independently the orientation of the positive and negative shapes. The fact that, when only one stimulus was presented at a time, the animals still discriminated as accurately between the oblique rectangles as between the horizontal and vertical rectangles was in marked contrast to my own powers of discrimination in relation to these shapes. In setting up the single oblique rectangles in the correct sequence, I had to proceed slowly and to double check every setting for fear of making an error. No such difficulty was experienced with the horizontal and vertical rectangles.

The finding that cats discriminate between two oblique rectangles as readily as between horizontal and vertical rectangles confirms the hypothesis that the relative ease with which animals discriminate rectangles in different orientations may depend at least partially on the number of neurons with receptive fields in particular orientations. The result is particularly striking when it is borne in mind that octopuses (*4*) and children under four (*6*) seem unable to solve the oblique discrimination at least with the training techniques so far used, while goldfish need about three times as many trials to learn to discriminate between two opposite oblique rectangles as they require to master the vertical-horizontal discrimination (*7*). From an evolutionary standpoint it is difficult to say why the cat should differ from the other three species in this way. Accurate recognition of oblique orientations may be of special importance to an animal jumping from branch to branch (*8*).

N. S. SUTHERLAND
Institute of Experimental Psychology, Oxford University, Oxford, England

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Neurogenic Component of Chronic Renal Hypertension

Abstract. *Infusion of angiotensin or renin in small quantities affects the sympathetic nervous system so that responses are increased to either drugs or reflexes that cause release of norepinephrine at nerve endings. Response to injected norepinephrine is relatively unchanged. This action of angiotensin is dependent upon an intact sympathetic nervous system. The direct vasoconstrictor action of angiotensin is not an essential part of the enhanced response. The phenomenon was shown to have relevance to acute and chronic experimental renal hypertension in dogs by the fact that in both the pressor response to tyramine was enhanced. We believe that the ability of angiotensin to intensify the effect of normal neurogenic vasomotor activity, along with an upward reset of the carotid sinus buffer mechanism, might account importantly for the neurogenic component of renal hypertension.*

Much evidence suggests that chronic hypertension, elicited by application of a clamp to a renal artery or by enclosing the renal parenchyma in a Cellophane-induced hull, is associated with the liberation of renin and the formation of angiotensin. There has been no reason to believe that the autonomic nervous system had concurrently ceased to participate in the maintenance of cardiovascular tone; but whether to a greater or lesser degree than in a normotensive animal was not known.

Participation of the autonomic nervous system might be increased if there was increased sensitivity to the neurohumoral mediator at the myoneural junction, but published observations on the pressor response of chronic renal hypertensives to several vasoactive drugs are contradictory. The most that can be said is that the responses are either normal or slightly increased. This applies in particular to the two key substances, angiotensin and norepinephrine. In the case of norepinephrine, response to injected, or exogenous, material has been studied. A possible change in response to endogenous norepinephrine liberated at the myoneural junction after stimulation has not been explored. The widely accepted view that some drugs, such as tyramine, act indirectly on blood vessels by causing liberation of norepinephrine, suggests the possibility to study the endogenously produced neuroeffector and to associate it with the known vasoactive humoral agent of renal origin, angiotensin.

We observed that when tyramine was injected during the hypertension elicited by crude renin in dogs anesthetized with pentobarbital the pressor response was considerably elevated above the control levels. The same response occurred when synthetic valyl^5-angiotensin was infused. It was then shown that ephedrine behaves similarly and that the ganglion stimulating agent, DMPP (1, 1′-dimethyl-4-phenyl piperazinium iodide), caused a greatly enhanced pressor response when it was given during the infusion of angiotensin. It appeared that angiotensin caused an increase of the pressor response to any drug which depends for its action on the release of norepinephrine at the myoneural junction. At the same time the response to injected norepinephrine was unchanged or only slightly increased.

The enhancing effect was not related to the vasopressor action of angiotensin for it occurred even when tachyphylaxis to angiotensin had been produced. The sensitizing action of angiotensin must be at receptor sites different from those concerned with its own vasoconstrictor activity.

If this newly observed phenomenon was to be related to the mechanism of renal hypertension, it was necessary to show in animals made hypertensive, and in which it is presumed that the kidneys provide a slow infusion of angiotensin, that increased responsiveness to tyramine is demonstrable. A Goldblatt clamp was tightened on a renal artery after removal of the opposite kidney. The systemic arterial pressure rose moderately and responses to tyramine and DMPP were augmented within from 15 to 30 minutes while those to norepinephrine were unchanged (Fig. 1, top).

Responses to tyramine were also enhanced in dogs several days after application of a Goldblatt clamp and contralateral nephrectomy (Fig. 1, bottom). In experiments performed with Y. Kaneko's aid, values of measured responses to tyramine were on the average 2½ times those of the values on controls after placement of the clamps and when hypertension had developed. During control tests, infusion of angiotensin caused the usual increase in response to tyramine. When the animals had de-

veloped hypertension, however, infusion of the same amount of angiotensin did not cause a significant change in the already enhanced response, presumably because release of endogenous angiotensin had already exerted a maximum effect. Results of one of these experiments is shown in Fig. 2.

The mean response to tyramine of a group of dogs made hypertensive (by the cellophane-perinephritis method of Page) several weeks or months before was 44 mm-Hg, to be compared with 29 mm-Hg in a control group of normotensive dogs. The difference was highly significant ($P < .001$). Concurrently, there was no change in response to exogenous norepinephrine.

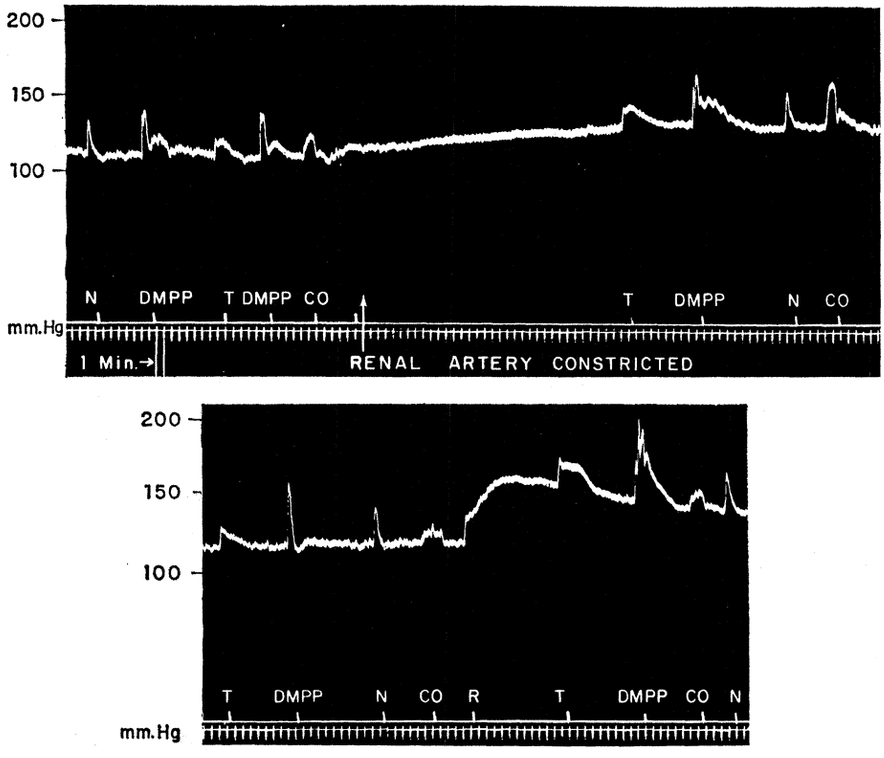

Fig. 1 (Top) Effect of cardiovascular responsiveness of renal artery constriction after contralateral nephrectomy. (Bottom) The effect on responsiveness to injection of renin (R) 40 minutes after removal of clamp on renal artery. N, 5 μg norepinephrine; DMPP, 50 μg; T, 100 μg tyramine; CO, occlusion of both common carotid arteries. Vagus nerves intact. Morphine-pentobarbital anesthesia. 10.5 kg dog.

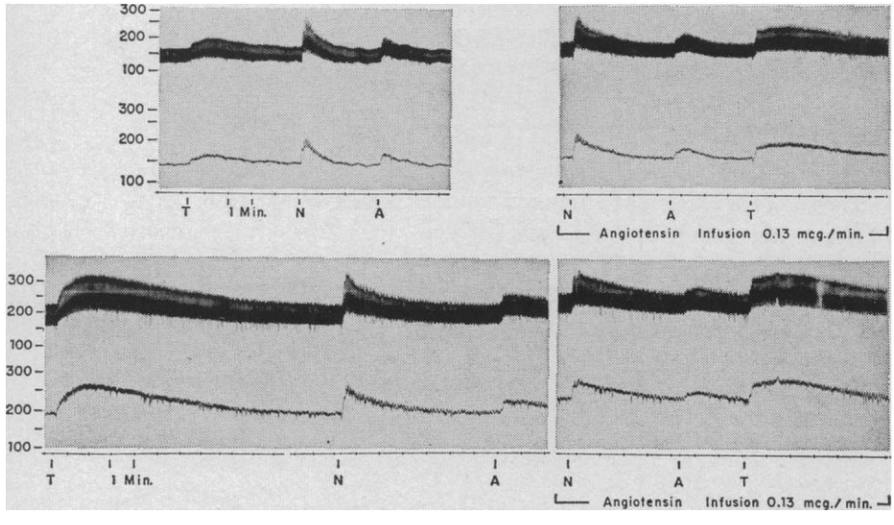

Fig. 2. Upper records show responsiveness of normal 11.2 kg dog anesthetized with pentobarbital both before and during infusion of angiotensin. Lower records show responsiveness of same dog when hypertensive 8 days after placement of renal artery clamp and contralateral nephrectomy. T, 0.5 mg tyramine; N, 2.5 μg norepinephrine; A, 0.4 μg angiotensin.

The next step was to show that in order to demonstrate the phenomenon the sympathetic nervous system must be intact. In dogs with the spinal cord cut at levels of C_6, after administration of ganglion blocking agents, and in pithed cats angiotensin failed to elicit the effect, nor did the effect appear immediately after injection of bretylium.

The splanchnic vascular bed is known to be uniformly constricted in hypertensive animals and for this reason we sought to demonstrate the phenomenon there. The superior mesenteric artery was perfused by the animal's own blood withdrawn from a carotid artery by a constant output pump. Changes in perfusion pressure reflected changes in resistance to flow. The responses to tyramine were increased by infusion of angiotensin and the reflex response to carotid occlusion was also reinforced in seven of eight experiments.

Since the response to carotid occlusion depends on release of norepinephrine, it was expected that angiotensin infusion would increase the rise in systemic pressure as it did the reflex rise in mesenteric artery perfusion pressure. In 15 experiments this was true, but in nine others the response was reduced. We have no explanation for this discrepancy other than that it may depend on the amount of angiotensin infused. To see if the carotid-occlusion reflex was affected by some central action of angiotensin, the electrical activity of the largely preganglionic splanchnic nerve was measured. During these particular experiments, angiotensin always caused an enhanced pressor response to carotid occlusion. The neurograms showed a less than expected increase in splanchnic impulse traffic during occlusion and rise in blood pressure while angiotensin was infused as compared with control responses. These experiments suggest that a fewer number of impulses were able to elicit the enhanced response to carotid occlusion.

JAMES W. MCCUBBIN
IRVINE H. PAGE
Research Division, Cleveland Clinic Foundation, Cleveland, Ohio

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