An intraperitoneal injection of 4-acetamidophenol (0.33–0.66 m-moles/kg) at the height of the fever abolished shivering almost immediately, and the rectal temperature started to fall within 15 min, reaching the control level in 1–2 hr. The rectal temperature rose again after about 4 hr unless a subsequent dose of 4-acetamidophenol was administered. The response to 4-acetamidophenol was dose dependent. If 4-acetamidophenol was administered before the intracerebral injections of 5-HT or TAB vaccine, the onset of fever was delayed for several hours and could be further delayed by subsequent injections of 4-acetamidophenol. In some animals an intraperitoneal injection of 4-acetamidophenol produced a slight fall in rectal temperature.

In one series of experiments, when injected alone into the cerebral ventricles 4-acetamidophenol (6.6 μ-moles) itself produced a fever similar in degree and time of onset to that produced by both 5-HT or TAB vaccine. This rise in rectal temperature could be reduced or delayed by the intraperitoneal injection of 4-acetamidophenol. In a second series of experiments a slight fall in temperature followed by only a slight rise was observed. When 4-acetamidophenol (6.6 μ-moles) was injected into the cerebral ventricles during fever it produced only a slight and transient fall in rectal temperature.

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Centrally evoked responses by cholinergic agents and their antagonism by drugs in the conscious mouse

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Peripheral autonomic actions of imipramine include inhibition of noradrenaline uptake (Axelrod, Whitby & Hertting, 1961) and antagonism of acetylcholine (Vernier, 1961); both mechanisms have been proposed as the basis for clinical efficacy of this drug (Sigg, 1959; Cairncross, Gershon & Gust, 1963). While central inhibition of noradrenaline uptake has been demonstrated (Glowinski & Axelrod, 1964) central anti-cholinergic activity of imipramine has yet to be established. Accordingly, the effects of acetylcholine, carbachol, tremorine and oxotremorine after injection into the cerebral ventricles of conscious mice, and their modification by imipramine and other drugs, have been determined.

Intraventricularly injected acetylcholine, in doses as high as 20 μg/mouse, failed to cause any cholinergic response or change in behaviour. Tremorine (1–20 μg) was also without effect, although very high doses (100 μg) caused some salivation, tremor and hypothermia. However, carbachol (0.5 -5 μg) and oxotremorine (0.1–2 μg) caused salivation, lacrimation, tremor and a fall in body temperature the intensities and durations of which were dose-dependent. The degree of hypothermia afforded a basis for quantitative drug-interaction studies. Because a rise in skin temperature preceded the fall in body temperature, the most likely mechanism of the centrally administered cholinergic agents in causing hypothermia was impairment of central sympathetic outflow.

The effects of peripherally and centrally acting drugs on hypothermia induced by intraventricularly administered carbachol (2 μg) and oxotremorine (2 μg) were next

investigated. Oral pretreatment (1 hr beforehand; doses expressed as mg/kg) with chlorpromazine (5), haloperidol (10), chlordiazepoxide (20), pentobarbitone (20), phenytoin (20), methaqualone (20), phenelzine (20), codeine (50) or morphine (50), or subcutaneous pretreatment (1 hr) with propantheline (20) or atropine methonitrate (20) failed to modify the hypothermic effects of intraventricularly injected carbachol or oxotremorine. Oral pretreatment with imipramine (7.3), amitriptyline (8.5), nortriptyline (11.9), atropine sulphate (2.0) and amphetamine (2.9), however, inhibited by 50% the hypothermia induced by carbachol. Similar results were obtained when the cholinergic agent was oxotremorine. To determine whether the inhibitory action of these drugs was mediated through a central mechanism, they were injected intraventricularly (1–40 μg/mouse) 30 min or 60 min before the intraventricular injection of carbachol or oxotremorine. Only atropine, in doses as low as 0.05–1.0 μg/mouse, markedly inhibited the hypothermia induced by intraventricular carbachol or oxotremorine. In the light of these results it seems improbable that the clinical usefulness of thymoleptic drugs depends on central anticholinergic activity.

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Pharmacological evidence for a cholinergic mechanism in brain involved in a special stereotyped behaviour of reserpinized rats

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Pharmacological studies have indicated that a cholinergic mechanism is involved in the "paradoxical" stereotyped behaviour in reserpinized rats, described by Schiørring & Randrup (1968).

Male Wistar rats housed in individual cages were treated with reserpine (7.5 mg/kg s.c., Serpasil, CIBA). As expected the general behavioural effect was a strong sedation followed by catalepsy (3 hours after the injection). About 4–4.5 hr after reserpine bursts of co-ordinated activity were observed, consisting of constant sniffing (head movements with nose on cage wires and synchronous breathing) accompanied by forward locomotion. During the locomotion the rats retained the characteristic hunched "bison"-posture. A "rearing" was often also observed (standing on hindlegs and sniffing the upper part of the walls). Since the locomotion and rearing followed a fixed pattern and the sniffing was continuous, the activity was of a stereotyped character. The duration of this activity varied between 2 min and more than 2 hr. Of seventy-one rats studied, forty-nine rats (69%) showed this behaviour 4–5.5 hr after reserpine. At 7, 9–11, and 19–21 hr after reserpine this behaviour declined to 26%.

A complete inhibition of the locomotion, rearing and sniffing was observed after the following central anticholinergic drugs given 5.5 hr after reserpine (each drug s.c. to six rats): scopolamine hydrochloride (5 mg/kg); benactyzine hydrochloride (10 mg/kg);