markedly decreased the formation of exudate in the Lewis strain at both times.

Table 1 summarizes the changes in the cell counts of the pleural exudate. In control animals the total number of cells at 5 h was greater than at 15 h. Differential cell counts showed that neutrophils were the predominant cells in both strains and at both times. However, after 15 h, the proportion of neutrophils to lymphocytes decreased in comparison with that at 5 h.

As with exudate formation, treatment with indomethacin decreased the cell number only in Lewis rats. This was still evident at 15 h after the 10 mg kg^{-1} dose.

The present results showed that in carrageenan pleurisy also there was a marked difference between strains in their sensitivity. This might partly explain the discrepancies in the results of different authors. The rats of the AVN strain appear to be much more resistant in this experimental model as was shown in our work with adjuvant-induced arthritis (Perlík & Zídek, 1973). Greater mobilization of the inflammatory cells in the Lewis strain may amplify and prolong the inflammation of this strain.

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On the relation between hypodipsia and anorexia induced by (+)-amphetamine in the mouse

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(+)-Amphetamine inhibits drinking when water is offered to thirsty rats which are nevertheless offered unrestricted access to food (Soulairac & Soulairac, 1970). However, its effect on the water intake of rats whose food is taken away immediately before water is given is less clear. Glick & Greenstein (1973) have reported that it fails to influence the water intake of such animals, whereas Nielsen & Lyon (1973) found that the presence or absence of food has little effect on the hypodipsic action of (+)-amphetamine in thirsty rats.

We have investigated the acute effects of (+)-amphetamine on drinking in water deprived mice because of the extensive use of mice in the screening of drugs for anorectic properties (Friedman, Weingarten & Janowitz, 1962; Clark, 1969), and because it would be useful to ascertain to what extent, if any, the anorexia produced by a drug such as (+)-amphetamine is secondary to hypodipsia or vice-versa.

Male albino mice, 20–25 g, of the CFLP-ICI strain 1, bred in our laboratories were caged in groups of 8 and housed at 25 ± 1°. They were fed on a conventional 41B cube diet (Spilsburys, Birmingham) and tap water was made available from standard feeder bottles with the nozzles all the same height (3 cm) above the floor of the cage.

Assessment of hypodipsic activity. The mice were deprived of water but not food for the 21 h, extending from 17.00 h till 14.00 h the following day when they were again allowed access to water. The effect of drugs on the total amount of water consumed by each group of 8 mice between 14.00 h and 15.00 h while having free access to food was then determined and expressed as a volume (ml) per unit body weight (kg), the mean water intake from 6 such groups being finally obtained. This was then compared with that obtained in a similar manner in mice treated with a saline control. The significance of any observed difference between the means of test and control groups in these and all subsequent experiments was determined by Student's *t*-test.

In a second set of experiments mice were similarly deprived of water, but their food was removed immediately before replacement of the supply of water. The effect of drugs on water intake in the absence of food between 14.00 h and 15.00 h was then determined and compared with that of a saline control.

The water intake measured over 1 h immediately following water deprivation was found to be 66·36 ± 3·74 ml kg^{-1} (group mean ± s.e.; n = 6) with food

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being available during the drinking period. This was not significantly reduced by saline (5 ml kg^{-1}) given either subcutaneously 15 min before or intraperitoneally 4 h before presentation of drinking water.

(+)-Amphetamine produced a dose dependent depression of water intake in these mice which was significant ($P < 0.05$) at 0·5 and 1 mg kg^{-1} and highly significant ($P < 0.01$) at 2, 4, 8 and 16 mg kg^{-1} (Fig. 1). The submaximal depression of water intake produced by (+)-amphetamine (2 mg kg^{-1}) was significantly reversed ($P < 0.01$) by α-MT (80 and 160 mg kg^{-1}) which, given alone did not affect water intake (Fig. 2).

The water intake of the mice which were deprived of food when allowed free access to water, was significantly less ($P < 0.01$) than that of the mice which had food available, although both groups had been water-deprived to the same extent. (+)-Amphetamine (4, 8–16 mg kg^{-1}) also produced a significant ($P < 0.01$) dose-dependent depression of water intake in the food-deprived mice (Fig. 1). The submaximal depression of water intake produced by (+)-amphetamine (8 mg kg^{-1}) was significantly reversed ($P < 0.01$) by α-MT (80 and 160 mg kg^{-1}) (Fig. 2). Again, when given at these doses, α-MT alone had no influence on the water intake of the mice.

Assessment of anorectic activity. The mice were again deprived of water for 21 h as described above, but were allowed free access to food over this period. Any uneaten food was removed at 14.00 h on the second day and replaced with 100 g of 41B pellets, paper being placed beneath the grid bottomed cages to collect any food spilt during feeding. Water was then offered to the mice as before, but in this instance, the effect of drugs on the food intake of the mice between 14.00 h and 15.00 h was determined in 6 groups of 8 mice as described above and compared to that of saline controls.

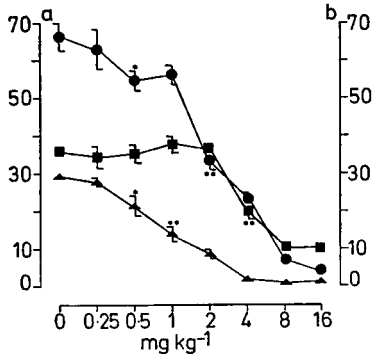

FIG. 1. (+)-Amphetamine hypodipsia and anorexia in mice deprived of water for 21 h. The effects on a—water (ml kg^{-1}) (●——●) and b—food (g kg^{-1}) (▲——▲) intake following water deprivation but with free access to food are shown as are its effects on water intake in the absence of food (■——■). (+)-Amphetamine (mg kg^{-1}) was given subcutaneously 15 min before water at the doses indicated. (* $P < 0.05$; ** $P < 0.01$).

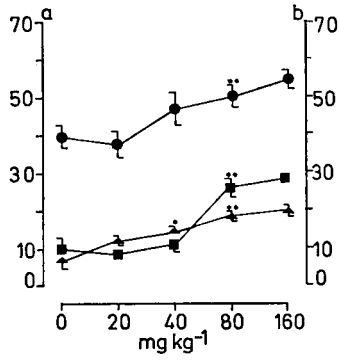

FIG. 2. The effect of α-MT on the hypodipsia (●——●) and anorexia (▲——▲) produced by 2 mg kg^{-1} of (+)-amphetamine in water deprived mice with free access to food. The effect of α-MT on the hypodipsia produced by 8 mg kg^{-1} (+)-amphetamine in water deprived mice in the absence of food is also shown (■——■). α-MT (mg kg^{-1}) was given intraperitoneally 4 h before water at the doses indicated and (+)-amphetamine subcutaneously 15 min before water (* $P < 0.05$; ** $P < 0.01$). a—Water intake (ml kg^{-1}), b—food intake (g kg^{-1}).

The mice in this experiment nevertheless fed vigorously when their drinking water was restored. This food intake was not altered by saline (5 ml kg^{-1}) given subcutaneously 15 min before water. (+)-Amphetamine produced an antagonism of this food intake, this being dose-dependent and significant ($P < 0.05$) at a dose of 0·5 mg kg^{-1} and highly significant ($P < 0.01$) at doses of 1–16 mg kg^{-1} (Fig. 1). The submaximal depression of food intake produced by a dose of 2 mg kg^{-1} of (+)-amphetamine was reversed in a dose-dependent manner by α-MT and was significant ($P < 0.05$ at a dose of 40 mg kg^{-1}) and highly significant ($P < 0.01$) at doses of 80 and 160 mg kg^{-1} (Fig. 2). These doses of α-MT had no effect on food intake when given alone.

The drugs used were: (+)-amphetamine sulphate (Light), α-methyl-*p*-tyrosine methyl ester hydrochloride (Sigma). (+)-Amphetamine was injected subcutaneously, 15 min before either food or water and α-methyl-*p*-tyrosine methyl ester hydrochloride (α-MT) was given intraperitoneally, 4 h before presentation of food or water. The doses of both these drugs are expressed in terms of their salts. Injections were made in 0·9% saline using a dose volume of 5 ml kg^{-1}.

The results confirm findings in the rat (Soulairac & Soulairac, 1970) that (+)-amphetamine produces a dose-dependent hypodipsic effect in water-deprived animals. The mice, on being allowed access to water after a period of water deprivation, also fed vigorously, even though they had not been deprived of food at any time, while (+)-amphetamine produced a dose-dependent depression of this food intake. The (+)-amphetamine-induced depression of both food and

water intake was reversed in a dose-dependent manner by α-MT, a centrally acting inhibitor of catecholamine synthesis (Spector, Sjoerdsma & Udenfriend, 1965). We have previously discussed the antagonism of (+)-amphetamine anorexia in the mouse by α-MT (Dobrzanski & Doggett, 1976) and the present findings demonstrating the reversal of (+)-amphetamine induced hypodipsia by α-MT confirm work in the rat (Holtzman & Jewett, 1971).

The depressant effect of food deprivation on water intake has been shown previously in several species (Kutscher, 1969) and we found that mice from which food was removed immediately before they were offered water, drank significantly less than mice whose food was not removed. Furthermore, low doses of (+)-amphetamine (0·5–2 mg kg^{-1}), which significantly depressed the water intake of the mice when food was available, failed to do so in its absence. Glick & Greenstein (1973) have stated that, in rats, the hypodipsic action of (+)-amphetamine is exclusively due to the inhibition of the increase in water intake associated with food intake or 'prandial drinking' (Teitelbaum & Epstein, 1962; Epstein, Spector & others, 1964). Our results similarly suggest that the hypodipsic action of low doses of (+)-amphetamine in the presence of food results primarily from the depression of the vigorous feeding which occurs in thirsty mice when they are offered water, which in turn inhibits drinking. Thus it could be argued that the α-MT-induced antagonism of the action of (+)-amphetamine on prandial drinking would be largely dependent on its antagonism of (+)-amphetamine anorexia.

Nevertheless, our results also conclusively show that high doses of (+)-amphetamine (4–16 mg kg^{-1}) did significantly inhibit the water intake of the mice, regardless of the presence or absence of food. Thus, although (+)-amphetamine inhibited non-prandial drinking, its depressant effects on prandial drinking were much more marked. This difference in sensitivity has also been observed in the rat (Neill & Grossman, 1971) although more recent studies in the same species (Nielsen & Lyon, 1973) failed to observe this effect.

In view of the high doses used, it could justifiably be claimed that the inhibitory effect of (+)-amphetamine on non-prandial drinking could be the result of an unspecific action unrelated to the adrenergic effects commonly associated with this drug (Andén, 1970). The antagonism of this (+)-amphetamine-induced hypodipsia by α-MT does provide some evidence of catecholaminergic involvement. However, it remains to be shown whether in depressing water intake through such a mechanism (+)-amphetamine acts specifically to abolish thirst.

Thus, these results show that the naturally occurring inter-relationship between water and food intake is parallelled by a similar relationship between (+)-amphetamine-induced hypodipsia and anorexia in the mouse. Hence, while (+)-amphetamine is specifically anorectic at low doses, the depression of food intake it induces also results in a depressed water intake. It is only at high doses that this drug induces hypodipsia independently of anorexia.

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