Special Article*

Aspects of Hormones and Hypertension

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1. Introduction

Among the endocrine diseases, Cushing's syndrome, pheochromocytoma and primary aldosteronism present hypertension as the chief manifestation. As regards so-called essential hypertension which constitutes the majority of hypertensives, Conn et al.¹⁾ have suggested that primary aldosteronism contributes about 7.5% of the cases currently classified as essential hypertension.

The author presents here his experience with endocrine diseases involving hypertension, together with the results of studies made by him and collaborators on endocrine participation in essential hypertension and other hypertensive diseases.

2. Cushing's syndrome

Among 28 cases 24 showed marked hypertension. In the remaining 4 cases, hypertension with systolic pressures around 160 mm. Hg had been observed sometime in the past despite their young age. No great difference in the degree of hypertension was found between cases of adrenocortical hyperplasia (17 cases) and those with adrenocortical adenomata (8 cases). In 1 case of adrenocortical carcinoma (16 year old female) no marked hypertension was present. In 2 cases of the ectopic ACTH syndrome (1 case each of malignant thymoma and colon cancer) marked hypertension was exhibited.

As treatment for these diseases, extirpation of the adrenocortical adenomata was carried out in 7 cases. Blood pressure was normalized in 6 cases, improved in one other case, and other symptoms disappeared in all 7 cases. In 9 of the 17 cases due to adrenocortical hyperplasia, subtotal extirpation of the adrenal or unilateral extirpation was carried out in addition to irradiation of the pituitary with ⁶⁰Co and administration of reserpine. As the result, remission was seen in 3, no change occurred in 5, and death ensued in 1. The therapeutic result by operation was poorer with hyperplasia than adenomata. On the other hand, in 5 of the cases of

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hyperplasia, a prolonged state of remission ensued by pituitary irradiation and reserpine administration, without operation. In all of these 5 cases, the increase of 17-OHCS excretion in response to Metopirone administration was normalized during reserpine treatment as opposed to the supernormal increase before reserpine.²⁾ The disharmony of the hypothalamus-pituitary system was probably readily influenced by reserpine in these cases. Treatment by a combination of reserpine and pituitary irradiation was ineffective in cases in which reserpine had failed to influence the Metopirone test.

3. Pheochromocytoma

The reported cases of pheochromocytoma in Japan, in which the presence of the tumor had been confirmed through operation or autopsy, were 136 in number by the end of 1968. The author has experienced 13 of them.

This disease is generally classified into the persistent type and the paroxysmal type according to the type of hypertension manifested. Among the cases reported in Japan, the description of the type is available in 89 cases of the persistent type and 39 cases of the paroxysmal type, the former being twice as common as the latter. Distributed according to the age group, the 20s and 30s are predominant and males and females were found to be almost equal in incidence. All the 8 cases below the age of 15 were of the persistent type. As the age advances, the proportion of the paroxysmal type increased, 25% between 16 and 20 years, 23% in the 20s, 34% in the 30s, 39% in the 40s, and 47% after 51.

The weight of the tumor was 11–100 g. in about 2/3 of cases. Funduscopic findings revealed advanced hypertensive changes in younger age groups in which the persistent type predominated. In patients in the advanced age group, on the other hand, mild cases were predominant.

Although in this disease, hypertension and advanced retinal changes are common and albuminuria is not rare, renal function is relatively well maintained. The results of renal function studies revealed an endogenous creatinine clearance of 52–112 ml./min. even in 6 cases with papilledema. Renal failure was not experienced.

The rate of positive reaction in various diagnostic tests conducted was 99% for the Regitine test, 78% for the histamine test, and 100% for the determination of urinary catecholamines and their metabolites. While the rate of positive reaction in the Regitine test was high, false positive reactions were also frequently seen in our experience. Determinations of urinary catecholamines and their metabolites gave the most reliable method. Sato³⁾ in our laboratory developed a simple screening method consisting of plotting urine on a filter paper, drying, spraying it with paranitroaniline diazo reagent, and developing a violet color with the metabolites. The chromatographic separation of metabolites was omitted in this method. This simplified method gave a rate of 80% for the positive reaction. A false-negative test was seen in cases with polyuria, and in the resting phase of the paroxysmal

type. Repeating the test on different days raised the rate of positive reaction. A false-positive reaction was seen after eating a large amount of vanilla-containing cake or citrus fruits.

The determination of plasma renin has had an increasingly important significance for the elucidation of the pathogenesis of hypertension and its differential diagnosis in recent years. In 7 cases of pheochromocytoma, we have measured the plasma renin activity (PRA) in peripheral venous blood by Yoshinaga's modification⁴⁾ of Helmer's method. An elevation was seen in 5 of them. After extirpation of the tumor, PRA normalized along with normalization of blood pressure and urinary catecholamines. The rise of PRA in this disease, along with the marked retinal changes, may lead to the erroneous diagnosis of malignant hypertension and renovascular hypertension, requiring special consideration.

4. Hypertension and catecholamines

The amount of urinary catecholamines and vanillylmandelic acid in hypertensive diseases other than pheochromocytoma usually remained within normal limits. No evidence was thus obtained on the role of the excessive secretion of catecholamines as the cause of hypertension in these diseases. The reaction of the rise of blood pressure in response to intravenous infusion of noradrenaline was, however, more pronounced in hypertension excluding pheochromocytoma, than in normotensives. The amount of infused noradrenaline required to raise the diastolic pressure by 20 mm.Hg was less in essential hypertension than in controls (Fig. 1, A). Similar results were obtained with angiotension II, another endogenous pressor substance (Fig. 1, B).

These results might indicate that hypertension is caused by an increased sensitivity to pressor substances such as noradrenaline despite the absence of increased production of these substances in essential hypertension. However, with the admin-

Fig. 1. Sensitivity to pressor substances in normal controls and essential hypertension (expressed as the amount of pressor substances required to raise the diastolic pressure by 20 mm.Hg).

istration of a certain amount of eledoisin, a polypeptide with a hypotensive effect, the fall of blood pressure was greater in essential hypertension as compared with normal controls (Fig. 2, A). The results with the use of prostaglandin E_1 (PGE_1), which is one of the endogenous vasodepressor substances, revealed similarly a greater depressor effect in essential hypertension than in normals (Fig. 2, B).

Fig. 2. Sensitivity to vasodepressor substances in normal controls and essential hypertension (expressed as the fall of systolic pressure in response to infusion of depressor substances).

Although it is still undecided whether the production of PGE_1 is excessive or deficient in hypertensive patients, we have demonstrated a several fold increase in the content of a PGE_1 -like substance in the renal medulla after perfusion with high pressure of the unilateral kidney in situ of a dog as compared with the contralateral kidney. The substance extracted from the kidney in this experiment correlated closely with PGE_1 in its solubility, heat stability, resistance to chymotrypsin, biological activities (on blood pressure, guinea pig ileum, blood vessel permeability and depression of lipolysis induced by adrenalin) and chromatographic motility in various systems.

As stated above, the sensitivity to pressor substances as well as to vasodepressor substances was increased in essential hypertension. It is unlikely that the increased reaction would appear only to pressor substances, inducing hypertension as the result.

5. Primary aldosteronism in Japan

According to the results of our survey using questionnaires, 191 cases of primary aldosteronism due to adrenocortical tumor were experienced in Japan by February 1969. Adenomata were found in 70 males and 119 females, for a total of 189 cases, with 1.7 times as high a frequency in females as in males. Adrenocortical carcinoma was responsible in 2 cases, both females. Cases of adenomata were most frequent in the fourth decade, followed in incidence by the fifth decade, cases in these two

decades occupying 80% of all cases. We have experienced with 21 cases, all of them due to adenomata.

Of the symptoms in these cases experienced in Japan, muscle weakness (73%), headache (72%) and polyuria (69%) were predominant, the incidence being close to the results of Conn's survey.⁵⁾ However, intermittent paralysis was very frequent (62%) in the Japanese as compared with those (21%) reported abroad. It is not clear whether this is because the diagnosis is made in Japan only when paralysis appeared or paralysis is more common in Japan due to a high salt intake. Four cases of normokalemic primary aldosteronism have so far been seen.

Adrenocortical adenomata were single in 150 cases and multiple in 9 cases. Left-sided adenomata were found in 111 cases, while right-sided adenomata were seen in 69 cases, the left side being 1.5 times as frequent as the right. The weight of the adenoma was less than 6 g. in 82%.

The effect of adrenal surgery on blood pressure was to normalization in 54% and improvement in 37%. Postoperative death was experienced in 5 cases (3%), and preoperative death in 12. Among the cases of preoperative death, cardiac failure was responsible in 3, cerebral apoplexy in 3 and renal insufficiency in 1.

6. The renin-angiotensin-aldosterone system and hypertension

During the last few years, the interrelationship between aldosterone and the renin-angiotensin system has been drawing increased attention. We have determined the aldosterone secretion rate (ASR) by the double isotope dilution derivative method⁶⁾ and PRA of peripheral venous blood by the modified Pickens' method,⁷⁾ and angiotensin II in the arterial blood by the radioimmunoassay method of Catt et al.⁸⁾

As a result, PRA stayed within the normal range in essential hypertension as shown in Fig. 3. In renovascular hypertension, especially in unilateral renal artery stenosis, a marked elevation was noted. A marked elevation was also noted in malignant hypertension. In primary aldosteronism, on the other hand, the level

Fig. 3. Renin activity in peripheral plasma in various hypertensive diseases (by a modified Pickens' method). The normal range is shown by the stippled area.

was subnormal. The concentration of angiotensin II in the arterial blood showed a tendency similar to that of PRA. A decidedly low value was obtained in primary aldosteronism (Fig. 4).

Fig. 4. Concentration of angiotensin II in the arterial blood in various hypertensive diseases. The normal range is shown by the stippled area.

7. Diagnosis of primary aldosteronism

To detect suppression of PRA for the diagnosis of primary aldosteronism, Conn⁹⁾ restricted Na intake to 10 mEq./day for 3 days, and carried out measurements of PRA after the patient had been upright for four hours on the 4th day morning. From his observations, such a procedure stimulating renin secretion induces a marked rise of PRA in normal people but not in this disease.

In our hospital, a strict restriction of salt intake is difficult in practice and even the "salt-free" diet contains about 30 mEq. of Na per day. Restriction to this degree might frequently not constitute an adequate stimulus for renin secretion. Besides utilizing this "salt-free" diet, we have administered 400 mg./day of Aldactone A and 75 mg./day of hydrochlorothiazide over 3 day period. On the 4th day, the patient stayed upright for 4 hours in the morning before obtaining blood samples.

In 15 cases of proven primary aldosteronism in our studies, a suppression of PRA was demonstrated with this method along with an increase of ASR. Operation revealed adrenocortical adenomata in all these cases except for a case of 17-hydroxylase deficiency.¹⁰⁾ However, such a procedure of stimulation might be too intense as compared with simple salt restriction. Consequently, the erroneous exclusion of primary aldosteronism cannot be denied. Among proven cases of primary aldosteronism in our experience, moreover, there was included a case in which chlorothiazide had been administered for 5 months before admission to hospital and a definite rise of PRA was obtained in response to the procedure of stimulation described above, after 15 days of withdrawal of the drug during hospitalization. In another case in which Aldactone was administered for 10 months, PRA again showed a marked rise in response to the above procedure conducted 10 days after withdrawal of medication. In performance of this method, special care should be taken as regards these points.

8. Incidence of primary aldosteronism in "essential" hypertension

In 1965, Conn¹⁾ reported the existence of normokalemic primary aldosteronism which is clinically indistinguishable from essential hypertension. Even in such a situation, the rise of ASR and the suppression of PRA make the diagnosis possible. He found such a normokalemic primary aldosteronism in 7.5% of cases which had been regarded as essential hypertension.¹⁾

During the 3 year period from September 1965, we have conducted tests on the stimulation of renin secretion as described above in 72 cases of "essential" hypertension. In cases with suppression of PRA, the ASR was also determined. As a result, 2 cases of primary aldosteronism due to adenomata were found, representing a frequency of 3%. Besides these 2 cases, there were 3 cases in which suppression of PRA and increase of ASR were found but consent for the operation was not obtained. In view of these facts, the frequency of primary aldosteronism in "essential" hypertension appears to be above 3%.

On the other hand, however, these 72 cases studied had been selected from among 810 hypertensive patients who visited our hypertension clinic during the 3 year period, as cases at a relatively young age with marked hypertension. Consequently, the predication of the frequency of primary aldosteronism in "essential" hypertension from this result appears to be difficult.

9. Conclusion

The diagnostic methods for various endocrine diseases with hypertension have shown remarkable progress in recent years. The treatment for these diseases has also become more definitive. However, the elucidation of the role of hormones in essential hypertension constituting the majority of hypertension cases is still as unsolved problem at the present time.

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