INCIDENCE OF HYPOKALAEMIA IN SEVERE HYPERTENSION

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The demonstration of an unexplained hypokalaemia in a patient with high blood-pressure is usually thought to be highly suggestive of primary aldosteronism, and has often been the first clue to the correct diagnosis of this disease. In many centres measurement of the serum potassium has become a routine screening test for the detection of cases of this rare and remediable disorder from among the general hypertensive population. This practice presupposes that in hypertension of non-adrenal origin the serum potassium concentration is normal. However, there is some evidence that this supposition is incorrect. De Wesselow and Thomson (1939) pointed out that many hypertensives have a low serum potassium concentration, and Hilden and Krogsgaard (1958) have confirmed this finding; both groups of workers found that hypokalaemia was particularly common in patients with malignant hypertension.

The present survey was undertaken to establish the incidence of hypokalaemia among patients with severe hypertension and, furthermore, to determine what types of hypertension are associated with this abnormality.

Material and Methods

The series consists of patients admitted for the investigation or treatment of hypertension under the care of Professor M. L. Rosenheim over a period of 22 months from January, 1959, and includes all such patients with the following exceptions: those previously admitted for hypertension or already receiving effective treatment; those suffering from diarrhoea, vomiting, congestive heart failure, or severe renal failure (blood urea above 150 mg./100 ml.); and those receiving either steroids or diuretic drugs. Sixty-four patients satisfied these criteria, and all of these had a resting diastolic blood-pressure of 120 mm. Hg or more at the time of admission to hospital. Approximately one-quarter had papilloedema ("malignant" hypertension); in the remainder hypertension was thought to represent a serious hazard to life or was causing severe symptoms.

Patients were thoroughly investigated in the hope of discovering the cause of hypertension. Such study usually included an intravenous pyelogram, and in many cases renal arteriography was performed as well. The plasma potassium was determined by flame photometry, and total carbon dioxide by the method of Van Slyke and Neill (1924). Quoted values of plasma potassium below 3.5 mEq/l. are the mean of at least two determinations on different specimens. The appearances of the optic fundi were classified according to the criteria of Keith *et al.* (1939).

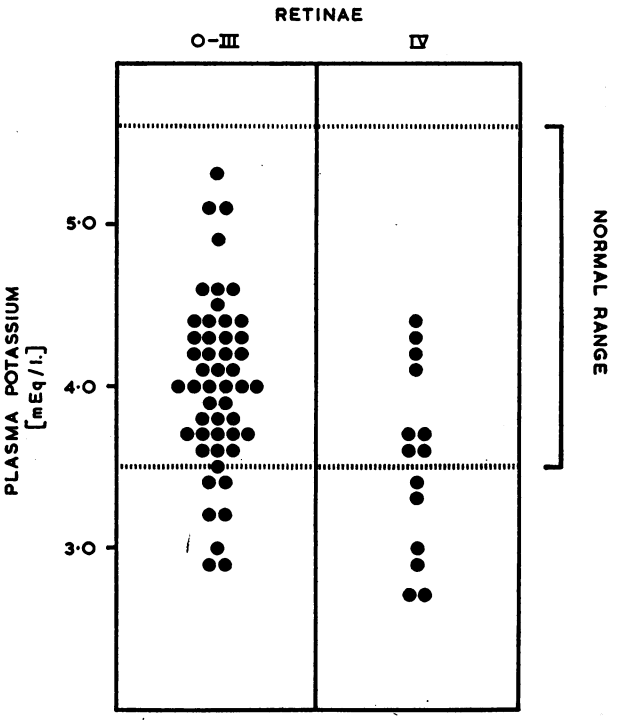
Results

In healthy adults the plasma potassium concentration is less than 3.5 mEq/l. in only 1% of observations (Wootton and King, 1953; Elkinton and Danowski, 1955); Table I and the accompanying Chart show that no fewer than 13 (20%) of the 64 hypertensive patients of this series had a plasma concentration below this figure. When these patients were further classified according to the absence or presence of papilloedema it was found that hypokalaemia was much more common in those with papilloedema (43%). The mean plasma potassium and standard deviation of patients without papilloedema was 4.0 ± 0.5 mEq/l., and of those with papilloedema it was 3.5 ± 0.6 mEq/l.; the difference between the two means is statistically significant ($t=2.9$; $P<0.01$). The incidence of hypokalaemia in each group does not differ significantly from the earlier figures of de Wesselow and Thomson and of Hilden and Krogsgaard (Table I).

TABLE I.—*Incidence of Hypokalaemia in Severe Hypertension*

	Total No. of Hypertensives	Plasma K Below 3·5 mEq/l.	No. Without Papilloedema (fundi O–III)	Plasma K Below 3·5 mEq/l.	No. With Papilloedema (fundi IV)	Plasma K Below 3·5 mEq/l.
Present series	64	13(20%)	50	7(14%)	14	6(43%)
de Wesselow & Thomson (1939)*	35	6(17%)	31	3(10%)	4	3(75%)
Hilden and Krogsgaard (1958)	32	5(16%)	25	1(24%)	7	4(57%)
Total	131	24(18%)	106	11(10%)	25	13(52%)

* One of de Wesselow's patients, in whom hypokalaemia might have been due to vomiting, is omitted.



Plasma potassium in hypertensive patients. The normal range includes 98% of normal observations (Wootton and King, 1953).

Some details of the 13 hypokalaemic patients of this series are given in Table II. The lowest plasma potassium encountered was 2.7 mEq/l. Many of the patients with hypokalaemia also had an alkalosis, and this finding was more frequent in those with malignant hypertension. Investigation revealed possible renal causes of hypertension in 9 (69%) of 13 patients, and five of these had evidence of renal ischaemia on one or both sides. No patient was shown to have an adrenal tumour; in Cases 9, 12, and 13 the adrenals were found to be tumour-free at subsequent necropsy, and in Case 8 the right adrenal appeared normal at the time of right nephrectomy.

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These hypokalaemic patients had few symptoms of potassium depletion. A single attack of tetany occurred in Case 8, but no patient had ever suffered from paralysis. The majority complained of nocturia, and some patients had to pass urine as often as eight times a night. Nocturia is a common symptom in primary aldosteronism (Brooks *et al.*, 1957), where it is associated with an inverted diurnal rhythm in the excretion of sodium and water (Lennon *et al.*, 1961): this inverted rhythm also appears to be usual in the syndrome under discussion (Gowenlock *et al.*, to be published). A history of nocturia was found to be of help in predicting whether a hypertensive patient would have hypokalaemia.

In only one hypokalaemic patient (Case 8) of this series was hypertension cured by renal surgery (nephrectomy and excision of phaeochromocytoma compressing renal artery), and in this patient the plasma potassium and total carbon dioxide returned to normal within a few days of operation. Since this study, Cases 2 and 11 have been treated with potent hypotensive drugs for a period of 14 months, and their blood-pressure has been satisfactorily controlled; the plasma potassium concentrations of both were in the low normal range when recently determined.

Discussion

The present demonstration of a high incidence of hypokalaemia in patients with hypertension, and in particular in those with malignant hypertension, confirms the findings of de Wesselow and Thomson (1939) and of Hilden and Krogsgaard (1958). Similar observations have been made by Laragh *et al.* (1960b), but their paper was primarily concerned with the measurement of aldosterone-secretion rates (see below), and it is not clear to what extent their hypertensive patients were an unselected group. The contrary finding, that in hypertension the serum potassium is normal, has been reported by Albert *et al.* (1958). These workers appear to have studied less severely hypertensive subjects than those cited above or the present series, for their 26 patients with "essential" hypertension were all out-patients and included only one case of malignant hypertension. Furthermore, in their discussion and conclusions they made no mention of the fact that their series of hypertensive subjects included three with definite hypokalaemia (serum potassium 3.1, 3.4, and 3.4 mEq/l.); whether one of these was the patient with malignant hypertension is not stated.

The fact which most clearly emerges from the present investigation and the two comparable studies is that a definite hypokalaemia (2.7–3.4 mEq/l.) is present in about 50% of patients with malignant hypertension (Table I). This hypokalaemia is often accompanied by a mild alkalosis. The more common causes of potassium depletion, such as increased alimentary loss or the diuresis produced by drugs of the chlorothiazide type, were excluded by the initial selection of the present series. Metabolic observations on some of these and similar patients (Gowenlock *et al.*, to be published) have shown that their hypokalaemia is accompanied by impaired renal conservation of potassium, between 40 and 70 mEq of this electrolyte being lost in the urine daily. Such renal wastage of potassium could theoretically result either from primary renal disease or from an excessive adrenal secretion of aldosterone or some other mineralocorticoid. Potassium-losing renal disease seems unlikely here, for it is almost invariably accompanied by an acidosis, not an alkalosis, and usually by other signs of renal tubular damage, such as amino-aciduria, glycosuria, or nephrocalcinosis, none of which were demonstrated in the present cases. But hyperaldosteronism when it causes potassium depletion also frequently results in an alkalosis. Measurements of urinary aldosterone were made in only two of our patients (Cases 8 and 11), and one of these (Case 8) was found to be excreting increased amounts (Gowenlock and Wrong, 1961).

Evidence that hypertension is commonly accompanied by hyperaldosteronism has appeared in the recent medical literature. Genest *et al.* (1960) have found that aldosterone excretion is increased in a large proportion of hypertensive patients, particularly so in those with malignant and renal hypertension. Garst *et al.* (1960) excluded from their series all patients with malignant hypertension or obvious renal disease, but nevertheless found that in a large proportion of patients with essential hypertension the excretion of aldosterone was raised.

Details of Hypokalaemic Hypertensives

Case No.	Sex and Age	Fundi	Plasma K mEq/l.	Plasma Total CO_2, mM/l.	Cause of Hypertension	Follow-up
				Without Papilloedema		
1	F 14	I	2·9	30·6	Renal (chronic pyelonephritis, double left ureter, urethral bar, and bilateral vesico-ureteric reflux)	—
2	M 26	0	3·4	29·6	?Essential. Idiopathic Hypoparathyroidism.	Plasma K 4 mEq/l. after 14 months' hypotensive therapy
3	F 32	I	3·2	27·6	Renal (stricture right renal artery)	Anxiety neurosis; unable to attend
4	M 45	II	3·2	27·7	?Essential (normal pyelogram, no family history)	—
5	M 46	II	3·0	32·8	?Essential. ?Renal (renal calculus 2 years ago, normal pyelogram, no family history)	—
6	M 47	II	2·9	31·4	Renal (recurrent attacks of pyelonephritis; pyelogram shows clubbed calices)	—
7	M 67	I	3·4	25·4	?Essential (no family history, normal pyelogram)	—
				With Papilloedema		
8	F 25	IV	2·7	32·5	Renal and adrenal medullary (phaeochromocytoma compressing right renal artery)	Normotensive 1 year after operation, plasma K 3·9 mEq/l. Right adrenal normal at operation
9	F 26	IV	3·3	31·2	Renal (aortic aneurysm involving both renal arteries)	Died after aortic resection. Adrenals infarcted as result of surgery, but no tumour
10	M 45	IV	2·9	28·8	Essential (strong family history)	Died in uraemia 6 weeks later; no necropsy
11	M 47	IV	3·0	33·3	Renal (multiple strictures on renal arteries)	K 3·9 mEq/l. after 14 months' hypotensive therapy
12	M 52	IV	2·7	28·7	Renal (chronic glomerulonephritis)	Died of hepatoma. Normal adrenals at necropsy
13	M 53	IV	3·4	27·3	Renal	Died in uraemia 4 months later; necropsy showed normal adrenals and thrombosis of right inferior renal artery

Laragh *et al.* (1960b) have measured secretion rates in a large number of patients with hypertension of various types. In 14 out of 15 patients with malignant hypertension the rate of secretion was greatly increased, lying between 600 and 2,000 μg./24 hours (normal 150–330 μg.). Five patients with primary aldosteronism secreted slightly less aldosterone (510–1,690 μg./24 hours), although the figures of the two groups overlapped. Patients with hypertension and renal or retinal complications other than papilloedema (grade III retinopathy) often had raised secretion rates, but the secretion rates of patients with uncomplicated essential hypertension were normal. Half the patients with malignant hypertension had their adrenal glands examined at subsequent operation or necropsy; no adrenal tumours were found, but bilateral cortical hyperplasia was present in several cases. This work constitutes impressive evidence that hyperaldosteronism is usual in malignant hypertension and common in hypertension of less severe degree. The rates of secretion are as high as those encountered in primary aldosteronism and might be expected to cause a similar hypokalaemia. Laragh *et al.* (1960b) remarked on the frequent finding of a hypokalaemic alkalosis in their patients; 6 out of 15 cases with papilloedema had a serum potassium below 3.5 mEq/l., and three cases had a plasma total carbon dioxide above 31 mM/l. In this respect Laragh's observations tally closely with mine.

From the observations cited above there can be little doubt that the hypokalaemia commonly present in severe hypertension is due to hyperaldosteronism. However, this condition is not primary aldosteronism. The present series and numerous earlier individual case reports (Wrong, 1957; Dollery *et al.*, 1959; Hoet and Molineaux, 1960; Laidlaw *et al.*, 1960; Gowenlock and Wrong, 1961) show that many such patients are discovered at investigation to have renal causes of hypertension—usually renal ischaemia. In such cases appropriate renal surgery alone has often resulted in cure both of hypertension and of the signs of hyperaldosteronism, which suggests that the adrenal hyperfunction is in some way the result of renal disease. Laragh *et al.* (1960a) have found that intravenous injection of angiotensin into normal subjects causes a marked increase in aldosterone secretion, and it may therefore be through the mediation of renin that renal disease brings about a state of hyperaldosteronism. Not all the hypokalaemia patients of this series were shown to have primary renal disease; but the above thesis is not thereby invalidated, for severe hypertension of any origin may damage the kidney and lead to focal areas of ischaemia. Alternatively, it may be that severe hypertension itself stimulates aldosterone secretion, but there is no experimental support for this hypothesis.

Conn (1960) has suggested that the diagnosis of primary aldosteronism would be made much more often if the plasma potassium were determined as a routine in cases of hypertension. While this conjecture is almost certainly true, the present study does suggest that the majority of untreated hypertensives who are found to have hypokalaemia are not, in fact, suffering from primary aldosteronism.

Summary

Of 64 patients with severe hypertension, 13 (20%) had a definite hypokalaemia (plasma potassium 2.7–3.4 mEq/l.), often accompanied by an alkalosis. The incidence of hypokalaemia was greatest in those with papilloedema (43%). Possible renal causes of hypertension were discovered in two-thirds of those with hypokalaemia.

The hypokalaemia of severe hypertension seems to be due to hyperaldosteronism, which is caused by renal ischaemia, the hypertension itself, or some closely related phenomenon. The term "primary" aldosteronism is not applicable to this syndrome.

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INTRATHECAL TUBERCULIN IN DISSEMINATED SCLEROSIS

A CONTROLLED TRIAL

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When Smith *et al.* (1957) published a hint of prolonged remissions in disseminated sclerosis after an experimental study of cerebrospinal fluid (C.S.F.) changes with intrathecal tuberculin injections (purified protein derivative—P.P.D.) we felt obliged to test this. For reasons which must be obvious (see also *British Medical Journal*, 1958) we set about a controlled trial.

In order to obtain early results we deliberately selected 20 patients with undoubted disseminated sclerosis in whom we thought further demyelination probable—that is, we chose patients with at least three episodes occurring at a rate of more than one a year, or with evidence of unremitting progression over six months. They all had some signs of damage to the central nervous system, but were still useful members of society or of their household, with measurable faculties to lose. They were unaffected by pulmonary tuberculosis or general medical diseases or psychiatric disorders.