Peterson, Hardinge & Tilton (1964) suggested that death from amphetamine may follow neuromuscular blockade. With *in vitro* studies they showed that the neuromuscular blocking action of amphetamine was enhanced by the addition of lactic acid to the bath. The concentration of lactate used by these investigators was based upon the report by Fletcher & Hopkins (1917) that, in fatigued muscle, lactate may reach a level of 0·25% (approximately equivalent to 28 μmoles/g). The relevance of these *in vitro* findings to the death of aggregated mice is questionable since, as shown here by direct measurement, the lactic acid content of skeletal muscle does not increase in the exhausted mice and is only one quarter of that used in the *in vitro* studies. However, as reported previously and substantiated here, the (+)-amphetamine treated mice which become depressed also develop a marked hypoglycaemia. This hypoglycaemia may be an important factor leading to the death of the aggregated mice (Moore & others, 1965).

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Blockade of the psychotic syndrome caused by nialamide in mice

SIR,—Inhibitors of monoamine oxidase, for example, nialamide, are known to cause a rise in noradrenaline and 5-hydroxytryptamine (5-HT) content of mouse brain whereas dopamine is hardly affected. This accumulation of amines is accompanied by a characteristic syndrome of stereotype movements of the animals involving restlessness, enhanced spontaneous motility, head movements, but no aggressiveness (Carlsson & Corrodi, 1964). These effects develop slowly after a high dose of nialamide (500 mg/kg i.p.) and are pronounced after 2½–3 hr.

By pretreating the animals with different inhibitors of the biosynthesis of noradrenaline, dopamine or 5-HT, or all three, the accumulation of these amines was blocked to discover whether the elevated level of noradrenaline or 5-HT, or of both, was responsible for the development of this syndrome.

Earlier work has shown that α-n-propyl-3,4-dihydroxyphenylacetamide (H22/54) and α-ethoxy-2,3-dihydroxyphenylacetamide (H33/07) could block this syndrome caused by nialamide (Carlsson, Corrodi & Waldeck, 1963; Carlsson & Corrodi, 1964). Both substances inhibit the hydroxylation of tyrosine and tryptophan, and so prevent the synthesis, in the animal, of dopamine, noradrenaline and 5-HT (Carlsson, & others, 1963; Carlsson & Corrodi, 1964). L-α-Methyldopa has been shown to inhibit the synthesis of

5-HT (Roos & Werdinius, 1963). The methyl ester of DL-α-methyltyrosine (H44/68) was chosen to inhibit the biosynthesis of dopamine and noradrenaline (Corrodi & Hanson, 1966).

The experiments are summarised in Table 1. Mice were treated with H22/54, H44/68 or α-methyldopa and nialamide. Three hr later the nialamide-treated control animals and the animals receiving nialamide and H44/68 had developed the characteristic syndrome, whereas the mice receiving nialamide and H22/54 or α-methyldopa looked normal. At this time the amine content in the brain was analysed fluorimetrically for noradrenaline (Bertler, Carlsson & Rosengren, 1958), dopamine (Carlsson & Lindqvist, 1962) and 5-HT (Bertler & Rosengren, 1959). In the nialamide-treated control animals there was a large increase in 5-HT (>300% of the normal value), noradrenaline was slightly elevated (~50%) whereas dopamine was unchanged. H22/54 and L-α-methyldopa blocked the rise in 5-HT and noradrenaline almost completely, whereas H44/68 blocked the rise in noradrenaline, and lowered the dopamine level. The accumulation of 5-HT, however, was not affected by H44/68. These results suggest that only substances blocking the synthesis of 5-HT are able to inhibit the development of the nialamide syndrome. Thus, the high excess of 5-HT in the mouse brain seen after nialamide treatment seems to be predominantly responsible for this model psychosis.

TABLE 1. NORADRENALINE, DOPAMINE AND 5-HYDROXYTRYPTAMINE (5-HT) IN MOUSE BRAIN 3 HR AFTER NIALAMIDE (500 MG/KG I.P.) AND OTHER SUBSTANCES. The animals (9 male Albino mice per group) were killed by decapitation; 3 brains were pooled for the 5-HT-determination and 6 brains for the determination of noradrenaline and dopamine. Values are % of normal level (range)

Treatment	No. of expts.	Syndrome	5-HT	Noradrenaline	Dopamine
Untreated controls	8	—	100 (82–110)	100 (90–110)	100 (87–112)
Nialamide	5	present	340 (300–350)	160 (125–190)	112 (98–127)
Nialamide + H 22/54 (500 mg/kg i.p.)	4	blocked	130 (125–145)	115 (105–125)	95 (88–102)
Nialamide + L-α-methyldopa (500 mg/kg i.p.)	3	blocked	135 (120–150)	100 (95–105)	108 (95–120)
Nialamide + H 44/68 (250 mg/kg i.p.)	4	present	315 (270–350)	80 (70–90)	50 (38–65)

Part of the mouse brains were examined by the histochemical technique of Hillarp and Falck for the demonstration of monoamines by fluorescence microscopy (Falck, Hillarp, Thieme & Torp, 1962; Falck, 1962; Hillarp, Fuxe & Dahlström, 1965). No overflow of 5-HT to noradrenaline or dopamine neurones or uptake at these sites could be observed 3 hr after nialamide (Fuxe, personal communication).

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2-Deoxyglucose and inflammation

SIR,—2-Deoxyglucose reduces oedema formation produced by injecting dextran into rats (Goth, 1959), and also inhibits the development of erythema in guinea-pigs exposed to ultraviolet irradiation (Görög & Szporny, 1964). The anti-inflammatory activity of 2-deoxyglucose is generally supposed to be connected with its effects on carbohydrate metabolism. However, 2-deoxyglucose also stimulates the release of catecholamines from the adrenal medulla (Brown & Bachrach, 1959; Hokfelt & Bydgeman, 1961), and evidence is presented which suggests that the anti-oedematous effect of this compound is mediated through this latter mechanism.

Groups of six female rats, 140–170 g, received an intraperitoneal injection of saline or 2-deoxyglucose, 250 mg/kg, 30 min before an injection beneath the left hind paw of 0·1 ml of the supernatant fluid from a 5% suspension of Brewers yeast. Foot volumes were recorded plethysmometrically before and 3/4 hr after the injection. Adrenalectomy or adrenal demedullation was performed 1 week before the experiment, and the adrenalectomised rats were maintained on 1% saline instead of tap water. Blood was taken by cardiac puncture at the time of the second foot-volume measurement. The % inhibition of oedema and % increase in blood sugar caused by 2-deoxyglucose were, in normal 58·9 and 81·7, in adrenalectomised 6·2 and 12·2 and in adrenal-demedullated rats 1·1 and 15·7 respectively. In adrenalectomised and demedullated animals this compound has no anti-oedematous effect and its hyperglycaemic activity is reduced but not abolished. Other irritants such as formaldehyde or silver nitrate have been used and the results were similar.

Propranolol, 10 mg/kg i.m., given 1 hr before 0·1 ml of the yeast extract, antagonises the anti-oedematous activity of adrenaline, 0·5 mg/kg s.c., and 2-deoxyglucose, 250 mg/kg i.p., given 30 min before the yeast extract. Propranolol, by itself does not affect oedema formation, a % inhibition of 3·1 being obtained, nor does it modify the anti-oedematous effects of cyproheptadine, phenylbutazone or hydrocortisone (Kellett, 1966). 2-Deoxyglucose caused a 62·9% inhibition of oedema, adrenaline 66·3, deoxyglucose + propranolol 27·4 and adrenaline + propranolol 29·3% inhibition. There were six rats per group.

While the assumption that 2-deoxyglucose inhibits inflammatory reactions by an effect on carbohydrate metabolism may still be correct, it seems that a direct effect on glycolysis is unlikely to be important. It is possible, however, that an indirect effect on carbohydrate metabolism, through catecholamine release from the adrenal medulla, may be involved. Impaired disposition of a glucose load is seen after the injection of 2-deoxyglucose into normal rats, but