MEDICAL PRACTICE

*Hospital Topics***Results of Adrenal Surgery in Patients with Hypertension, Aldosterone Excess, and Low Plasma Renin Concentration**

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Summary

Fifty patients with hypertension, aldosterone excess, and low plasma renin concentration underwent adrenal surgery. There was a highly significant fall in mean systolic and diastolic pressures after the operation. The mean postoperative diastolic pressure fell to strictly normal levels, however, in only 19 out of 38 patients from whom an adrenocortical adenoma was removed and in only two out of 10 non-tumour patients.

There was a significant correlation between the fall in blood pressure during spironolactone treatment and after adrenal surgery though levels were generally slightly lower during the former therapy. It is suggested that removal of an aldosterone-producing adenoma is the treatment of choice provided a good preoperative hypotensive response to spironolactone occurs, while the treatment of choice for non-tumour patients is often long-term spironolactone.

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Introduction

Though patients with hypertension, aldosterone excess, and low plasma renin often harbour an adrenocortical adenoma tumours are not always found; the adrenal glands then show either hyperplasia of the zona glomerulosa—often with nodular changes—or normal histological appearances.¹⁻² Removal of an aldosterone-producing adenoma usually results in a considerable fall in blood pressure,¹⁻⁷ but total or subtotal adrenalectomy in patients without a tumour has been reported to have little or no hypotensive effect.⁴⁻¹⁰

We describe here the results of adrenal surgery in 50 patients with hypertension, aldosterone excess, and low plasma renin concentration and compare the postoperative blood pressures in patients with and without an adrenocortical adenoma. The results of treatment with spironolactone in some of these patients have been reported elsewhere.¹¹

Patients and Methods

A total of 50 patients aged 18 to 66 years and including 31 women were studied. None of the patients had taken diuretics—including spironolactone—potassium supplements, or a low sodium diet for at least four weeks before investigation. While in hospital 23 patients ate a diet of constant normal sodium and potassium content (fixed at a point within the range 101-145 mEq Na⁺/day and 44-79 mEq K/day), and the remainder ate a normal ward diet. Blood samples for estimation of the plasma concentrations of renin, angiotensin, and aldosterone were taken between 08.00 and 10.00 hours, when the patients had been fasting and recumbent since 22.00 hours on the previous day.

All the patients had a raised plasma aldosterone concentration (>18 ng/100 ml) on at least one occasion, while plasma renin concentration was below the normal mean (8.4 U/l.) at

least once in all cases and below the normal range (4-20 U/l.) at least once in 38 patients.

The blood pressure readings quoted are those taken in the outpatient department using an ordinary clinical sphygmomanometer with the patient sitting, and on no hypotensive drug treatment; the means of all the available readings during each review period were used. The postoperative blood pressure readings were taken during eight arbitrarily chosen review periods: at 3-5 weeks, 2-3 months, 4-6 months, 7-12 months, 2 years, 3 years, 4 years, and at 5-6 years.

Of the 50 patients 33 had a course of spironolactone (Aldactone-A) for at least four weeks before operation (mean dose 275 mg/day, range 150-400 mg/day; mean duration of treatment 26 weeks, range 4-91 weeks).

Blood pressure readings and biochemical values obtained during the first four weeks after adrenalectomy or after the start of spironolactone therapy and all the postoperative biochemical measurements in patients who underwent total adrenalectomy were excluded from the analysis. Blood pressure readings within 1 S.D. of the means found in the population study by Hamilton *et al.*,¹² when matched for age and sex, were taken as "normal."

Adrenal tissue taken from 40 of the 50 patients was available for independent review and classification by Professor T. Symington and Dr. A. M. Neville, using criteria previously described.¹³

LABORATORY METHODS

Plasma and serum electrolytes, blood urea, plasma concentra-

tions of renin, angiotensin II, and aldosterone, as well as total exchangeable sodium, exchangeable potassium, extracellular fluid volume, total body water, and plasma volume, were measured as previously described.^{11, 14} Though plasma is preferable to serum for potassium measurements¹⁵ plasma values were not always available and for this analysis plasma and serum estimations were both used.

Statistical calculations were performed with a Hewlett-Packard 9810 A desk computer.

Results

SURGICAL FINDINGS AND FOLLOW UP

A unilateral adrenocortical adenoma was found in 38 patients and no tumour was identified in 10; in the remaining two cases a definitive pathological diagnosis was not reached because some histological features were consistent with adenoma while others favoured nodular hyperplasia.

The mean duration of follow-up for the 50 patients was 95 weeks (range 5-286 weeks). There was no significant difference in the duration of follow-up of tumour patients (mean 99 weeks) and non-tumour patients (mean 78 weeks, $t=0.67$, $P>0.5$).

The operative procedures undertaken and the pathological findings in the individual patients are shown in table I.

BLOOD PRESSURE AFTER OPERATION

There was a highly significant fall in both the systolic and diastolic blood pressures after operation in the 50 patients taken

TABLE I—Pathological Findings, Surgical Procedures, and Mean Blood Pressures before and after Operation in 50 Patients with Hypertension, Aldosterone Excess, and Low Plasma Renin Concentration

Case No.	Age and Sex	Adrenal Pathology	Pathology Reviewed	Surgery	Mean Blood Pressure	
					Before Treatment	After Operation
1	54 F.	A + M.M.H.	Yes	U.	202/124	146/98
2	22 M.	A + M.N.H.	Yes	U.	190/130	160/106
3	37 M.	A. + M.N.H.	Yes	U.	230/150	210/130
4	66 M.	A. + M.N.H.	Yes	U.	195/115	190/117
5	27 F.	A. + M.N.H.	Yes	U.	220/140	143/97
6	49 M.	A. + M.N.H.	Yes	U.	192/125	179/119
7	36 M.	A. + M.N.H.	Yes	U.	250/140	151/104
8	44 F.	A. + M.N.H.	Yes	U.	200/120	157/97
9	48 F.	A. + M.N.H.	Yes	T.	213/125	167/113
10	56 M.	A. + M.N.H.	Yes	U.	230/120	200/130
11	53 F.	A. + M.N.H.	Yes	U.	160/105	127/90
12	50 F.	A. + M.N.H.	Yes	U.	230/130	135/85
13	41 F.	A. + M.N.H.	Yes	U.	163/106	129/83
14	34 M.	A. + M.N.H.	Yes	U.	200/130	125/95
15	39 F.	A. + M.N.H.	Yes	S.T.	208/114	142/94
16	18 F.	A. + M.N.H.	Yes	U.	210/135	140/93
17	39 F.	A. + M.N.H.	Yes	U.	180/120	133/85
18	48 F.	A. + M.N.H.	Yes	U.	205/115	120/78
19	50 M.	A. + M.N.H.	Yes	U.	195/118	150/93
20	24 F.	A. + M.N.H.	Yes	P.U.	210/133	130/78
21	30 F.	A. + M.N.H.	Yes	U. + A.	164/102	113/80
22	48 F.	A.	Yes	U.	205/132	146/97
23	44 M.	A.	Yes	U.	180/110	139/90
24	52 M.	A.	Yes	U.	250/148	200/113
25	38 M.	A.	Yes	U.	190/112	158/91
26	60 F.	A.	Yes	U.	235/115	185/108
27	24 M.	A.	Yes	S.T.	200/128	145/101
28	24 F.	A.	Yes	U.	150/100	123/78
29	21 F.	A.	No	U.	150/110	137/88
30	35 F.	A.	No	U.	236/127	134/90
31	25 F.	A.	No	U.	200/110	150/90
32	36 F.	A.	No	U.	220/140	240/150
33	58 F.	A.	No	U.	215/125	173/102
34	39 F.	A.	No	P.U.	185/115	125/80
35	63 M.	A.	No	U.	203/123	150/95
36	42 M.	A.	No	U.	260/160	163/114
37	48 M.	A.	No	U.	180/113	205/130
38	59 F.	A.	No	S.T.	220/140	148/99
39	56 F.	M.N.H.	Yes	S.T.	214/125	204/123
40	52 F.	M.N.H.	Yes	S.T.	168/103	161/101
41	57 M.	M.N.H.	Yes	S.T.	240/130	158/104
42	48 M.	M.N.H.	Yes	U.	200/120	134/99
43	49 F.	M.N.H.	Yes	U.	220/120	195/135
44	62 F.	M.N.H.	Yes	S.T.	193/121	162/99
45	53 F.	M.N.H.	Yes	T.	260/145	182/108
46	41 F.	H.	Yes	T.	260/160	230/145
47	46 F.	N.A.	Yes	U.	235/140	205/126
48	35 F.	N.A.	Yes	S.T.	210/130	164/115
49	35 M.	D.D.	Yes	P.U.	180/121	159/111
50	39 M.	D.D.	Yes	U.	192/124	125/90

A = Adrenocortical adenoma. M.N.H. = Hyperplasia of zona glomerulosa with micro-nodules. H. = Hyperplasia of zona glomerulosa. N.A. = No abnormality D.D. = diagnostic doubt—that is, some histological features of adenoma others of nodule. T = Total adrenalectomy. S.T. = Subtotal adrenalectomy. U. = Unilateral adrenalectomy. P.U. = Partial unilateral adrenalectomy. U. + A = Removal of one adrenal and pedunculated adenoma from opposite gland.

TABLE II—Comparison of Variables before and after Adrenal Surgery (with paired T-Test). Values are expressed as Means ± S.E.

	Before Treatment		After Operation		No. of Pairs	t	P
Blood Pressure (mm Hg):							
Systolic	206	± 3.89	157	± 3.93	50	12.57	<0.001
Diastolic	125	± 1.98	103	± 2.47	50	9.76	<0.001
Plasma Na (mEq/l.)	142.2	± 0.44	138.8	± 0.36	43	6.39	<0.001
Plasma K (mEq/l.)	2.9	± 0.09	4.3	± 0.06	43	11.08	<0.001
Plasma Total CO ₂	29.8	± 0.57	24.4	± 0.45	39	6.67	<0.001
Blood urea (mg/100 ml)	31.9	± 1.25	41.7	± 1.79	40	6.32	<0.001
Plasma renin (U/l.)	4.2	± 0.34	11.7	± 1.01	33	6.72	<0.001
Plasma angiotensin II (pg/ml)	5.1	± 0.90	23.9	± 0.85	2	375.0	<0.01
Plasma aldosterone (ng/100 ml)	44.8	± 8.6	9.2	± 1.1	27	5.84	<0.001
NaE (mEq)	3058	± 116.1	2679	± 110.2	15	5.03	<0.001
NaE (mEq/kg body weight)	47.9	± 1.5	40.7	± 1.2	14	4.92	<0.001
KE (mEq)	2374	± 117.9	2625	± 141.4	14	1.74	N.S.
KE (mEq/kg body weight)	36.4	± 2.13	38.9	± 0.83	14	1.15	N.S.
Total body water (l)	37.2	± 2.50	36.7	± 2.58	9	0.44	N.S.
Extracellular fluid (l.)	18.3	± 1.05	16.0	± 1.38	8	2.13	N.S.
Plasma volume (l.)	2.9	± 0.22	2.7	± 0.24	8	1.18	N.S.

NaE = Exchangeable sodium
KE = Exchangeable potassium

as a whole (fig. 1; table 2). The mean diastolic pressure after operation was less than 100 mm Hg in 27 patients, 24 of whom had an adenoma, and the readings were "normal" in 22 patients, 19 of whom had an adenoma.

Because of the difficulties in classifying adrenal lesions^{13 16} further comparison of the postoperative blood pressures in the tumour and non-tumour groups was confined to those 40 patients in whom adrenal tissue was available for independent histological review.

FIG. 1—Blood pressure (mean ± 1 S.E.) before and after adrenal surgery in 50 patients. Number of patients included in the various analyses, reading from left to right, were 50; 18; 36; 27; 26; 18; 13; 6; and 5. Fall at 3-5 weeks was highly significant (systolic $t=5.39$, $P<0.001$; diastolic $t=4.24$, $P<0.001$).

FIG. 2—Blood pressure (mean ± I.S.E.) before and after operation. Reading from left to right, number of patients included in reviews in adenoma group, and non-adenoma group, respectively, were 28 and 10, 8 and 7, 20 and 9, 15 and 7, 12 and 5, 11 and 4, 7 and 3, and 4 and 2.

The postoperative blood pressure readings in the adenoma group were usually lower than in those patients without tumour (fig. 2). Such a simple comparison, however, is not strictly valid, since though the differences were not significant, the mean blood pressure ($\pm$ S.E.) before operation was lower in the 28 patients with an adenoma than in the 12 without (adenoma group $202/123 \pm 5/2$; non-tumour group $220/129 \pm 9/5$; systolic $t=1.89$, $P<0.1$, diastolic $t=1.27$, $P<0.3$).

When the fall in systolic blood pressure after the operation was studied (fig. 2) a significant change was noted in both groups (adenoma $t=3.99$, $P<0.001$; non-adenoma $t=2.62$, $P<0.02$ at the first review). In the adenoma group there was also a significant fall in diastolic pressure about one month after operation ($t=2.97$, $P<0.01$), but the mean fall in diastolic pressure in the non-adenoma group was not significant either at the first or second postoperative reviews. The fall in diastolic blood pressure in the non-adenoma patients became significant, however, in the subsequent reviews and also when the all postoperative readings in this group were pooled ($P<0.02$, <0.05 , <0.05 at the third, fourth, and fifth reviews respectively and <0.02 for the whole group; fig. 2). The mean postoperative fall in blood pressure in the adenoma group was 53/26 mm Hg and in the non-tumour group 41/14 mm Hg. The difference between these changes in systolic pressure in the two groups was not very great ($t=1.36$, $P>0.1$), but the fall in diastolic pressure was significantly greater in the adenoma group ($t=2.31$, $P<0.05$).

BIOCHEMICAL CHANGES

After adrenal surgery there was a highly significant fall in plasma sodium, total CO₂, and aldosterone concentrations and a highly significant rise in plasma potassium, blood urea, and plasma renin concentration (table II).

Plasma angiotensin II concentration was measured before and after operation in two patients only and in each case a considerable increase was observed (6.0 to 24.7 pg/ml and 4.2 to 23.0 pg/ml). After surgery there was a significant decrease in exchangeable sodium with a smaller increase in exchangeable potassium. In fewer patients total body water and the extracellular and plasma volumes were measured, and the changes were not significant (table II).

COMPARISON OF SPIRONOLACTONE AND SURGERY

Blood pressure during spironolactone therapy and after subsequent operation was compared in 32 patients. Though the blood pressures during spironolactone therapy were usually slightly lower than the postoperative values there was a significant correlation between the fall in blood pressure with each treatment (systolic $r=+0.66$, $P<0.001$; diastolic $r=0.54$, $P<0.01$). In general the biochemical changes and the alterations in body composition were greater during spironolactone therapy than after operation.¹¹

OPERATIVE MORTALITY

Two patients who underwent adrenal surgery died without leaving hospital. Subtotal adrenalectomy had been undertaken in each case since no tumour was found. One of these patients died 48 hours after operation with large intraperitoneal and retroperitoneal haemorrhages. The second patient had a myocardial infarction 24 hours after operation; seven days later a pulmonary embolus occurred and he was treated with anticoagulants. A retroperitoneal haematoma was subsequently diagnosed; this became infected and he died six weeks later after another myocardial infarction.

Discussion

SURGICAL ASPECTS

Despite increasing experience of adrenal surgery in this syndrome debate continues on the choice of the operative approach. For the posterior approach (as used routinely by one of us, K.O.), the patient is supine with the break of the table flexed at the level of the lower ribs. The incision is then made through the line of the 11th rib, the pleura retracted upwards and the adrenal exposed after dividing a few fibres of the diaphragm. This approach gives extremely good access. Despite recent advances in preoperative localizing techniques, bilateral exposure is necessary in some patients and simultaneous inspection can be done easily by making a second similar incision.

The anterior approach (as used routinely by A.W.K.) is through a transverse incision placed 5-6 cm above the umbilicus and extending to both flanks. The left adrenal is exposed after mobilizing the spleen and the right gland is readily brought into view by incising the overlying peritoneum while the kidney is held downwards. When the preoperative localization is uncertain the left adrenal is exposed first (because this gland harbours an adenoma more often than the right) and mobilized until its thickness can be palpated easily. If an adenoma is not found the right gland is then examined in a similar fashion. If a tumour is not found in either gland it has been our custom to excise the left adrenal and await the pathologist's immediate report before proceeding to the opposite gland. The main advantage of the anterior approach is that it permits examination of both adrenals in all patients; the main disadvantages are that the spleen is occasionally damaged and that removal of the right gland can be difficult in fat patients.

The amount of adrenal tissue which should be removed at operation in patients without tumour is still not clearly established. Total adrenalectomy removes the site of aldosterone production, but the patient is thereafter dependent on replacement therapy. By preserving a remnant of one gland we hope to avoid the need for replacement therapy and at the same time cure the aldosterone excess; corticosteroid replacement therapy was not necessary in any of the five patients so treated in the present series. Recurrence of hyperaldosteronism after extensive adrenal surgery, however, has been reported.⁵⁻¹⁷ It seems reasonable to suppose that the more adrenal tissue preserved at operation the greater the chance of such recurrence. Less extensive adrenal surgery also seems to lead to a smaller fall in blood pressure. We suggest that if surgery is to be worthwhile in such patients removal of one adrenal and at least 7/8ths of the other should be undertaken.

BLOOD PRESSURE AFTER ADRENAL SURGERY

Removal of an aldosterone-producing adenoma is said to reduce blood pressure to arbitrary "normal" levels in most patients. The results reported here indicate that excision of an adenoma restored blood pressure to the strictly normal range in only 44% of patients.

Other groups have reported that the blood pressure after

operation in patients without adrenal tumours remains higher than the postoperative readings in cases with an adrenocortical adenoma.⁵⁻⁷ To some extent this was true in our own study, but this could have been due, in part at least, to the higher preoperative blood pressures in the non-tumour cases. Biglieri *et al.*⁷ reported that in cases of this type the more radical the adrenal surgery the greater was the postoperative blood pressure fall. Our own results and the data of Baer *et al.*⁶ show a similar trend but even in this group of patients severe hypertension may continue after total adrenalectomy (see table I).

LONG TERM MANAGEMENT

In patients in whom hypertension, aldosterone excess, and low plasma renin concentration are associated with an adrenocortical adenoma and in whom preoperative spironolactone has resulted in a fall of blood pressure to normal or near-normal levels we suggest that removal of the tumour-bearing gland is usually the treatment of choice. When surgery is refused or contraindicated, however, long-term treatment with spironolactone is an acceptable alternative. Present evidence suggests that when there is an unsatisfactory hypotensive response to spironolactone in adequate dosage (300-400 mg/day) the likelihood of a significantly greater fall in blood pressure after adrenal surgery is small.¹¹ Irrespective of the effect on blood pressure electrolyte abnormalities are invariably corrected either with spironolactone or appropriate adrenal surgery. Similar results were reported recently using the potassium-sparing diuretic amiloride;¹⁸ this therapy seems to be valuable, particularly when spironolactone causes troublesome side effects.

In those patients in whom no adrenocortical tumour is found adrenal surgery must necessarily be more extensive and carry the alternative risks of adrenal insufficiency or recurrence of adrenal hyperplasia. Long-term treatment with spironolactone again offers an acceptable alternative and is probably the treatment of choice for many of these patients.

These conclusions emphasize the importance of preoperatively differentiating tumour and non-tumour patients with low-renin hyperaldosteronism. The computer-assisted technique of quadric analysis has so far been a valuable aid in making this distinction,¹³⁻¹⁹ and adrenal venography and aldosterone measurements on adrenal vein plasma are also useful.²⁰⁻²² The results obtained by scintillation scanning of the adrenal glands are likewise encouraging.²³

References

- Conn, J. W., *Harvey Lectures*, 1968, 62, 257.
- Brown, J. J., *et al.*, *Lancet*, 1968, 2, 55.
- Conn, J. W., Knopf, R. F., and Nesbitt, R. M., *American Journal of Surgery*, 1964, 107, 159.
- Rhamey, R. K., *et al.*, *Annals of Surgery*, 1968, 107, 718.
- George, J. M., Wright, L., Bell, N. H., and Bartter, F. C., *American Journal of Medicine*, 1970, 48, 343.
- Baer, L., *et al.*, *Circulation Research*, 1970, 26, and 27, Suppl. 1, p. 203.
- Biglieri, E. G., *et al.*, *Circulation Research*, 1970, 26 and 27, Suppl. 1, p. 195.
- Katz, F. H., *Annals of Internal Medicine*, 1967, 67, 1035.
- Laragh, J. H., Ledingham, J. G. G., and Sommers, S. C., *Transactions of the Association of American Physicians*, 1967, 80, 168.
- Spark, R. F., and Melby, J. C., *Annals of Internal Medicine*, 1968, 69, 685.
- Brown, J. J., *et al.*, *British Medical Journal*, 1972, 2, 729.
- Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C., *Clinical Science*, 1954, 13, 13.
- Ferriss, J. B., *et al.*, *Lancet*, 1970, 2, 995.
- Davies, D. L., and Robertson, J. W. K., *Metabolism*, 1973, 22, 133.
- Brown, J. J., *et al.*, *British Medical Journal*, 1970, 2, 18.
- Neville, A. M., and Symington, T., *Cancer*, 1966, 19, 1854.
- Kawasaki, T., Omae, T., Tanaka, K., Matsunaga, M., and Emoto, K., *Journal of Clinical Endocrinology*, 1971, 33, 474.
- Kremer, D., *et al.*, *Clinical Science and Molecular Medicine*, 1973, 45, 213s.
- Aitchison, J., *et al.*, *American Heart Journal*, 1971, 82, 660.
- Melby, J. C., Spark, R. F., Dale, S. L., Egdahl, R. H., and Kahn, P. C., *New England Journal of Medicine*, 1967, 277, 1050.
- Kahn, P. C., Kelleher, M. D., Egdahl, R. H., and Melby, J. C., *Radiology*, 1971, 101, 71.
- Davidson, J. K., *et al.*, *Scottish Medical Journal*, 1972, 17, 330.
- Conn, J. W., *et al.*, *Archives of Internal Medicine*, 1972, 129, 417.