seemed unlikely that increased transaminase activity in the late stages of tumor growth resulted from an enhanced liver mitotic activity.

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Selective Depression of Sympathetic Transmission by Intravenous Administration of Iproniazid and Harmine.* (26061)

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Gertner(1) demonstrated that when the superior cervical ganglion of the cat was perfused with monoamine oxidase (MAO) inhibitors, transmission through the ganglion was blocked. With low concentration of the inhibitors, the depression of transmission developed gradually, unlike the immediate blocking effects of hexamethonium. The present study was designed to compare the effects of intravenous administration of 2 MAO inhibitors, iproniazid and harmine, on transmission through sympathetic and parasympathetic ganglia of the dog and cat.

Methods and materials. (a) Dog Experiments: Mongrel dogs of both sexes were anesthetised with a mixture of pentobarbital, 15 mg/kg and barbital 225 mg/kg administered intravenously. Vagus nerves were cut bilaterally in the neck and mechanical respiration was provided. The chest was opened transversely, 2nd and 3rd ribs were removed, and a Walton strain gauge arch was sutured to the right ventricle. Heart contractile force and carotid arterial pressure were recorded with a Grass Polygraph as previously described(2). The stellate ganglion and sympathetic trunk were exposed on one side. The sympathetic trunk was crushed and ligated at the level of the 4th thoracic ganglion and a shielded 27 gauge silver wire electrode was placed on a presynaptic sympathetic nerve between 2nd and 3rd thoracic ganglia. A similar electrode was placed on a suitable postsynaptic sympathetic nerve. Pre- and post-synaptic nerves were stimulated by means of a Grass Model S-4G stimulator for 10 sec. periods at a frequency of 17 cycles/sec. with monophasic pulses of 0.5 sec. duration. Maximum increments in heart rate to increasing voltage was ascertained for pre- and post-synaptic nerves and the nerves were stimulated alternately with such voltage (ranging from 3-15 volts) during the course of experiment. The vagus was stimulated at 5-10 minute intervals with a fixed voltage which had previously been found to produce marked bradycardia. Anatomical dissection in the dog is described by Mizeres(3) and the technic for stimulation is essentially that de-

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TABLE I. Effects of Iproniazid and Harmine on Transmission through Stellate Ganglion of Dog in 8 Experiments.

Inhibitor	Dose, mg/kg	Before inhibitor H.R.,* beats/min.	% increase Pre.	% increase Post.	After inhibitor H.R., beats/min.	% increase Pre.	% increase Post.	% inhibition† Pre.
Iproniazid	100	125	44	72	110	18	64	59
"	150	160	44	50	145	18	50	59
"	150	160	59	68	173	11	54	82
"	175	173	45	60	155	10	67	78
Harmine	5	167	49	49	120	25	63	49
"	5	130	66	62	70	21	144	68
"	10	175	37	57	130	0	69	100
"	15	115	130	118	105	14	95	89

* Heart rate. % increase in heart rate after preganglionic stimulation and after post ganglionic stimulation.

† $100 - \frac{\%\text{ increase pre. after inhibitor}}{\%\text{ increase pre. before inhibitor}}$.

scribed by Perry and Wilson for the cat(4). (b) Cat Experiments: Cats of both sexes were anesthetized with Dial-Urethane in a dose of 0.7 cc/kg administered intraperitoneally. Each cc contained 0.1 g diallyl barbituric acid, 0.4 g of urethane, and 0.4 g of monoethyl urea in aqueous solution. Pre- and postsynaptic sympathetic nerves of the superior cervical ganglion were separated from the vago-sympathetic chain, using care to leave intact the blood supply to ganglion and nerves. The ipsilateral nictitating membrane was connected to a Grass PR-4 strain gauge unit and isometric contractions of the membrane were amplified and recorded on a Grass Polygraph. Recordings of carotid artery pressure and electrical stimulations of the nerves were the same as described above. (c) Materials. Iproniazid phosphate (Marsilid, Hoffmann-LaRoche) and harmine, calculated as their bases, were administered intravenously in doses shown in Tables I and II. In the dog experiments, both agents were administered intermittently over a 15 minute period; in the cats, the drugs were given over a period of 30 to 120 minutes, to minimize their effects on the cardiovascular system.

Results. The actions of iproniazid and harmine on ganglionic transmission in both types of experiments were calculated as percent inhibition(4).

(a) Dog Experiments: The effects of iproniazid and harmine on transmission through the dog stellate ganglion are shown in Table I. As noted, both agents produced marked depression of the tachycardia resulting from preganglionic stimulation without decreasing the response to postganglionic stimulation.

The bradycardia produced by vagal stimu-

TABLE II. Effects of Iproniazid and Harmine on Transmission through Superior Cervical Ganglion of the Cat in 6 Experiments.

Inhibitor	Dose, mg/kg	Before inhibitor N.M.–Pre.* (mm)	Before inhibitor N.M.–Post.† (mm)	After inhibitor N.M.–Pre. (mm)	After inhibitor N.M.–Post. (mm)	% inhibition Pre.‡
Iproniazid	50	20	30	9	27	55
"	50	20	36	4	32	80
"	100	10	10	0	10	100
Harmine	12	31	31	23	31	26
"	20	29	23	16	22	45
"	25	26	28	7	25	73

* Height of recording of nictitating membrane contraction after preganglionic stimulation.
† *Idem* postganglionic " .

‡ $100 - \frac{\text{N.M. pre. after inhibitor}}{\text{N.M. pre. before inhibitor}}$.

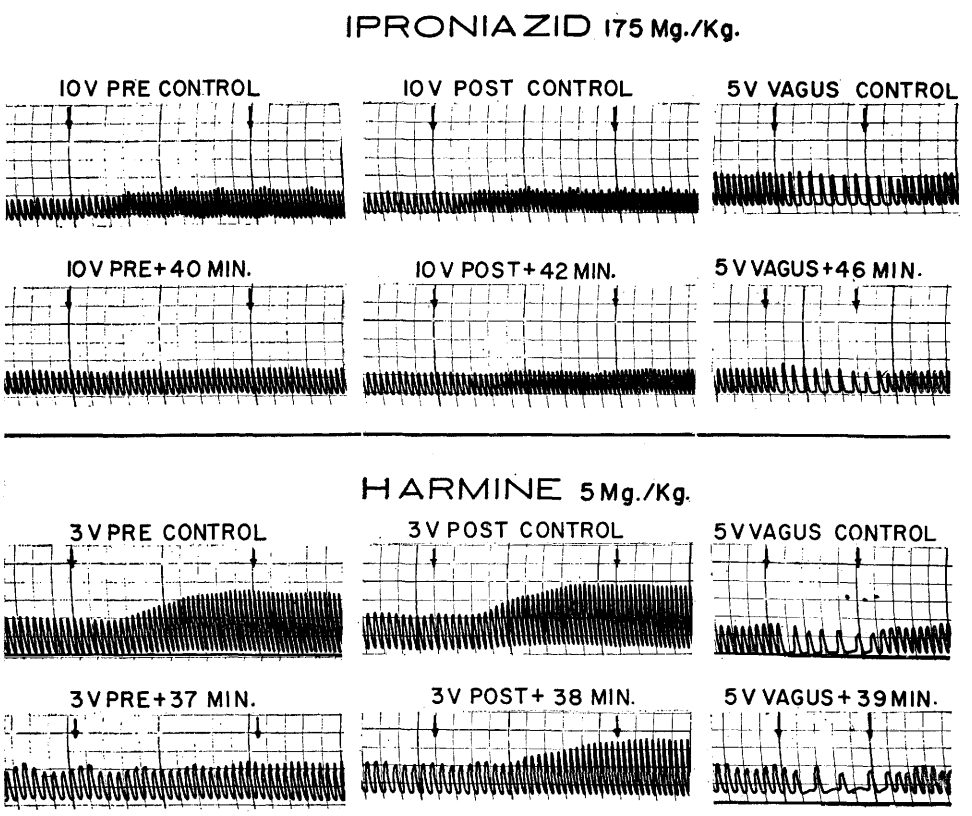

FIG. 1 (upper tracings). Effects of iproniazid, 175 mg/kg, intrav., on increases in heart rate and contractile force produced by maximal pre- and postganglionic stimulation of the stellate ganglion and on the bradycardia produced by stimulation of the vagus in an open-chest, anesthetized dog. The sympathetic nerves were stimulated for 10 sec. (indicated by the arrows), with 10 volts at a frequency of 17 cycles/sec. Vagus was stimulated for 5 sec. with 5 volts. Upper panels were obtained before and lower panels at designated time after completion of drug administration. (Lower tracings) Effects of harmine, 5 mg/kg, in a similar experiment. Conditions were the same except that maximal effects on heart rate and contractile force were obtained by stimulating pre- and postganglionic nerves with 3 volts.

lation was not affected by either agent and is therefore, not included in the table. In 2 additional experiments, the effects of stimulating the vagus at varying frequencies with constant voltage was also unchanged following intravenous administration of harmine, 10 mg/kg, and iproniazid, 150 mg/kg. Hexamethonium, 2 mg/kg, administered later in these experiments, completely blocked the effects of vagal stimulation. Fig. 1 illustrates increments in heart rate and contractile force produced by preganglionic stimulation which were almost totally blocked by the inhibitors. Also shown are the relatively unaffected postganglionic and vagal responses.

The sympathetic block produced by harmine was usually more rapid in onset and of shorter duration than that occurring with iproniazid. In 3 of the 4 harmine experiments, preganglionic responses had returned to between 60% and 90% of control values during the 120 minute period of observation. Preganglionic responses returned to only 20% of control values during a comparable observation period after administration of iproniazid.

Both iproniazid and harmine exerted marked cardiovascular actions and harmine also caused transitory convulsive movements in the large doses used, as previously described(2,5). In all experiments, harmine produced marked bradycardia which occurred immediately and was of relatively short duration. This effect preceded and was of shorter

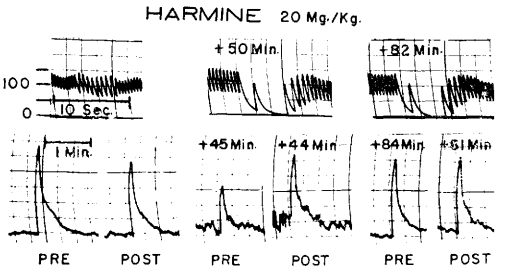

FIG. 2. Effects of harmine, 20 mg/kg, in an anesthetized cat. Upper tracings illustrate changes in arterial blood pressure (scale to left of tracing is mm Hg) and heart rate resulting from stimulation of the vagus nerve with 10 volts for 5 sec. at a frequency of 17 cycles/sec. Lower tracings are recordings of contractions of the nictitating membrane to stimulation of pre- and postganglionic fibers of the superior cervical ganglion with 10 volts for 10 sec. at a frequency of 17 cycles/sec. The first panels are before and the others are at designated times after completion of drug administration.

duration than the sympathetic block. Administration of iproniazid resulted in an immediate drop in mean blood pressure from levels of 100 to 140 mm Hg to values of 50 to 60 mm Hg without affecting heart rate or contractile force. This effect also preceded onset of significant sympathetic block, but persisted for duration of experiment.

As noted in Table I, 100% inhibition of sympathetic ganglionic transmission was observed in only one experiment. Attempts were made in several additional experiments to produce total block of sympathetic transmission by giving even larger doses of the inhibitors, but hypotension produced by iproniazid and convulsions and bradycardia caused by harmine usually became more pronounced and prevented evaluation of the ganglionic effects. In one experiment, however, an additional increment of 65 mg/kg of iproniazid was injected in divided doses during a 60 minute period and the 59% inhibition produced by 100 mg/kg of iproniazid was increased to 100%, without further hypotension. This experiment demonstrated that the hypotensive effect can be dissociated from the ganglionic action produced by iproniazid.

To evaluate the effects of a hydrazine which is not an MAO inhibitor, 150 mg/kg of isonicotinic acid hydrazide (INH) was administered intravenously in one experiment. There was no change in the effects of pre- and postganglionic stimulation during a 120 minute period of observation. Typical sympathetic block, however, resulted from the later administration of 150 mg/kg of iproniazid. Gertner(1) had previously demonstrated that INH did not inhibit transmission through the isolated superior cervical ganglion of the cat.

(b) Cat Experiments: Depression of transmission through the superior cervical ganglion was observed in 3 experiments with iproniazid and 3 with harmine (Table II). Bradycardia produced by vagal stimulation was not inhibited by either agent. Fig. 2 illustrates the pronounced depression of amplitude of contraction of the nictitating membrane to preganglionic stimulation and little change in amplitude to postganglionic stimulation following administration of harmine. The bradycardia produced by vagal stimulation was not inhibited, and in fact, appeared to be potentiated. A similar increase in vagal effect was noted in one other harmine experiment, but was not seen with iproniazid. Cardiovascular effects of the inhibitors were similar to those observed in the dog except that hypotensive effects of iproniazid were transient.

Discussion. Inhibition of transmission through sympathetic ganglia produced by intravenous administration of harmine and iproniazid in these experiments have confirmed the results obtained by Gertner(1) with the isolated superior cervical ganglion of the cat. The present results have additionally demonstrated that these agents exert a selective inhibitory action on the sympathetic synapse without depressing parasympathetic ganglia. More typical ganglionic blocking agents, such as hexamethonium, also inhibit parasympathetic ganglia, presumably by interfering with the action of acetylcholine (6). It is possible, therefore, that the depression of sympathetic transmission occurring with iproniazid and harmine results from a different mechanism of action. As iproniazid and harmine are otherwise similar only in ability to inhibit MAO, it is tempting to relate effects at the sympathetic ganglion to accumulation of amines metabolized by MAO. Administration of epinephrine and norepine-

phrine, for example, results in depression of ganglionic transmission(7).

One may only speculate that the selective sympathetic inhibition produced by large intravenous doses of iproniazid and harmine in the dog and cat is the mechanism responsible for postural hypotension in man after administration of MAO inhibitors. It is interesting, however, that the predominant autonomic effect of these agents in man appears to be sympathetic depression without parasympathetic block(8).

Summary. Large doses of iproniazid and harmine administered intravenously to the anesthetised cat and dog inhibit transmission through sympathetic ganglia without depressing the function of parasympathetic ganglia.

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Selenium and Torula Yeast in Production of Exudative Diathesis in Chicks.* (26062)

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Factor 3 and selenium have been shown to prevent exudative diathesis in chicks fed a Vit. E free Torula yeast diet(1,2). This, however, does not indicate that selenium is essential in nutrition of chicks when adequate Vit. E is present in the diet. Schwarz *et al.* (3) have suggested that Vit. E and selenium might participate in alternate pathways in metabolism in spite of marked structural differences. Participation of selenium in certain metabolic reactions has been reported by various workers(4,5,6). This element has also been reported to promote growth in chicks and rats(1,4,5). Dried brewers yeast, which is free of Vit. E but is a potent source of Factor 3(7), will replace Vit. E in preventing exudative diathesis in chicks (8). A growth response attributed to Vit. E was observed in chicks fed a high fat diet(9) but recent work shows that Vit. E was not needed by chicks fed a diet low in fat(10,11). Bieri *et al.*(12) reported that addition of Torula yeast to an otherwise purified chick diet resulted in production of exudative diathesis in 16-18 days, and provided evidence for existence of factors of a fatty and mineral nature in Torula yeast which stimulated production of exudative diathesis in chicks fed a Vit. E free diet. The experiments reported here were designed to study the effects of selenium, Vit. E and dried brewers yeast on growth of chicks fed a purified diet containing soybean protein, in an attempt to provide additional information on the role of such ingredients in nutrition of chicks. Investigations were also made of the relation between Torula yeast and production of exudative diathesis in the chick.

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