Development of cross-tolerance to intravenous hexobarbital was also found in the treated mice. In contrast to the median anesthetic dose of 52 mg/kg in nontreated mice, those estimated in mice two and three days after treatment were 81 and 71 mg/kg, respectively.

In this experiment, tolerance was evaluated in terms of both decreased intensity of barbiturates and elevation in the median anesthetic dose. Although a change in the rate of barbiturate metabolism could account in part for the shortened duration of the drug action, our present results apparently suggest that one of the essential factors in the development of tolerance to barbiturates must be attributed to some form of adaptation of cells in the nervous system.

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POTENTIATION OF BARBITURATE ANESTHESIA BY CATECHOLAMINES

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It has already been reported that epinephrine as well as certain other substances, when injected into animals on awakening from barbiturate anesthesia, causes a return to sleep (1).

In an attempt to further the understanding of the interaction between catecholamines and adrenergic blocking agents in barbiturate anesthesia, the ability of *alpha* or *beta* blocking agent to antagonize the catecholamine-induced potentiation of barbiturate anesthesia was investigated.

Rats were anesthetized by intraperitoneal injection of hexobarbital (100 mg/kg) or thiopental (35 mg/kg). When they became light, 5 mg/kg of phentolamine or propranolol was injected intraperitoneally. When rats had awakened sufficiently to respond, catecholamine was injected and the return to sleep was obser-

TABLE I. Effect of adrenergic blocking agents on the catecholamine-induced potentiation of thiopental anesthesia in rats.

Pretreatment		Potentiating material*	Number of animals	Number showing a return to sleep
Drugs	Dose (mg/kg)			
—	—	Epinephrine	8	8
Phentolamine	5.0	Epinephrine	6	1
Propranolol	5.0	Epinephrine	10	4
—	—	Norepinephrine	7	7
Phentolamine	5.0	Norepinephrine	7	2
Propranolol	5.0	Norepinephrine	7	5
—	—	Isoproterenol	10	0

* On awakening from thiopental anesthesia, rats were injected intraperitoneally with 0.25 mg/kg of the potentiating material.

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ved. Control experiment showed that epinephrine as well as norepinephrine at a dose of 0.25 mg/kg effectively potentiated the anesthetic effect of hexobarbital or thiopental. However, isoproterenol in doses of 0.1–1.0 mg/kg was found to be inactive.

As shown in Table 1, the return to sleep following administration of epinephrine or norepinephrine was significantly blocked by phentolamine and partially by propranolol. Potentiation of barbiturate anesthesia by epinephrine or by norepinephrine was also confirmed in mice and guinea pigs. In these species, both phentolamine and propranolol effectively antagonized the above-mentioned catecholamine action. Therefore, some doubt has been raised as to the specificity and mechanism of such a blocking action.

Recently, Brooker *et al.* (2) have reported that the lipolytic activity of norepinephrine can be inhibited by both types of adrenergic blocking drugs. Ohshika in our laboratory has found that thiopental bound to serum albumin can be easily displaced by nonesterified fatty acid (3). He suggested that catecholamine-induced increase in plasma nonesterified fatty acid might account in part for the potentiation of barbiturate anesthesia. It seems of interest, therefore, to investigate whether this type of displacement is also applicable in whole animal. Further studies are in progress.

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VARIANCE OF THE GROWTH OF *TETRAHYMENA* BY THE COMPOUNDS WHICH AFFECT ON THE ADRENERGIC MECHANISM

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In an earlier communication, Janakidevi *et al.* (1) reported that catecholamine (CA) was isolated from *Tetrahymena pyriformis* and the cell was also able to biosynthesize adrenaline. On the basis of these findings, Blum *et al.* (2) started the studies on the influences of reserpine on CA content and on the growth of *Tetrahymena*. They found that the content of CA was reduced and the growth was inhibited by the addition of reserpine.

In the course of our studies on the possible physiological roles of tetrahymanol, whose structure has been established by Tsuda *et al.* (3), and its related substances in *Tetrahymena*, we have examined the influences of the compounds, which affect on the adrenergic mechanism in mammals, on the morphological changes and on the growth rate of this protozoa.

The following chemicals were used in these experiments; ergotamine tartrate, dibenamine-HCl and chlorpromazine-HCl as prototypes of α-adrenergic blocking agents, dichloroisoproterenol-HCl (DCI) and propranolol as β-adrenergic blocking agents, phenylethylhydrazine dihydrogen sulfate (Nardil) and β-phenylisopropylhydrazine-HCl (Catron) as monoamine oxidase inhibitors, reserpine phosphate as CA releaser and pyrogallol as inhibitor of catechol-O-methyl transferase.

Tetrahymena pyriformis W cells were cultured in the medium composed of 2% polypepton and 0.1% yeast extract at pH 7.2, for 72 hours at 26°C after the addition of the compounds tested. All procedures were car-

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