nitely not due to acidity alone. Virulent type 1 poliovirus can be attenuated by heating in 10 mM $AlCl_3$ at pH 4.‡ Virus survivors of $AlCl_3$-heat treatment were propagated further, and the virus harvests were heated again in $AlCl_3$ at 50°C. After numerous passages, with intervening heating in $AlCl_3$ and passage of survivors, we obtained virus that was completely stabilized to heat in 10 mM $AlCl_3$, and that was no longer paralytogenic for monkeys by intracerebral inoculation even with 10^8 PFU/dose. By similar procedures using 2 mM HCl at pH 4, an HCl-heat resistant line was developed after the same number of passages. However, this virus line retained the neurovirulence of the parent, as it paralyzed monkeys after intracerebral inoculation.

Summary. Type 1 attenuated poliovirus (LSc) was stabilized at 50°C at pH 4.0 to 5.0 in acetic, oxalic and lactic acids. The type 1 virulent strain (Mahoney) was inactivated to a greater degree in all concentrations of these acids at 50°C than in distilled water. Citric, tartaric, benzoic and salicylic acids at pH 4.0 stabilized the attenuated strain to a high degree but the virulent strain only slightly. Inorganic acids (HCl, HNO_3, H_3PO_4 and H_2SO_4) stabilized the attenuated strain from pH 3.0 to 5.5, but had no effect on the virulent strain. Thus another *in vitro* character, the acid marker, is available for distinguishing between attenuated and virulent polioviruses.

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Pharmacological Action of Tyramine on the Cardiovascular System in Man.* (27776)

M. L. MASHFORD,† J. BION PHILIPSON, D. A. WOLOCHOW AND W. A. MAHON‡
(Introduced by T. C. Chalmers)
Clinical Pharmacology Division of Medical Services, Lemuel Shattuck Hospital, Massachusetts Dept. of Public Health, and Dept. of Medicine, Tufts University School of Medicine, Boston

Tyramine bears a close structural relationship to norepinephrine and since 1909 has been known to have a pressor effect. Its action has been shown in animals to depend entirely upon the release of norepinephrine from tissue stores(1) since, when these are absent following denervation or reserpine administration, tyramine is without effect. Studies in man have confirmed its sympathomimetic action(2,3). In view of its mode of action, tyramine has been used to gauge the state of tissue norepinephrine stores in the cardiovascular system of human subjects(4). This study describes some cardiovascular effects of tyramine in man, the reproducibility of the pressor response, and a dose-response curve.

Materials and methods. Thirty-nine subjects were studied. Except for one healthy volunteer, all had been hospital in-patients for a considerable time and were free of obvious cardiovascular disease. They were not receiving hypotensive agents, sympathomimetic amines or monoamine oxidase inhibitors.

Eleven patients were the subjects of the first study. Observations were made while

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† Present address: Department of Medicine, University of Western Australia, Perth, Australia.

‡ Present address: Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada.

TABLE I. Hemodynamic Effects of Tyramine 0.2 mg/kg in Eleven Subjects.

	MAP, mm Hg		CO, l/min		TPR	
	Initial	Peak rise	Initial	1½′ change after tyramine	Initial	1½′ change after tyramine
Mean	90.9	43.7	4.41	−.05	1673.7	+876
S.D.	12.8	23.0	.80	1.06	260.5	374

they were lying supine on a couch in the cardiac laboratory. Blood pressure was registered continuously through a brachial artery catheter, either as an instantaneous record or as the electrically derived mean pressure. Cardiac outputs were estimated by indicator dye dilution using indocyanine-green and a Colson 110-IR cuvette densitometer. After a control period during which at least 2 dye curves were obtained, tyramine 0.2 mg/kg was given as a single i.v. injection. The blood pressure record was continued for at least 20 minutes and dye curves obtained at 1½, 5 and 10 minutes after the injection. Total peripheral resistance (TPR) was calculated in the usual way and pulse rate was obtained from the brachial artery tracing or from an electrocardiogram.

The reproducibility of the pressor response to tyramine was examined in 18 subjects who received 2 i.v. injections of tyramine 0.2 mg/kg within an interval of 1-4 hr (Day I). Eight of these subjects received 3 further i.v. injections of tyramine on the succeeding 2 days; 0.2 mg/kg and then 0.4 mg/kg (Day II) and 0.4 mg/kg (Day III). Response was determined by auscultatory estimation of systolic and diastolic B.P. with a mercury sphygmomanometer, at 30-second intervals. Response was expressed in 3 ways; as peak rise in systolic arterial pressure, peak rise in mean arterial pressure (calculated from MAP = diastolic + ⅓ pulse pressure) and as the area enclosed between the curve of mean arterial pressure and the baseline level.

The remaining 10 subjects were each studied on a single day to obtain dose-response data; 4 doses of tyramine were given by i.v. injection. The highest dose, 0.4 mg/kg, was always given last but the other 3 doses, 0.05 mg/kg, 0.1 mg/kg and 0.2 mg/kg, were given in random order. The blood pressure was allowed to return to a stable baseline between each injection. Blood pressure observations were again made with a sphygmomanometer as described above and dose-response curves constructed using respectively the peak systolic rise, peak mean rise and area as the response statistics. Electrocardiograms were obtained in some of the subjects receiving the larger doses.

Results. Injection of tyramine caused elevation of both systolic and diastolic blood pressure in all subjects. The rise in B.P. began one-half to one minute after administration, reached a peak in one to 3 minutes and began to fall without any significant plateau. The pre-injection level was attained after 4 to 12 minutes and in 7 of the 9 subjects who were followed sufficiently long, a further fall below the baseline was observed; this lasted for as long as 20 minutes and was 5 to 10 mm Hg in magnitude.

The mean initial values for MAP, CO and TPR and the changes following tyramine injection, for the 11 subjects studied in the laboratory are given in Table I. The pulse rate rose by 16-27 beats/min in 4 of these subjects and fell by 12-27 beats/ min in 6. Increase in pulse rate reached a peak in 1-2 minutes, but in those whose pulse rate fell the maximum change occurred at 3 minutes; CO changes were very variable in size and direction.

The mean pressor response to 0.2 mg/kg and 0.4 mg/kg tyramine for the subjects whose blood pressure response alone was followed is shown in Table II. Data illustrating

TABLE II. Pressor Effect of Intravenous Tyramine.

	Systolic peak rise, mm Hg	Mean peak rise, mm Hg	Area, sq mm
.2 mg/kg (28)	64.3	34.3	1,168.7
S.D.	17.4	10.3	678.2
.4 mg/kg (17)	90.2	53.2	2,264
S.D.	19.2	13.4	1,301

Numbers in parentheses denote No. of subjects.

TABLE III. Mean* Difference in Tyramine Response.

	Systolic peak rise, mm Hg	Mean peak rise, mm Hg	Area, sq mm
.2 mg/kg, day I *vs* day I	−5.0 (3.2)	−1.8 (2.5)	+ 28.9 (81.4)
.2 " , day II *vs* day I	+ .4 (7.4)	+1.6 (5.3)	+380.3 (367.7)
.4 " , day III *vs* day II	+1.4 (4.7)	+3.0 (4.6)	−339.6 (317.2)

* Mean difference with S.E. in parentheses.

the reproducibility in the same patient of the tyramine response measured as the peak rise in systolic and mean arterial pressures and as the area of the MAP curve are given in Table III. The first line gives the mean difference (with S.E.) when 2 doses of 0.2 mg/kg were given on the same day within an hour or 2 of each other. The second line refers to 2 doses of 0.2 mg/kg on succeeding days and the last line refers to 2 doses of 0.4 mg/kg on succeeding days. None of the differences were significant by a paired, t-test but the variability between days was greater for all methods of measurement than that for the same day. Part of the duplicate variability can be attributed to variation in baseline; an elevation of the baseline pressure being associated with a diminished response (Table IV). This is most marked when the peak rise in mean pressure is considered.

The dose response curve is plotted in Fig. 1 using mean values from 10 subjects and showing one S.E. around the means. The response to both 0.2 and 0.4 mg/kg fell on the steep part of the curve and there was no evidence of a plateau.

In virtually every case electrocardiographic monitoring has revealed frequent periods of abnormal atrial rhythms (notably coronary sinus rhythm(5)) and occasional short runs of idioventricular rhythm, individual ectopic beats or atrioventricular dissociation. These have in common a more or less abrupt, repetitive, shift of the dominant pacemaker.

TABLE IV. Correlation Coefficients (r) △ Baseline *vs* △ Response.

	Mean peak rise	Area
.2 mg/kg (8 subjects)	−.735 P <.025	−.692 P <.05
.4 mg/kg (7 ")	−.891 P <.005	−.690 P <.05

Data from .2 mg/kg on succeeding days and .4 mg/kg on succeeding days.

Discussion. It is now widely recognized that patients treated with reserpine are liable to collapse during anaesthesia. This has been attributed to the depletion of tissue norepinephrine which is characteristic of the action of reserpine in animals. Crandell(6) has stated that injection of ephedrine prior to operation would detect impaired ability of the patient to react to the stress, since ephedrine exerts its effect in part by release of tissue catecholamine. However ephedrine also has some direct effect(7) and has a rather prolonged action. Tyramine has neither of these disadvantages and would seem to be an ideal tool to test the function of the peripheral part of the sympathetic mechanism. Administration of tyramine in doses up to 0.4 mg/kg has proved to be a safe procedure although one patient not included in this study developed a supraventricular tachycardia beginning 5 minutes after injection when the blood pressure was falling, and another had runs of ventricular ectopic beats. In view of this,

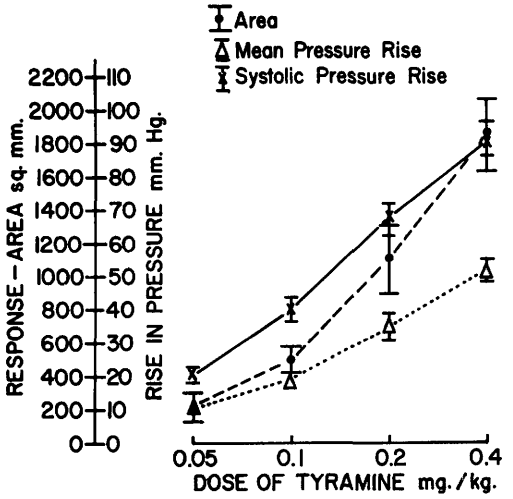

FIG. 1. Dose response curve for pressor effect of I.V. injection of tyramine in man.

it is probably desirable to take an electrocardiogram if giving high doses. A few patients reported throbbing headache at the height of the blood pressure rise. The cardiovascular effects of tyramine are similar to those reported for norepinephrine(8), which also causes increase in blood pressure and TPR, but inconsistent changes in CO and pulse rate. The ECG changes following tyramine are also similar to those reported with norepinephrine by Miller *et al.*(9).

The use of the blood pressure response to a small dose of tyramine as a test of the adequacy of tissue catecholamine stores is complicated by the considerable variability between patients. The response would have to be quite small to differ significantly from the normal group. Since at a dose of 0.4 mg/kg the response is more marked and still on the linear part of the dose-response curve but with a similar variation, the response at this dosage would probably provide a more sensitive indication of reactivity than that at the smaller dose. Determining a dose-response curve should be more informative than administration of any single dose. The peak rise in systolic and mean pressures are equally satisfactory statistics, and both are superior to the area of the mean pressure curve.

The variation from time to time in the same patient is much smaller than that between patients. Thus repeated testing of a patient should be more satisfactory in detecting change in reactivity than a single test would be in classifying a patient as normal or deficient. Tyramine has been used in this way in man to display the effect of reserpine on the tissue norepinephrine stores(4).

Summary. 1. Intravenous injection of tyramine in man causes elevation of blood pressure and TPR, but inconsistent effects on CO and pulse rate. Changes in the site of impulse formation and conduction were seen in the ECG. 2. The reproducibility of the tyramine response was studied in 18 subjects to assess its value as a test of tissue catecholamine stores. 3. The dose-response relationship of the pressor effect of tyramine was determined.

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Effect of Adrenalectomy on Mitotic Proliferation of Gastric Epithelium.* (27777)

RAY H. CLARK† AND BURTON L. BAKER
Department of Anatomy, University of Michigan Medical School, Ann Arbor

Mitotic activity in the gastric epithelium of rats occurs almost exclusively in 2 cell types, the non-differentiated forms of surface mucous cells and the mucous neck cells. We have found that mitotic activity in both cell types follows a circadian periodicity. The peak of activity occurs at about 10 a.m. and the low point between 8 p.m. and 12 midnight (to be published). The objectives of this investigation were to determine (a) the effect of adrenalectomy on mitotic activity, (b) the relationship of possible changes to circadian periodicity, and (c) how the influence of adrenalectomy is modified by standardization

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