thesia. Blood gases showed PaCO_2 well in excess of 60 torr. A check of the anaesthesia circuit demonstrated a large leak around the sensor due to a damaged T connector, causing an inadequate fresh gas inflow to the circuit.¹ All connectors checked subsequently have shown the same defect at one time or another.

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have shown may be of academic interest but are of no clinical significance.

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Glycopyrrolate and human plasma cholinesterase

To the Editor:

I read the paper by Zsigmond *et al.*¹ with great interest, as I have been involved in many clinical studies with glycopyrrolate.² The extrapolation of their results to speculation about possible prolongation of the effects of succinylcholine or local anaesthetics is too far fetched. The IC_{50} of glycopyrrolate on plasma cholinesterase was shown to be 1.0 mM. With the molecular weight of 398 a 1.0 mM concentration of glycopyrrolate would be equivalent to 0.398 mg or 398 $\mu\text{g}\cdot\text{ml}^{-1}$.

Commonly used doses of glycopyrrolate in premedication range from 0.2–0.4 mg. Maximum plasma concentrations of glycopyrrolate in volunteers using a sensitive radio-immunoassay technique were about 35 $\text{ng}\cdot\text{ml}^{-1}$ after 0.4 mg IV (personal communication, C.J. Jones, A.H. Robins Co. Ltd., Horsham, England). Thus the IC_{50} of 1.0 mM demonstrated *in vitro* is over 11,300 times the maximum plasma concentration in man after 0.4 mg glycopyrrolate IV. Such concentrations would not be attained even with relatively larger doses (10–15 $\mu\text{g}\cdot\text{kg}^{-1}$) of glycopyrrolate used at the time of antagonism of neuromuscular block. Glycopyrrolate has been used in many thousands of cases without any reports of prolonged action of succinylcholine or ester-type local anaesthetics.

The results Dr. Zsigmond and his colleagues

REPLY

Dr. Mirakhur is correct in that the results of our studies have "academic interest," but he can not deny that the findings may also have clinical importance as we succinctly stated that: "Glycopyrrolate and atropine possess low inhibitory effect on human PChE, therefore it is unlikely that PChE *in vivo* would be inhibited to an extent that interferes with the hydrolysis of succinylcholine and/or local anaesthetics of the ester-type." Indeed, their experience concurs with our own observations that no clinically recognizable interactions take place between glycopyrrolate and succinylcholine. Nonetheless, only experiments involving the combination of glycopyrrolate with succinylcholine or procaine can scientifically answer this question.

Contrary to Dr. Mirakhur's claim that we extrapolated the *in vitro* inhibitory effects of glycopyrrolate to the clinical effects of succinylcholine and local anaesthetics, we are well aware of the studies of Foldes and Smith.¹ Those studies showed that extrapolation to the *in vivo* anticholinesterase effect from its *in vitro* inhibitory effect is not permissible, since the I_{50} values of other anticholinesterases used in the management of myasthenia gravis demonstrated no correlation to their *in vivo* therapeutic effectiveness.

At the other extreme, hexafluorenum, which markedly inhibits PChE *in vitro*, causes a predictable and potent inhibition of the *in vivo* hydrolysis of succinylcholine and is, therefore, employed to prolong its effect for muscle paralysis.² Moreover, in anticholinesterase poisoning, the large atropine doses required, e.g., 0.2–1.0 g daily, might lead to a marked *in vivo* PChE inhibition as predicted from its *in vitro* anticholinesterase effect also corroborated by Radic.³

PChE is present as "reserve cholinesterase" in other cholinergic transmission sites.⁴ Surprisingly, we find complete inhibition of the reserve cholinesterases by fractions of the I_{50} of several anticholinesterases in the