concentration of xylose in the non-raffinose compartment exceeds that of the medium (1 mM) after incubation for 10 min and this accumulation against a concentration gradient depends upon the sodium concentration of the medium. Under these conditions a gradient of sodium ions from the raffinose to the non-raffinose compartment could be detected.

The uptake of xylose has been determined in a phosphate medium and not only was there no accumulation of xylose by the non-raffinose compartment but also no sodium gradient could be detected across the two compartments. These results suggest that the active transport of xylose in the bicarbonate medium may depend on asymmetries of the transport system due to interaction between the carrier and sodium ions. Of particular importance might be the effects of sodium ions upon the apparent dissociation of the carrier-xylose complex at the inner and outer edges of the membrane independently.

Acetazolamide can influence xylose uptake by the slices (Gilbert, Gray & Heaton, 1971). It has also been reported to increase the sodium gradient (Na_0/Na_i) in brain (Woodbury, Koch & Vernadakis, 1958). If the accumulation of xylose by cerebral cortex slices results from asymmetries induced by sodium ions then acetazolamide might be expected to increase the degree of accumulation. In fact, acetazolamide (20 μM) prevented the active transport of xylose and it also prevented xylose from equilibrating with the total slice water over a 15 min incubation period (medium xylose concentration 1 mM). However, determinations of the sodium contents of slices incubated in the bicarbonate medium showed that, in contrast to the observation of Woodbury, Koch & Vernadakis (1958), acetazolamide (20 μM) did not significantly alter the sodium gradient. Initial velocity studies of xylose uptake indicated that the drug altered both the apparent dissociation constant of the carrier-xylose complex and the maximal transport rate in a manner compatible with previous observations (Gilbert, Gray & Heaton, 1971) and with the inhibition of xylose uptake from a medium containing 1 mM xylose.

A high concentration of acetazolamide (200 μM) did not inhibit the active transport of xylose by the tissue but significantly increased the sodium gradient. These results are compatible with the concept that active xylose transport depends to some extent on the sodium gradient and further suggest that the membrane component involved in xylose transport has separate sites for interaction with xylose and sodium. Acetazolamide may interact with the sodium site effectively only at the high concentration whereas the sugar site may be sensitive to the low concentration and probably also to the high concentration of the drug.

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Possible role of dopamine-containing neurones in the behavioural effects of cocaine

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Cocaine and drugs of the imipramine group are believed to act on sympathetic postganglionic neurones through inhibition of the noradrenaline neuronal uptake

mechanism. *In vitro* cocaine inhibits the uptake mechanisms into central dopamine-containing and central noradrenaline-containing neurones in similar concentrations, while imipramine-like drugs inhibit the dopamine uptake mechanism only in concentrations 100 times greater than those which block central noradrenaline uptake (Ross & Renyi, 1967). The interaction of drugs with central dopamine-containing neurones can be investigated in rats with unilateral lesions of the dopamine nigro-neostratial pathway (Andén, 1966). These rats rotate towards the lesioned side after treatment with drugs of the amphetamine group (Ungerstedt, 1969; Christie & Crow, 1971).

Cocaine (5–20 mg/kg) stimulates locomotor activity but does not invoke turning (Christie & Crow, unpublished observation), although at the highest dose there is a tendency for movements to deviate towards the lesioned side. After pretreatment with nialamide (100 mg/kg), cocaine (20 mg/kg) induces marked turning towards the side of the lesion, an effect which is maximal 60 min after cocaine administration and lasts 3–4 hours. Desipramine (10–100 mg/kg), with or without nialamide pretreatment, merely depresses locomotor activity and does not induce turning.

When cocaine is administered 15 min before (+)-methylamphetamine (5 mg/kg), the turning produced by the latter drug is considerably reduced over the first hour although the effect of (+)-methylamphetamine is prolonged (Fig. 1). Desipramine (20 mg/kg) pretreatment has no initial inhibitory effect on turning but does prolong the duration of the amphetamine response, an effect which may be due to reduced metabolism of amphetamine in the liver delaying urinary excretion (Consolo, Dolfini, Garattini & Valzelli, 1967).

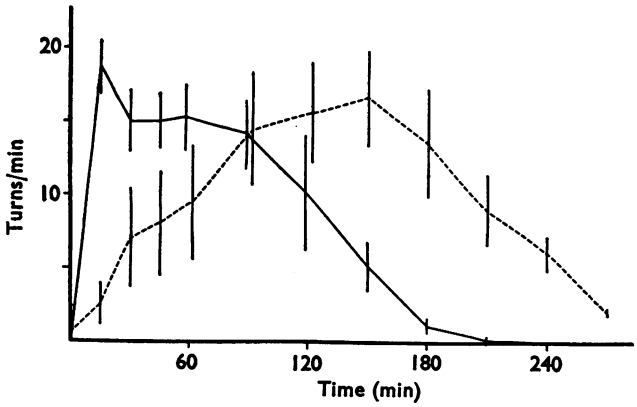

FIG. 1. Effect of pretreatment with cocaine on turning. Abscissa, time (min) after injection of (+)-methylamphetamine (5 mg/kg). Ordinate, turns/min (——), No cocaine; (– – –), 15 min after cocaine (20 mg/kg). Vertical bars indicate S.E. of means.

These results indicate that cocaine differs from desipramine and suggest that cocaine may interact with central dopamine-containing neurones in addition to central noradrenaline-containing neurones. This interaction may explain the central stimulatory effects of cocaine.

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Atropine sulphate absorption in humans after intramuscular injection of a mixture of the oxime-P2S and atropine

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The accepted therapy for poisoning by anticholinesterase compounds is atropine sulphate and pralidoxime mesylate (P2S). The former, depending on the severity of poisoning, can be given in repeated intramuscular doses of 2·0 mg and the oxime as 1·0 g given either by slow intravenous infusion or intramuscularly. The feasibility of administering this combined therapy as a single intramuscular injection has been studied in human subjects with particular reference to the effects which such a combination would have on the absorption rate of atropine.

The minimum intramuscular dose of P2S required to produce adequate therapeutic plasma P2S levels is 500 mg per man and this dose plus a higher one, 750 mg, has been used, in combination with 2·0 mg atropine sulphate, in these studies.

Subjects were twenty-two healthy volunteers. The uptake of atropine after injection was measured in terms of the change in heart rate as revealed in a continuous recording of a single chest lead electrocardiogram (e.c.g.).

For 1 h before commencement of the experiment, subjects lay quietly on a bed with minimal disturbance, and a continuous e.c.g. record was made for the last 5 min of this period. The intramuscular injections were then given into the outer aspect of the thigh and the e.c.g. then continuously recorded for 2 hours.

The influence on heart rate of the following was determined:

(a) Water for Injection B.P.	subjects 1–5
(b) 500 mg P2S in 2·0 ml Water for Injection B.P.	
(c) 750 mg P2S in 2·5 ml Water for Injection B.P.	subjects 1–5
(d) 2·0 mg atropine sulphate	subjects 1–22
(e) Combination of (b) and (d)	subjects 13–22
(f) Combination of (c) and (d)	subjects 1–12.

At least 5 days elapsed between intramuscular injections of atropine alone and combined with P2S.

From the e.c.g. records, measurements were made of the times to reach (a) peak bradycardia, (b) return to control and (c) peak tachycardia. For each individual, values obtained for mixed injections were subtracted from those for the atropine alone