Adrenal Factors in Hypertension

By Jerome W. Conn, M.D.

The relation of adrenal function to hypertension in man is discussed. It is pointed out that hypertension accompanying hyperaldosteronism may recur after removal of the tumor and correction of the electrolyte abnormality. The complex relationship between blood pressure, excretion of sodium loads, total body sodium and aldosterone excretion is emphasized. Results following bilateral adrenalectomy in man indicate a permissive role for the adrenal cortex; this is further supported by the occasional clinical observation that certain patients with Addison's disease who have an unusual pressor response to substitution therapy have had a prior hypertension or a prominent family history of this disease.

Our group has done no research in either experimental or human hypertension. We have, however, uncovered a group of hypertensive people who have in common a unique disturbance of electrolyte metabolism which is produced by excessive adrenal production of aldosterone and have suggested that this condition be called primary aldosteronism.1 The clinical and biochemical manifestations of this disease are analogous in most details to those observed in desoxycorticosterone-induced hypertension in dogs. Surgical removal of the source of the excessive aldosterone production results in disappearance of the hypertension in most cases, just as does cessation of desoxycorticosterone administration in dogs at a certain state in the hypertension.

We have become acquainted with some details of approximately 50 proved cases of primary aldosteronism, many of which are not yet published. It is of interest that over 90 per cent of these cases have disclosed a single adrenal cortical adenoma, removal of which has resulted in reduction of blood pressure to normal in the majority, and to significantly lower levels in the rest. The few with bilateral adrenal hyperplasia have responded well to total or 90 per cent subtotal adrenalectomy. A few patients, however, have exhibited a postoperative fall in blood pressure for weeks or months, and then in time the blood pressure has returned to hypertensive levels. Although this is the exception, it is significant because in these cases, as in the others, the characteristic abnormality of electrolyte metabolism has disappeared. In some of these cases this response may be explainable on the basis of chronic pyelonephritis secondary to long-standing kaliopenic nephropathy. On the other hand, there are at least 2 instances in which excretory function of the kidneys was normal both before and after operation, but hypertension failed to improve after removal of the aldosteronoma, despite return of electrolyte metabolism to normal. We think that perhaps this is analogous to what Selye has called metacorticoid hypertension,2 representing persistence of hypertension even after cessation of administration of desoxycorticosterone. In those experiments, relief or persistence of hypertension upon cessation of DOC was dependent on the duration of its administration.

If one attempts to focus on metabolic aberrations most likely to be involved in the production of the hypertensive state, he would have to emphasize the sodium ion. Some of the people participating here today have been involved in demonstrating that there appears to be somewhat more sodium than necessary, and perhaps too little potassium, in the body of an animal with experimental hypertension.

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This observation is in the same direction, but in much smaller degree than that we have observed in primary aldosteronism in which exchangeable sodium is somewhat higher and exchangeable potassium very much lower than normal. If this type of electrolyte shift is important in the evolution of hypertension, it would seem that eventual maintenance of hypertension is not dependent on its presence.

Some aldosterone determinations have been done in essential hypertension, but it is too early to evaluate the meaning of the small increases in urinary excretion of this compound which have been reported. One should keep in mind that urinary excretion of aldosterone is a very poor index of production of aldosterone. In our experience at least, much less than one per cent of that administered was picked up in the urine. There may be major changes in production which are difficult to detect as urinary excretion products by present methods. In any case, there appears to be some slight increase in urinary aldosterone in essential hypertension. I think it is important for us to realize too that this may not be primary, but secondary to the hypertension. Barger has shown, for example, that a lesion in the heart which is insufficient to produce any increase in venous pressure is associated with a decreased rate of excretion of a salt load. This suggests that the cardiac lesion has set off a form of secondary aldosteronism even though the precise mechanism is unknown. It would be interesting—I do not believe this has been done yet—to put a Goldblatt clamp on a dog's renal arteries and see whether aldosterone excretion increases quickly and in relation to the hypertension.

We have another bit of evidence which militates against increased sodium and decreased body potassium as being etiologic or of primary importance in essential hypertension. This has to do with our recent studies in periodic paralysis. We find that total exchangeable sodium in this disease is just as high as it is in primary aldosteronism. The finding is confirmed by analysis of multiple muscle biopsies. In addition, total exchangeable body potassium is decreased in this disease, although not as much as in primary aldosteronism, yet there is no hypertension at all.5

Before leaving the electrolyte question, I should mention the interesting phenomenon that you will be hearing more about. Drs. Findley, Braun-Menéndez, Weller, and others participating today, have shown that this phenomenon occurs both in patients with essential hypertension and in animals with experimental hypertension. I refer to the fact that such people and animals excrete a sodium load at a somewhat faster rate than normal controls. This seems paradoxical in view of what we have already mentioned with respect to total body exchangeable sodium in hypertension. There are several possible mechanisms for this phenomenon, but I do not think anybody really knows what this is all about. One can show the same phenomenon in DOC hypertension. A rat made hypertensive with a sodium-retaining corticoid, like DOC, excretes a sodium load at a faster rate than does his normal control.

Finally, I would recall the 1950 to 1952 era when many bilateral adrenalectomies were done for essential hypertension.6 It soon became evident that if the adrenal is important in essential hypertension it is playing a secondary, perhaps permissive, role in allowing a pressor system to become activated. Those of you who have seen many cases of Addison's disease realize that when one gives standard substitution therapy to certain patients with Addison's disease they become hypertensive. In fact, some remain hypertensive on suboptimal therapy. When one goes into the histories of these people he finds that some were hypertensive before they developed Addison's disease; in other cases there is a history of much hypertension in the family. It is of interest, too, that occasionally one sees such a patient in whom a small amount of cortisone, without any mineralocorticoid, causes severe hypertension. In such instances there seems little doubt that the cortisone is permissive in action. Perhaps this introduction helps set the stage for some of the material that follows.
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