function were studied by means of a constant infusion technic in 10 subjects with congestive heart failure. 2. In contrast to normal subjects, urine flow, sodium excretion and filtration rate increased during sleep in 6 patients with persistent peripheral edema. Four subjects with congestive heart failure who were edema-free or undergoing diuresis showed a diurnal pattern with respect to urine flow and filtration rate similar to that seen in normal subjects. 3. The endogenous 'creatinine' chromogen clearance is substantially lower than the inulin clearance in patients with congestive heart failure and edema.

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## Effect of Certain Amines on the Blood Pressure of Normotensive and Hypertensive Rats.* (17979)

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Differences in the usual degree of response of the blood pressure to various pressor substances in experimental hypertension have been described(1,2). Tyramine, epinephrine, pitressin, and renin appear to be more vasoactive in hypertensive dogs and rabbits than in normotensive animals. In the present investigation the pressor responses of isoamylamine, phenethylamine, tyramine, arterenol, and epinephrine have been studied in normal rats and rats with experimental renal hypertension. It was found that the degree of pressor response in the two groups varied with the amine tested. In hypertensive rats isoamylamine showed less, phenethylamine and tyramine the same, and arterenol and epinephrine more effect on blood pressure than in normotensive rats.

*Method.* Albino rats, of approximately 200 g, were anesthetized by intraperitoneal injection of sodium pentobarbital (4.5 mg per 100 g body weight). By a flank incision the left kidney was isolated and the renal artery freed from the vein. A copper wire, 0.48 mm in diameter, was placed along the artery and a nylon ligature tied tightly around both the artery and the wire. When the wire was removed the artery was left partially constricted. About 70% of the operated animals developed an elevation of systolic blood pressure as measured by a photoelectric plethysmograph, the hind leg being occluded by a pneumatic cuff. After a period of at least 3 weeks to allow for recovery from operative trauma, the hypertensive rats were used for pressor assay. The rat, either hypertensive or normotensive, was again anesthetized and a tracheotomy performed to maintain a patent airway. The right femoral artery was exposed and a saturated solution of novocaine applied to it to prevent constriction. A curved 23 gauge needle connected to a Hamilton optical manometer was inserted into the artery through a small incision. The left femoral vein was isolated and cannulated for the intravenous administration of the substance to be studied. After stabilization, this preparation exhibited levels of blood pressure which were constant within the limits of $\pm$ 5 mm Hg for over 2 hours. The minimal quantity of each amine necessary to produce a pressor response in the normotensive rat was determined.

*Results.* The following amounts of free base, in gammas per 100 g body weight of rat, produced a "minimal" reproducible pres-

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1. Verney, E. B., and Vogt, M., *Quart. J. Exp. Physiol.*, 1938, v28, 253.

2. Page, I. H., and Helmer, O. M., *J. Exp. Med.*, 1940, v71, 495.

TABLE I.
Elevation of Blood Pressure of Normotensive and Hypertensive Rats After Graded Doses of Pressor Amines.

| Amine | Dose, γ/100 g | Normotensive Rise of B.P.* (mm Hg) No. | High | Avg | Low | Hypertensive Rise of B.P.* (mm Hg) No. | High | Avg | Low |
|---|---|---|---|---|---|---|---|---|---|
| Isoamylamine | 80 | 8 | 25/25 | 20/18 | 15/11 | 6 | 10/ 9 | 6/6 | 0/0 |
| | 160 | 8 | 35/33 | 30/27 | 18/17 | 7 | 14/14 | 11/ 9 | 9/8 |
| | 320 | 8 | 52/51 | 44/37 | 40/35 | 17 | 35/28 | 22/16 | 7/7 |
| Phenethylamine | 6.6 | 7 | 22/14 | 17/10 | 12/ 8 | 14 | 36/24 | 19/14 | 12/ 4 |
| | 13.2 | 6 | 23/22 | 21/15 | 19/11 | 9 | 32/27 | 26/21 | 20/15 |
| | 26.4 | 5 | 43/30 | 36/27 | 22/21 | 11 | 53/37 | 34/22 | 17/10 |
| Tyramine | 4.8 | 9 | 16/19 | 14/12 | 11/ 5 | 13 | 23/19 | 14/11 | 4/3 |
| | 9.6 | 8 | 34/20 | 27/18 | 19/14 | 11 | 39/29 | 28/22 | 20/13 |
| | 19.2 | 8 | 63/37 | 45/34 | 29/17 | 11 | 52/37 | 45/36 | 36/38 |
| DL-arterenol | .06 | 10 | 17/12 | 12/ 9 | 7/8 | 12 | 37/34 | 35/27 | 25/24 |
| | .12 | 12 | 35/25 | 26/19 | 18/11 | 5 | 102/57 | 77/46 | 47/35 |
| | .24 | 8 | 60/46 | 52/41 | 44/32 | 6 | 121/46 | 85/47 | 48/30 |
| L-epinephrine | .06 | 7 | 24/14 | 17/11 | 9/8 | 8 | 42/32 | 29/23 | 19/ 9 |
| | .12 | 8 | 31/23 | 23/19 | 15/13 | 6 | 70/49 | 57/27 | 36/16 |
| | .24 | 8 | 52/35 | 39/26 | 21/ 8 | 6 | 135/54 | 75/35 | 35/17 |

* "High" indicates the second largest rise; "Avg" the arithmetical mean; "Low" the smallest rise but one. The first figure is the systolic, the second the diastolic rise. All injections are included in these calculations.

sor response: isoamylamine—80.0, phenethylamine—6.6, tyramine—4.8, DL-arterenol—0.06, and L-epinephrine—0.06. A series of responses was obtained for "minimal," twice "minimal" and 4 times "minimal" dose in both the normotensive and hypertensive animals (Table I). The results given are the average values obtained using at least 5 normal and hypertensive rats for each amine. One-half to three-fourths of the "minimal" dose usually elicited inconstant responses.

The minimal reproducible pressor response to each compound studied in the normal rat was approximately the same; the quantity of the base required to produce this response was, however, quite different. With increasing dosage the pressor response seemed to follow a linear progression. When the normotensive series was compared to the hypertensive series a striking difference was noted. In the case of arterenol rats with an elevated blood pressure were more than twice as vasosensitive as normal rats; similar alterations in response to epinephrine were seen principally in systolic pressure. Conversely, hypertensive rats were found to be less than half as sensitive to isoamylamine as the animals with normal blood pressure. However, in the case of phenethylamine and tyramine, the pressor response in the hypertensive group was approximately the same as in the normotensive series.

The duration of the rise of blood pressure was relatively short in normal rats, the effect usually being over in approximately 2 minutes, with certain notable exceptions. Diastolic pressure remained elevated 10 mm Hg or more for 5 minutes after 23% of the injections of phenethylamine, 19% of the injections of tyramine, 12% of the injections of arterenol, 8% of the injections of epinephrine and 7% of the injections of isoamylamine. In hypertensive rats prolongation of the response occurred after approximately the same number of injections of tyramine and epinephrine, while in the case of arterenol and isoamylamine about half as many injections caused prolonged diastolic elevation. Only 8% of injections of phenethylamine produced this effect. None of these substances induced tachyphylaxis.

*Discussion.* Numerous comprehensive stud-

ies have been made in an attempt to discover a relation between pressor response and chemical structure, carried out on many isolated organ preparations and animals(3). However, no thorough reports contrasting the response of normotensive and hypertensive animals has appeared. Such a correlation would seem to be of value in a search for the possible site of metabolic dysfunction in hypertension. In the present investigation the effect of representative compounds has been utilized: isoamylamine—a branched chain aliphatic amine, phenethylamine—an aromatic amine, tyramine—a phenolic aromatic amine, arterenol—a catechol derivative with an aliphatic hydroxyl group. In the case of isoamylamine, normotensive rats gave the usual pressor response. However in hypertensive rats a notched curve was obtained—an initial increase, a temporary fall, and a secondary increase in blood pressure. This difference has also been noted in comparison of normotensive and hypertensive patients, the latter in some cases showing only a decrease in blood pressure when isoamylamine was injected intravenously. Due to inherent errors in the bioassay method and the progressive nature of hypertension fine differences in structure may not be appreciated but the more important ones can be detected by procedures such as those here reported.

Explanation of these results is difficult in the light of present knowledge. Increased sensitivity of hypertensive animals to pressor agents is explicable upon application of known laws relating peripheral resistance to arteriolar diameter; when arterioles are already constricted, further constriction by a drug causes much greater changes in resistance than when they are dilated. The results found with arterenol are therefore in agreement with this hypothesis. The paradoxical effect of isoamylamine is not. One possible explanation involves the substitution of a substance with slight pressor activity for one with marked activity. If renal hypertension in the rat is accompanied by circulating pressor substances of considerable vasoactivity, "flooding" the circulation with a competitive substance of less activity would give rise to a lessened response. Isoamylamine may act in this manner, although a cardiac effect may be important.

*Summary.* The pressor response of various amines in anesthetized normotensive and hypertensive rats have been studied. The two groups of animals responded differently to different amines. Whereas phenethylamine and tyramine elicited the same degree of elevation of blood pressure in normotensive and hypertensive rats, arterenol and epinephrine caused greater responses and isoamylamine effected much smaller responses in the hypertensive animals.

3. Hartung, W. H., *Chem. Rev.*, 1931, v9, 389.

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## The Use of Radon Seeds to Produce Deep Cerebral Lesions.* (17980)

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Experimental neurophysiology has long made use of the classical method of ablation of various nervous structures and observation of subsequent alteration in function to evaluate the physiological significance of these structures. No problems are encountered when the structures lie on the surface of the brain or spinal cord. When they are deep in the brain substance, however, difficulties are presented in localization and mode of destruction. Although several different technics are available for accomplishing these things in the depths without disturbing superficial structures beyond the small lesion necessary to introduce an instrument, they all have attendant features which are not entirely satisfactory. Among the technics used in the past are injection of chemical substances(1),

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