Figure 4 illustrates the inhibitory ($p < 0.01$) effect of dopamine in terms of a ratio of

$$\frac{\text{D} - \text{L}}{\text{D}} \quad \frac{\text{dopamine convulsion} - \text{CSF convulsion}}{\text{dopamine convulsion}}.$$

According to this ratio, the intracerebral injection of dopamine resulted in a 157% inhibition of the withdrawal response at peak difference. The duration of action was at least 8 h, a finding similarly observed for morphine and alcohol.

Acute administration of morphine resulted in a marked inhibition of ethanol-induced withdrawal convulsions in mice. It is suggested on the basis of these in vivo experiments that dopamine may be an important link between morphine and ethanol actions. In vitro ethanol promotes the formation of tetrahydropapaveroline (THP), conjugate of dopamine with dihydroxyphenylacetaldehyde, which is the requisite intermediate in morphine biosynthesis in the opium poppy *Papaver somniferum*[28]. Evidence suggests that dopamine derived alkaloids are formed after the ingestion of ethanol[29] and may contribute to its addiction liability[30] and for neuropharmacological actions[31]. Other research shows[7,24] that morphine, ethanol and the dopamine conjugate of acetaldehyde (salsolinol) deplete regional brain calcium. This effect is selectively antagonized by the stereo-specific narcotic antagonist, Naloxone. Naloxone inhibits ethanol-induced withdrawal reactions[9] and also blocks the dopamine-derived alkaloid induction of seizure activity in mice[9]. Morphine abstinence results in diminished dopaminergic activity which is reversed to normal following Naloxone administration[25].

Morphine-induced suppression of ethanol withdrawal convulsions persists for a longer period of time than its duration of analgesia; thus suggesting that the inhibitory effect of morphine is not due to its intoxication but rather to some other specific interaction between ethanol and morphine[32].

It is possible that dopamine may play a significant role as a modulator in the withdrawal convulsions induced by ethanol and may even account for morphine suppression of this convulsion response. Other biochemically directed research may eventually delineate this interaction between morphine and ethanol and provide a further rationale for its treatment of withdrawal symptomatology.

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The Influence of Lithium on Serum Ceruloplasmin

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Summary. Serum ceruloplasmin oxidase activity did not change in mice treated orally for 120 days with Li_2CO_3 (0.58 mEq/kg/day). After a single i.p. injection of LiCl (20 mEq/kg), a significant activation of ceruloplasmin was observed.

It is well established that lithium carbonate is a prominent therapeutic agent against manic-depressive psychosis[2,3], but the mechanism of lithium effects is still an open question[4,5]. According to our bibliographic search reports on the effect of Li^+ on ceruloplasmin are lacking. Since this plasma oxidase may be involved in some forms of mental disease[6] and in the mechanism of action of centrally active drugs[7], the present study was conducted in an attempt to examine the possible influence of Li^+ on ceruloplasmin activity.

Material and methods. Male Swiss mice (mean body weight 29 g) maintained on a standard balanced diet ad libitum were used. In long term experiments mice received as drinking water a solution containing 100 mg of Li_2CO_3/l. To the control group distilled water was given. After 120 days of treatment the mice were killed by decapitation, blood samples were collected and the sera separated and stored at −20 °C. The maximum storage time was 24 h. Ceruloplasmin oxidase activity was determined by the method of RAVIN[8] and values expressed in mg/100 ml of serum. In experiments with LiCl or NaCl, a *M* solution was administered i.p. at the dose of 20 mEq of Li^+ or Na^+/kg and blood samples were taken by decapitation 2 h after the injections. The sera were separated, stored and ceruloplasmin determined as above. The significance of the differences were evaluated by the Student *t*-test[9].

Results and discussion. The mean daily intakes of water or Li_2CO_3 solution throughout the period of experimentation were 6.3 and 6.4 ml/mouse, respectively. This dose corresponds to 0.58 mEq lithium/kg body weight/day.

From the results presented in the Table, it is clear that long-term administration of Li_2CO_3 does not change the levels of ceruloplasmin, since the difference between Li^+ treated and control mice is not significant ($t=1.565$, $p < 0.2$). The dose of 20 mEq/kg NaCl does not have any influence on ceruloplasmin, since the difference between these mice and the normal controls (Table) is not significant ($t=0.559$, $p > 0.5$). In contrast to these findings, the group of mice treated i.p. with LiCl presented a ceruloplasmin activity higher than the NaCl-injected

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Serum ceruloplasmin oxidase activity in Li^+ treated mice

Treatment	Route of administration	Dose (mEq/kg)	Period	No. of mice	Ceruloplasmin (mg/100 ml of serum)
Li_2CO_3	os	0.58/day	120 days	20	12.1 ± 0.4
Controls (H_2O)	os	—	120 days	20	13.5 ± 0.8
LiCl	i.p.	20	2 h	10	19.5 ± 1.6
NaCl	i.p.	20	2 h	8	14.0 ± 0.4

Each value of ceruloplasmin represents the mean ± SEM.

group, and this difference was found to be statistically significant ($t = 3.333$, $p < 0.01$). The same result was obtained comparing LiCl-treated mice with normal control animals ($t = 3.353$, $p < 0.01$).

It is interesting to recall that the dose of Li_2CO_3 used in the long-term experiment is in the range of that employed in manic-depressive psychosis[3]. In our previous reports with this schedule of Li_2CO_3 administration, we obtained inhibition of aconitase[10] and activation of succinate dehydrogenase[11] and fumarase[12] in cerebral tissues of mice. The patterns of oral and i.p. absorption of Li_2CO_3 and LiCl are similar[13], reaching measurable plasma levels rapidly and with a slow movement of Li^+ into the brain. The results of the present study indicate that the activation of ceruloplasmin by Li^+ is probably a function of the concentration achieved by the ion in blood.

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Effect of Colchicine on Polymerization of Tubulin from Rats, Mice, Hamsters and Guinea-Pigs[1]

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Summary. Colchicine-inhibition of polymerization of tubulin from rats, mice, golden hamsters and guinea-pigs was studied to determine if species differences in tubulin sensitivity to colchicine might parallel species variation in colchicine toxicity. It was found that polymerization of tubulin is nearly equally sensitive to colchicine in all four species.

It is well known that the golden hamster (*Mesocricetus auratus*) is highly resistant to the toxic effects of the alkaloid colchicine as compared to other species of rodents[2]. Among the hypotheses suggested for this phenomenon has been the possibility of a unique or different metabolic or excretory pathway for colchicine in the hamster, but this now seems unlikely in view of recent investigations[3,4]. Midgeley et al.[5] have demonstrated that the hamster has a cellular resistance to colchicine as revealed by the 100-fold higher dose of colchicine required to inhibit mitosis in hamster tissues. Since it is generally felt that colchicine's toxic effects are a result of interaction of colchicine with microtubule protein (tubulin) and breakdown of microtubules in various tissues, it is of interest to ask if hamster tubulin polymerization is more resistant to blockade by colchicine than polymerization of tubulin from species more susceptable to colchicine. In order to make this comparison we have determined the ability of colchicine to inhibit polymerization of tubulin from rats, mice, hamsters, and guinea-pigs.

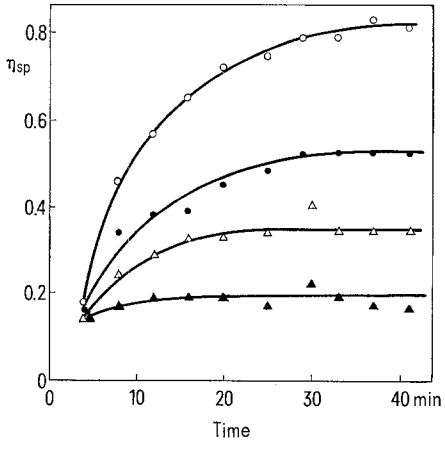

Fig. 1. Development of viscosity in hamster brain extracts with time and the effect of colchicine. Control (○); colchicine, 2.2×10^{-7} *M* (●); colchicine, 6.6×10^{-7} *M* (△); colchicine, 2.15×10^{-5} *M* (▲).

Polymerization of tubulin was measured in high speed supernatant fractions of brain homogenates from the various animals. Animals were killed by cervical dislocation. The brains were removed and homogenized in a cold glass homogenizer with 1.5 volumes (ml) of ice cold PEG buffer (100 m*M* PIPES, 1 m*M* EGTA and 2.5 m*M* GTP; pH 6.94). The homogenate was centrifuged at

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