Letters to the Editor

Potentiation of chlorpromazine-induced behavioural changes by anticholinesterase agents

SIR,—A recent report indicated that phenothiazine derivatives may exacerbate the symptoms of poisoning induced by phosphate insecticides (Arterberry, Bonifaci, Nash & Quinby, 1962). Because of current interest in the possible interaction of therapeutic agents with pesticides, an investigation of the effects of chlorpromazine with several anticholinesterase agents has been undertaken in conditioned animals.

A group of 10 male albino rats (375–450 g), trained for discrete avoidance responding to a level of 95% or better, was used (Goldberg, Johnson, Knaak & Smyth, 1963). Ten control sessions of 120 avoidance trials/hr revealed an average of 4·7 ± 0·6 (s.e.) shocks/animal during the first hr of a 2 hr session. Drugs were injected intraperitoneally twice weekly, with control sessions at a similar time of day three times a week. Chlorpromazine was given at a dose of 1·23 mg/kg. The three reversible cholinesterase inhibitors and the doses used were 1-naphthyl *N*-methyl carbamate [Sevin, 1·25 mg/kg (low dose) and 5·00 mg/kg (high dose)], 3-isopropylphenyl *N*-methyl carbamate (Compound 10854, 0·50 mg/kg) and physostigmine (eserine, 0·16 mg/kg). When given in combination experiments, chlorpromazine and the cholinesterase inhibitor were administered as separate injections. A theoretical additive value of any anticholinesterase agent when given in combination with chlorpromazine is equal to the sum of the individual effects minus the average control values for the animals.

The results, as summarized in Table 1, clearly indicate that potentiation of chlorpromazine-induced behavioural alteration is accomplished with the concomitant administration of any of the cholinesterase inhibitors studied regardless

TABLE 1. ACTION OF CHLORPROMAZINE AND ANTICHOLINESTERASE AGENTS ON DISCRETE AVOIDANCE BEHAVIOUR

Treatment	Shocks/animal ± s.e. (first hr after drug)	Degree of significance from controls	Theoretical additive shock values
Controls	4·7 ± 0·6	—	—
Chlorpromazine	24·5 ± 5·1	$P < 0.01$	—
Sevin (low dose)	4·3 ± 2·2	$P > 0.05$	—
Sevin (high dose)	18·3 ± 6·6	$P < 0.05$	—
Compound 10854	10·5 ± 4·9	$P > 0.05$	—
Eserine	9·4 ± 3·0	$P > 0.05$	—
Chlorpromazine + Sevin (low dose)	43·5 ± 12·8	$P < 0.01$	24·1
Chlorpromazine + Sevin (high dose)	70·4 ± 10·3	$P < 0.001$	38·1
Chlorpromazine + Compound 10854	62·1 ± 13·2	$P < 0.001$	30·3
Chlorpromazine + Eserine	59·0 ± 14·2	$P < 0.001$	29·2

TABLE 2. ACTION OF CHLORPROMAZINE AND SEVIN IN 15 MIN INCREMENTS ON DISCRETE AVOIDANCE BEHAVIOUR

Treatment	Shocks/animal (min after injection)							
	0–15	15–30	30–45	45–60	60–75	75–90	90–105	105–120
Control	1·3	1·1	1·2	1·1	1·0	1·1	1·2	1·1
Chlorpromazine	6·8	6·4	6·3	5·0	5·5	5·2	4·4	3·9
Sevin (high dose)	8·2	5·7	2·2	2·2	2·6	2·7	2·0	1·1
Chlorpromazine + Sevin (high dose)	14·7	16·4	20·4	18·9	17·8	18·6	18·2	18·4

of whether significant behavioural alteration was accomplished by the enzyme inhibitor when given alone. In addition to an exaggerated response which occurred during the first hour, a prolongation of behavioural disruption was apparent. This is revealed in Table 2 in which the average number of shocks during each 15 min period after treatment is given for one of the cholinesterase inhibitors.

Chemical Hygiene Fellowship,
Mellon Institute,
4400 Fifth Avenue,
Pittsburgh, Pennsylvania 15213,
U.S.A.
November 12, 1963

M. E. GOLDBERG
H. E. JOHNSON

References

Arterberry, J. D., Bonifaci, R. W., Nash, E. W. & Quinby, G. E. (1962). *J. Amer. med. Ass.*, **182**, 848–850.
Goldberg, M. E., Johnson, H. E., Knaak, J. B. & Smyth, H. F., Jr. (1963). *J. Pharmacol.*, **141**, 244–252.

Toxicity of a nucleotoxic agent, mustine hydrochloride, and its enhancement by 5-hydroxytryptamine pretreatment

SIR,—It has been shown by numerous workers that 5-hydroxytryptamine (5-HT) possesses a marked radioprotective activity. The effects of nucleotoxic drugs show certain similarities with the effects produced by ionizing radiation. Many radioprotective agents also provide a protection against the nucleotoxic substances (Scarborough & Thomas, 1962). We have now examined the influence of 5-HT upon the toxicity of mustine hydrochloride (nitrogen mustard), a typical representative of radiomimetic poisons. For testing the specificity of the phenomenon to be described, another toxic agent, chloral hydrate, was used.

Three groups of 20 albino rats were injected intravenously with mustine hydrochloride. The first group received saline, the second 5-HT creatinine sulphate and the third chloral hydrate intraperitoneally 30 min before being given the agent. The survival was observed every 12 hr during 30 days. The results are summarised in Table 1.

TABLE 1. ENHANCEMENT OF MUSTINE HYDROCHLORIDE TOXICITY BY 5-HYDROXYTRYPTAMINE PRETREATMENT

Treatment	Pretreatment	Mortality rate after 30 days (percentage)	Mean survival time in days ± s.e.m.	"t" test (survival time)
Mustine HCl 1 mg/kg i.v.	Saline i.p.	15	26·3 ± 2·0	—
,,	5-HT creatinine sulphate 21·2 mg/kg i.p.	55	17·3 ± 2·7	$P < 0.02$
,,	Chloral hydrate 270 mg/kg i.p.	20	25·0 ± 2·3	$P > 0.05$

A significant decrease in mean survival time in the group pretreated with 5-HT was noted. The animals pretreated with chloral hydrate showed no significant alteration in survival after mustine hydrochloride. The doses of 5-HT