ERNST, A. M. & SMELIK, P. G. (1966). *Experientia*, **22**, 837.
HUSZTI, Z., FEKETE, M. & HAJÓS, A. (1969). *Biochem. Pharmac.*, **18**, 2293–2301.
ROOS, B.-E. (1969). *J. Pharm. Pharmac.*, **21**, 263–264.
SEDVALL, G. C., WEISE, V. K. & KOPIN, I. J. (1968). *J. Pharmac. exp. Ther.*, **159**, 274–282.
THER, L. & SCHRAMM, H. (1962). *Arch. int. Pharmacodyn. Thér.*, **138**, 302–310.
UNGERSTEDT, U., BUTCHER, L. L., BUTCHER, S. G., ANDÉN, N.-E. & FUXE, K. (1969). *Brain Res.*, **14**, 461–471.

Pharmacological actions of pralidoxime in relation to therapeutic doses

Several years ago we referred (Berry, Davies & Rutland, 1966) to speculations that pyridinium aldoximes, used as antidotes to organophosphorus anticholinesterase poisoning, might exert a biphasic action at neuromuscular junctions, but pointed out that none of these speculations were accompanied by measurements of the concentration of oxime reached in end-plates after the administration of therapeutic amounts of the drugs. Berry & others (1966) found that the maximum concentration of TMB-4 [1,3-di(4-hydroxyiminomethylpyridinium)propane dichloride] in diaphragm muscle did not exceed 0·1 mmol/kg with therapeutic doses, but higher concentrations were produced by toxic doses. Goyer (1970) has recently revived these speculations about a biphasic action by showing that concentrations of PAM (pyridine-2-aldoxime methiodide) around 1 mM caused optimal stimulation of the release of acetylcholine from the rat phrenic-diaphragm preparation. Concentrations of drug reached *in vivo* are too low to stimulate the release of acetylcholine, and hence oxime-induced release of this substance could have no influence on the therapeutic action of the drug (Table 1).

Table 1. *Concentration of P2S in the diaphragm after intramuscular injection of 30 mg/kg.* Values, in μg/g fresh weight, are the mean of six observations (i.e. 36 animals of each species)

	Time after injection, min					
	5	10	20	40	60	90
Guinea-pig ..	10·2	15·0	17·7	13·2	11·0	8·6
Rat	12·2	16·8	20·3	21·0	25·7	12·2

A dose of 30 mg/kg of P2S (pyridine-2-aldoxime methylmethanesulphonate) affords excellent protection against organophosphates when used in conjunction with atropine (Davies & Willey, 1959). Rats or guinea-pigs were given this dose intramuscularly, and groups of six animals were killed at intervals thereafter. The concentration of P2S in the diaphragm was measured by a modification of the method of Creasey & Green (1959). The Table shows that the peak concentration reached in rat diaphragm was 26 μg/g, or about 0·11 mmol/kg calculated as pyridine-aldoxime methylmethane sulphonate. According to Goyer's (1970) data this concentration would not significantly alter the release of acetylcholine from the muscle.

Chemical Defence Establishment,
Porton Down,
Wilts, U.K.
February 24, 1970

W. K. BERRY
M. P. MAIDMENT

REFERENCES

BERRY, W. K., DAVIES, D. R. & RUTLAND, J. P. (1966). *Biochem. Pharmac.*, **15**, 1259–1266.
CREASEY, N. H. & GREEN, A. L. (1959). *J. Pharm. Pharmac.*, **11**, 485–490.
DAVIES, D. R. & WILLEY, G. L. (1959). *Br. J. Pharmac. Chemother.*, **14**, 5–8.
GOYER, R. G. (1970). *J. Pharm. Pharmac.*, **22**, 42–45.