

NEW LOOK INTO THE HUMORAL CONCEPT OF ESSENTIAL HYPERTENSION*

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The story of hypertension began in 1836 with Richard Bright who was struck with the frequency with which large heavy hearts without valvular disease were associated with a small granular kidney. He felt that this strongly indicated some important relationship between the diseases of the kidney and enlarged heart and inclined to the belief that the kidney was the chief promoter of cardiac hypertrophy. Knowing nothing of hypertension or vascular disease he suggested that kidney damage might lead to the accumulation of chemical factors in blood which acted either directly upon the heart to cause its hypertrophy or so affected the minute capillary circulation as to require the heart to work harder to force the blood through the distant subdivisions of the vascular system. One recognises in the latter suggestion the first expression of the modern humoral concept of essential hypertension.

The modern era for the hypertensive problem dates back only about 25 years and it was ushered in by the development of two methods by which hypertension could be predictively achieved in experimental animals. The first of these achieved a type of hypertension of neurogenic character by the removal of sinoaortic buffer system. In the second method a type of hypertension termed renal hypertension was produced in the classical experiments of Goldblatt by a partial constriction of the main renal artery.

At present two main concepts are put forward regarding the pathogenesis of essential hypertension. (1) A purely mechanical theory suggesting a primary disease of arterioles leading to increased peripheral resistance. Goldblatt (1947) has slightly modified this theory to say that the primary arteriolar disease alters renal hemodynamics which causes release of pressor substances from kidney which are responsible for the elevated blood pressure. (2) More favourite theory is humoral. Various humoral factors which are postulated can be classified as under —

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- A— Neurogenic : Sino-aortic buffer system interference
 Sympathetico-adrenal stimulation
 Cerebral vaso-active factors
- B— Renal : Renin
 Pressor amines
 V E M (increase)
- C— Hepatic : Renin substrate
 V D M (decrease)
- D— Adrenocortical hormones.

Not one of the above factors explains the course and the characteristics of essential hypertension. It is well known that the sino-aortic buffer system is as active in hypertension as in normal persons if not more (Doyle and Black, 1955). In hypertensives the blood and urinary catecholamine levels are within normal limits. The renin hypertension differs from essential hypertension in various respects (Tobian, 1960). The V E M and V D M changes are unpredictable and not the constant accompaniments of essential hypertension. There is usually no evidence of adrenal cortical hyperplasia or increased 17- ketosteroid excretion in urine. Hence, despite so much of experimental work the exact aetiology of essential hypertension remains unelucidated.

If we look at the presently known aetiological factors of essential hypertension we would find that everywhere a factor which positively raises the blood pressure has been postulated. If the picture of essential hypertension is scrutinised one finds that the patients show supersensitivity to nor-adrenaline (Doyle and Black, 1955). The positive cold pressor test and increased rise of blood pressure in response to carbon dioxide inhalations are invariably obtained in essential hypertension. These reflex rises of blood pressure are due to release of sympathomimetic amines and may be due to increased release of these substances in response to a standard stimulus in hypertensives as compared to normal persons or the amount of these substances released is the same but the vascular response of these amines is greater in hypertensives than in normal persons. Taking into consideration the facts that the hypertensive patients are supersensitive to nor-adrenaline and that in the hypertensive patients the catecholamine values are mostly normal, one is inclined to believe that the positive cold pressor test is another indication of supersensitivity of the vascular bed to sympathomimetic amines. Thyroxine and the adrenocortical hormones increase the sensitivity of the vascular bed to nor-adrenaline; but the function of these endocrines is known to be normal in essential hypertension. The supersensitivity may also develop by a lack of a substance which normally desensitises the blood vessels to the action of nor-adrenaline. This substance may be a new hormone and the syndrome of essential hyper-

tension may be just another hormone deficiency syndrome. This possibility is further strengthened by the great similarity between the syndrome of diabetes mellitus and the syndrome of essential hypertension.

- (1) Both occur in benign form in late middle age.
- (2) When they occur early they are usually severe and malignant.
- (3) Heredity plays an important role in both conditions.
- (4) Other hormones influence both conditions.
- (5) No gross pathological lesion is detected in uncomplicated cases.
- (6) In symptomless mild condition no treatment is needed.
- (7) Pre-hypertensive state can be recognised as is pre-diabetic state.
- (8) Stimuli causing a rise of blood pressure are known to precipitate hypertension in a susceptible individual.

If we think on the basis of these facts that there is a hormonal basis for essential hypertension we would feel inclined to believe that the kidney is the site for the production of such a hormone. From the vast experimental data it appears highly probable that the kidney has a role in the regulation of blood-pressure. No abnormalities are demonstrated in the structure or function of the kidney in uncomplicated cases; but no changes are demonstrable in the pancreas either in diabetes mellitus. Recently attention has been focussed on the juxtaglomerular cells. These cells appear to be secretory cells containing granules. They are mainly found in the cells of afferent arterioles. In general, whenever a kidney is exposed to increased blood pressure the granularity of these cells decreases (Hartroff, 1957; Tobian *et al.*, 1958). If the blood pressure in these arterioles is decreased the granularity of the cells increases (Tobian *et al.*, 1958). In the normal isolated kidney also similar changes in the granularity can be demonstrated (Tobian *et al.*, 1959). It is quite possible that these cells act as stretch receptors changing their rate of secretion with changes in the wall of the afferent arterioles. Hence one would believe that the hormone is produced by these cells. The stimulus for the release of the hormone is the persistently raised blood pressure because the above changes in the granularity have been observed after the pressure in the renal artery was elevated over many hours. The physiological function of such a hormone is to maintain the basal blood pressure by reducing the sensitivity of the vascular bed to nor-adrenaline.

If we postulate such a hormone there may be cases with hyperfunction of this hormone as well since most of the endocrine disturbances are manifested in both directions. We feel that the syndrome of hypotension and the cases of hypotension where no adreno-cortical abnormality is detected may really

be the cases with hyperfunction of this antihypertensive hormone. We will have to study these cases more carefully.

We do not postulate that there is such a hormone. We only feel that the facts suggest that there might be such a hormone. Our argument is not based on any direct experimental work but we feel that the experimental work carried out on these lines will pay rich dividends.

The treatment of essential hypertension is not very satisfactory. If such a hormone could be isolated and used therapeutically it will form a real rational and complete treatment of essential hypertension.

REFERENCES

- Doyle, A. F. and Black, H. (1955) . *Circulation (N. Y.)* **12**, 974.
Goldblatt, H. (1947) . *Physiol Rev.* **27**, 120.
Hartroff, P. M. (1957) . *J. Expt. Med.*, **105**, 501.
Tobian, L , Thompson, J., Twedt, R., Janeczek, J. (1958) . *J. Clin. Inv.*, **37**, 660.
Tobian, L., Tomboulian, A., Janeczek, J. (1959) . *J. Clin. Inv.*, **38**, 605.
Tobian, L. (1950) . *Physiol. Rev.*, **40**, 280.
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