values for the original plasma pools were $10^{-1.6}$ (1:44) against Type 1 virus, $10^{-1.3}$ (1:22) against Type 2 virus, and $10^{-1.1}$ (1:13) against Type 3 virus.

Summary. Neutralizing antibody content of 7 lots of human serum gamma globulin against the 3 immunologic types of poliomyelitis viruses were studied in roller tube cultures of monkey kidney tissue. Antibody against the 3 immunologic types of viruses was found to be present in all lots tested. The average of 50% neutralization end points in tests of the individual lots of gamma globulin for type 1 virus was $10^{-3.0}$, for Type 2 virus $10^{-2.7}$, and for Type 3 virus $10^{-2.5}$.

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Potentiating Effect of Iproniazid on the Pharmacological Action of Sympathomimetic Amines.* (20757)

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The antitubercular compound iproniazid (1-isonicotinyl-2-isopropyl hydrazine) was shown by Zeller *et al.*(1,2) to produce a marked *in vitro* and *in vivo* inhibition of mammalian monamine oxidase (MO) while isoniazid (isonicotinic acid hydrazide) was almost without effect. In accordance with these results Schayer demonstrated that iproniazid, but not isoniazid, reduces the deamination of C^{14} labeled epinephrine injected into rats(3). Since MO oxidizes and inactivates several other sympathomimetic amines such as phenylethylamine and tyramine(4,5,6) and thus may limit their pharmacological activity, the question arose as to whether or not the blocking of mammalian MO by iproniazid would change the response to these monamines. In this study the reaction of the nictitating membrane of the cat to the administration of various amines before and after the application of iproniazid is described.

Methods. Cats were anesthetized with pentobarbital and prepared for recording contractions of the right nictitating membrane and the carotid blood pressure. The injections of the drugs, except iproniazid and isonazid, were made into a saline infusion cannula and then flushed into the femoral vein with 2.5 to 3 ml of normal saline. Injections made in this way were prepared in 1 ml volume. Since iproniazid was found to cause equal enzyme inhibition whether given intravenously or intraperitoneally, 0.18 millimoles/kg were administered intraperitoneally. Isoniazid was administered in the same amount and manner. Phenylethylamine, tyramine and epinephrine were given in equal pressor doses to determine the contraction of the normal nictitating membrane; following this iproniazid was administered, and a period of 1 to 2 hours allowed to elapse to permit the enzyme to become inhibited. The three drugs were again administered in the same dosages as before. MO activity was determined for liver and brain homogenates ac-

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TABLE I. Cat Nictitating Membrane Responses to Intravenous Injections of Equal Pressor Doses of 3 Amines before and after Administration of 0.18 Millimoles/kg Iproniazid.

Injected amine	No. animals	Contraction index* Before iproniazid	Contraction index* 2 hr after iproniazid	T values
Phenylethylamine	6	.0 ± 0†	52.87 ± 19.18	2.75
Tyramine	5	.78 ± 1.09	76.46 ± 20.80	2.57
Epinephrine	8	3.71 ± .79	3.18 ± .62	.70

Control responses

Injected amine	No. animals	Contraction index Initial	Contraction index 2 hr after control, saline inj.	T values
Phenylethylamine	5	.32 ± .64	.09 ± .19	.14
Tyramine	3	3.59 ± 2.75	4.78 ± 2.23	.95
Epinephrine	7	3.30 ± .89	4.08 ± .93	.49

* Contraction index is avg value representing magnitude and duration of contraction of the nictitating membrane obtained by determining the area in square centimeters under the curve on the kymograph tracing by means of a planimeter.

† Stand. errors of the means are included.

The T values greater than 2 indicate the second response is statistically significantly greater than the first.

cording to the method described previously(1).

Results. The magnitude and duration of contraction of the nictitating membrane in response to the amines was found by circumscribing the perimeter of the curve with a planimeter and calculating the area under the curve in square centimeters. The mean area of response to similar doses of a given amine before iproniazid was found for a number of animals, and the mean for all animals tested was then determined. The responses 2 hours after iproniazid administration were determined in the same manner. The resulting values are indicated in Table I. These values may be compared with those determined on animals which were handled similarly except that iproniazid was not administered.

Two hours after the administration of iproniazid the response of the nictitating membrane to phenylethylamine rose from zero to a very marked contraction. Tyramine produces a measurable contraction of the nictitating membrane in normal animals in some cases, but this is greatly potentiated two hours after iproniazid administration. Fig. 1 shows a typical response of the nictitating membrane and blood pressure to tyramine before and after iproniazid. Epinephrine responses were essentially unchanged. Liver and brain homogenates were prepared for MO activity determinations from a number of the animals used in these experiments (Table II). Ammonia production and oxygen uptake drop sharply for both liver and brain, indicating a significant decrease in MO activity due to the administration of 0.18 millimoles/kg iproniazid.

Isoniazid used at the same molar concentration as iproniazid did not show a potentiating effect on the action of phenylethylamine or tyramine on the nictitating membrane.

Discussion. Iproniazid strongly potentiates the contraction of the nictitating membrane produced by phenylethylamine and tyramine. These results corroborate the experiments carried out with *in vivo* and *in vitro* studies on monoamine oxidase (MO), but they do not necessarily prove that the blocking of MO is the only or main reason for this observation. However, since MO is the only enzyme known which is inhibited much more by iproniazid than by isoniazid [isoniazid is more effective as an inhibitor of diamine oxidase(1) and spermine oxidase(7)] and since no potentiation takes place after the application of the latter drug, it is highly probable that MO is involved. The activity of MO appears to be a factor regulating the pharmacological action of phenylethylamine and tyramine.

No significant potentiation of the action of epinephrine on the nictitating membrane was noted. Again this does not necessarily mean that MO does not play some role in the metabolism of epinephrine as Schayer's work indicates. It is possible that epinephrine can

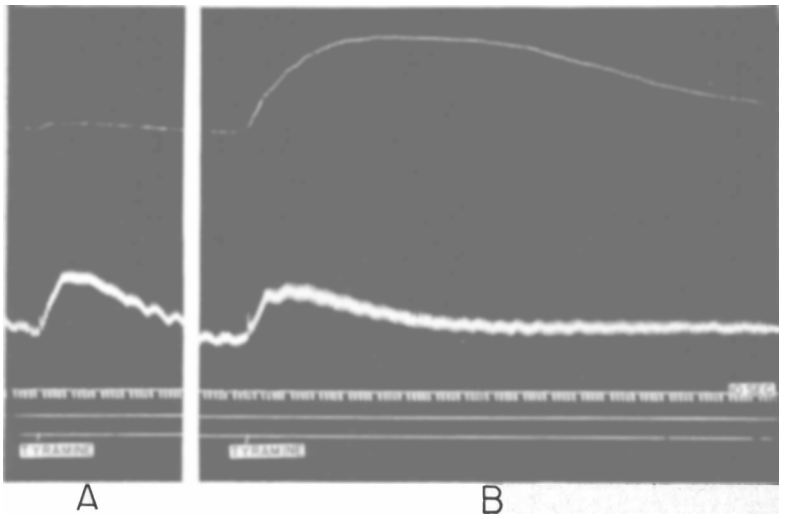

FIG. 1. Cat, 2.8 kg. Pentobarbital anesthesia. From top to bottom: Nictitating membrane; carotid blood pressure; time in 10 sec. intervals; zero blood pressure; signal. A. 5.7×10^{-3} millimoles (1 mg) tyramine hydrochloride intrav. B. Repeat dose of tyramine hydrochloride 2 hr after 0.18 millimoles/kg iproniazid.

utilize degradation pathways which are not available to the other two amines tested. Besides attack by MO epinephrine may undergo degradation by various other enzymes, attacking the catechol configuration and the alcoholic hydroxyl group. Iproniazid by inactivating MO blocks a greater part of the metabolic degradation of phenylethylamine than of epinephrine. The MO activity therefore, would be less of a limiting factor for the action of epinephrine than for phenylethylamine. Studies are being conducted on other related amines to determine whether or not their activity is influenced by MO inhibition. Experiments have indicated that tryptamine is potentiated while ephedrine and norepinephrine are not.

Blood pressure responses to phenylethylamine and tyramine were not potentiated by iproniazid. The exact explanation of this is not clear, but since a pronounced tachyphylaxis occurs with respect to the vasopressor responses, but not to the nictitating membrane responses, it is possible that the tachyphylaxis may obscure the potentiating effect of iproniazid.

TABLE II. Monoamine Oxidase Activity in Liver and Brain of the Cat after Administration of Iproniazid (0.18 Millimoles/kg).

	Normal values*	Iproniazid-treated animals
Liver	135.1 ± 2.88 (6)†	1.7 ± .5 (12)
Brain	17.8 ± 2.17 (5)	1.5 ± .4 (13)

* Expressed in terms of millimoles NH_3 produced per g of tissue in 2 hr incubation, employing 1 to 10 homogenates in M/15 phosphate buffer at pH 7.1, 1 ml/vessel with a final vol of 2 ml and a final concentration of tyramine • HCl of M/100. Stand. errors of the means included.

† No. of animals indicated in parentheses.

Summary. Iproniazid, in a dose of 0.18 millimoles/kg potentiates the action of phenylethylamine and tyramine upon the nictitating membrane of cats. The action of epinephrine is not changed significantly. Isoniazid does not have this effect when given in equivalent doses.

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