Waddington 1978).

In discussing the therapeutic potential of baclofen, particularly in schizophrenia, Kerwin & Pycock (1978) have failed to note both that reduced activity of the GABA-synthesizing enzyme glutamic acid decarboxylase in postmortem brain tissue from schizophrenic patients is not a replicable finding (McGeer & McGeer 1977; Crow et al 1978) and that placebo-controlled trials of baclofen in schizophrenia have clearly indicated its lack of antipsychotic effect (Gulmann et al 1976; Bigelow et al 1977).

In the light of its duplicity of action and low potency, baclofen would seem to be a poor pharmacological tool for the study of GABAergic mechanisms in experimental animals and in the clinic.

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An observation on the determination of thiomersol at preservative concentration by flameless atomic absorption spectroscopy

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The determination of organomercurial compounds by flameless atomic absorption spectroscopy is a well established technique involving oxidative digestion of the compound to inorganic mercury and subsequent reduction to atomic mercury with stannous chloride (Thompson & Hoffman 1975; Ure 1975).

In a study of the organomercurial preservative content of eye drops, Calder & Miller (1976) reported a rapid (5–10 min) cold sulphuric acid-perchloric acid digestion procedure which was claimed to give complete recovery of mercury from solutions containing phenylmercuric nitrate and acetate and thiomersal. During investigations into the stability of thiomersal (Meakin & Khammas 1978) we have been unable to repeat this finding, even after prolonged treatment with the cold digestion mixture. Fig. 1 shows plots of absorbance against concentration (ppm of mercury) in the sample to be treated for solutions of thiomersal (B.P. quality recrystallized from 95% ethanol, M.P. 229 °C, acidimetric assay 101·8%) subjected to the cold sulphuric acid-perchloric acid process (A) and a more conventional hot permanganate-sulphuric acid digestion process (B). The absorbance obtained for solutions of mercuric chloride ($HgCl_2$ content 99·8%) is shown for comparison. Absorbances were measured on a Hilger-Watts H1170 Atomspek fitted with a mercury cold

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