Vascular Reactivity in Experimental Hypertension Measured after Hexamethionium

By James Conway, M.D.

The characteristics of the response to pressor and depressor drugs in hypertensive animals suggest that structural changes in the arteriole play an important role in the development of hypertension.

One of the few observations made in hypertension upon which there is almost universal agreement is the increased response of the blood pressure to pressor drugs. It is found in nearly all types of hypertension, both experimental and clinical. Nevertheless, the mechanisms responsible for it have not been adequately investigated.

I have studied the vascular reactivity in rabbits, comparing the blood pressure responses to pressor and depressor drugs in the same animal in the normotensive and hypertensive states. The animals were studied in the conscious state and the blood pressure was recorded by a condenser manometer from the central artery of the ear. In order to overcome the homeostatic reflexes which would modify the blood pressure response, all experiments were performed after large doses of hexamethionium had been administered.

From this work and from the literature there are certain characteristics of the increased vascular reactivity which provide some evidence of its real nature: 1. In both normotensive and hypertensive animals the blood pressure responses are not related to the initial level of blood pressure. 2. The increased vascular reactivity in hypertension occurs in response to a large variety of vasoconstrictor agents, epinephrine, norepinephrine, posterior pituitary extract, tyramine and renin. These effects are not, in fact, confined to vasoconstrictor drugs but are also seen in response to vasodilator drugs, acetylcholine and nitroglycerin. The use of large doses of hexamethionium to inactivate the regulatory reflexes allowed the duration of the effect of drugs to be measured. The administration of norepinephrine or nitroglycerin by injection under these conditions leads to a greater response in the hypertensive animal, and yet the duration of the response is not prolonged. An unusual state therefore exists in which certain drugs provoke an augmented response while the duration of their effect is unchanged.

These facts suggest that the increased reactivity is a nonspecific effect, somehow related to the hypertensive process; yet its relationship with the rising blood pressure is not as straightforward as might be expected. In the rat increased reactivity has been reported to appear before the onset of hypertension and my experience with the rabbit shows that the blood pressure response to noradrenaline increases gradually over about a month after the hypertension has been fully established (fig. 1). This timing appears to coincide with the passage from the acute "renal" phase of hypertension to the chronic "non-renal" phase and to the time when increased sensitivity to renin is noted.

The effect of vascular spasm itself on reactivity has also been investigated by measuring the blood pressure response to infusions of norepinephrine at different initial levels of blood pressure. This was achieved by producing acute hypertension with infusions of posterior pituitary extract or injections of...
norepinephrine. The response to a standard dose of norepinephrine was then measured as the blood pressure passed from normal to hypertensive levels (figs. 2 and 3). Raising the initial level of pressure did not affect the magnitude of the response. (I should like to acknowledge here that the renin used in these experiments was kindly given me by Dr. H. Goldblatt.)

From this evidence it seemed that the increased reactivity in hypertension could not be the mere consequence of the elevation of blood pressure or narrowing of the arterioles by vascular spasm. Two possibilities therefore remain. The increased response could result from a greater strength of contraction in the vascular smooth muscle (a true increase in sensitivity), or it could be the result of structural changes in the arterial wall.

A true increase in the sensitivity of the vascular muscle seemed unlikely for 2 reasons. First, the change was completely nonspecific, being evoked by a large variety of pressor and depressor drugs. Secondly, the duration of the effect was not prolonged. It seemed, therefore, that the possibility of structural changes should be given serious attention. If there were thickening of the inner layers of the arterial wall at the expense of the lumen of the vessel (fig. 4), vas-
cular reactivity would be increased but not prolonged, and it would be nonspecific.

This hypothesis was investigated by studying the ability of the blood vessels to dilate. After hexamethonium had been given to inactivate the regulative reflexes, injections of nitroglycerin were given in progressively increasing doses until the lowest level of blood pressure it could produce had been ascertained. When nitroglycerin was given in this way on repeated occasions to animals in their normotensive and hypertensive state, it was found that the lowest level of blood pressure became progressively raised as hypertension developed (fig. 5). It seemed, therefore, that nitroglycerin could not completely reverse the hypertensive process; some residual resistance remained.

While experiments of this kind must be interpreted with caution, these results indicate that in hypertension the arteries were, in fact, unable to dilate fully. Evidence supporting this suggestion has already been reported in human hypertension. It has been found impossible in response to heat and reactive hyperemia to reduce the peripheral resistance in the vessels of the forearm to the same level in hypertensive patients as in normals.\(^{13}\)

In conclusion, therefore, there is evidence to suggest that structural changes encroaching upon the lumen of the arterioles may well be one of the important factors in hypertension. The vascular muscle fibers themselves may respond normally to constrictor and dilator agents but the resulting changes in the lumen of the vessel would be greater in the thickened vessel. Under these circumstances pressor substances in normal or slightly increased amounts would readily lead to hypertension.

**SUMMARY**

The response of the blood pressure to pressor drugs is greater in hypertensive than in normal animals. This increased reactivity is not the mere consequence of elevation of blood pressure nor of vascular spasm. Its characteristics suggest that it is not the result of increased sensitivity of the smooth muscle fibers themselves, since it is of the same duration as the normal one.

It seemed possible, therefore, that increased reactivity might result from structural changes in the arterial wall. In support of this possibility it has been found that when
nitroglycerin was used in supramaximal doses, the lowest level of blood pressure achieved by it becomes progressively elevated with the onset of hypertension. It seemed, therefore, that some residual resistance was present in hypertension which could not be overcome by the nitrite.

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JAMES CONWAY

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