Physiologic and Surgical Problems in the Management of Primary Aldosteronism *

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IN 1955 Conn described the syndrome of hypertension, hypokalemia, and metabolic alkalosis associated with excessive production of a mineral-regulating steroid of adrenal origin.[8] In an addendum to his original paper he reported the surgical removal of an adrenal tumor and later reports described complete regression of all evidence of the disease.[9] Subsequently, a number of other cases which had been reported at about the same time as resulting from "potassium losing nephritis" or other obscure situations involving excessive postassium excretion were recognized probably to be on the basis of this highly specific type of hyperadrenalism [14, 16, 44, 33, 34] The possibility of the existence of such a syndrome had been considered by investigators and clinicians for many years. That the adrenal secreted three groups of hormones concerned respectively with androgenic function, protein-carbohydrate metabolism, and mineral regulation had been generally accepted. The work of Greep and his colleagues indicated moreover that the three groups of hormones had their origin in separate portions of the adrenal cortex and that the release of salt-regulating substances could be invoked by a mechanism which was independent of that by which the other two were controlled.[11, 22] In 1937, McQuarrie showed hypokalemic alkalosis to be an occasional occurrence in cases of the Cushing syndrome, from which finding alone one might expect that eventually instances of pure electrolyte disturbances would be found without the physical changes which are commonly associated with other types of hyperadrenalism.[35] The recognition of this entity, however, did not take place until after the isolation of the adrenal mineral-regulating steroid which is now known as aldosterone.[47] Since that time adequate methods for the quantitative measurement of this extraordinarily potent substance have been developed. Whereas more than 30 cases have been reported since Conn's paper, more have obviously been treated and many are in the process of being reported. Patients with this disease present themselves usually with a history of hypertension of considerable duration in addition to which they commonly complain either of muscular weakness or of paralysis of an intermittent or recurrent nature. In association with metabolic alkalosis, the carpal and pedal spasm of tetany is frequently seen and Trousseau and Chvostek signs may be elicited. Interesting and strikingly consistent findings are polyuria and polydipsia, phenomena which are in consonance with older observations that chronic administration of mineralocorticoids results

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in a "diabetes-insipidus-like" picture.[18, 43] The usual aldosteronism complex does not include edema though a syndrome of idiopathic edema with excessive aldosterone production has been observed.[32]

Of the cases which have been reported, the great majority have been caused by benign cortical adenomata.[1, 5, 7, 9, 10, 13, 19, 23, 24, 37, 42] Less frequently, the syndrome has been related to non-neoplastic hyperfunction with or without gross or microscopic evidence of hyperplasia.[2, 25, 26, 36, 49, 51] In most instances, including that discussed here, these patients have been children or young adults. The question of how such individuals without tumors are to be managed surgically is one of considerable importance. Adrenal carcinoma seems to be the rarest cause.[4, 20] In one such reported case, a malignant tumor of one adrenal was completely removed, but the patient eventually succumbed to metastases.[20] In a second a massive carcinoma could not be removed.[4] A third case of carcinoma is among those reported below and illustrates as do the previously recorded cases, the highly malignant character of these tumors.

It is now apparent that increasing numbers of patients with aldosteronism will require surgical exploration, and problems of exact diagnosis, preoperative care and surgical methods present themselves. The studies which we have carried out on five such patients, four of whom have undergone surgery, are reported below as they pertain to various aspects of the altered physiology and surgical problems in this disease. Detailed clinical descriptions have been omitted.

Case Reports

Patient 1. J. B. (UH #756239), a 46-year-old woman, was admitted for the sixth time on September 17, 1956 for hypertension of 15 years' duration with hemiparesis and a history of three cerebral vascular catastrophes. She had undergone a bilateral thoracoabdominal sympathectomy. Her complaints included weakness, nocturia, and headaches. Blood pressure was 230/126; CO_2: 38 mEq/L; Cl: 100; Na: 148; K: 2.5; urine pH was 7 to 8. Exploration was carried out on October 25, 1956. On inspection, both adrenals were normal in appearance. With the initial impression that there was no tumor, the right adrenal was excised. On mobilization of the left gland, a tumor about 1 cm. in diameter was palpated. This was removed and about ⅓ of the left adrenal left in place. Postoperatively she did poorly and it was difficult to maintain a normal circulatory status despite very large amounts of hydrocortisone, 9-alpha-fluorohydrocortisone and vasopressor agents. On the next day she suffered cardiac arrest, was resusscitated, but succumbed on the second postoperative day.

Patient 2. A. J. P. (UH #918221), an 18-year-old girl, was admitted because of hypertension noted on a routine college physical examination. There was an 8-year history of muscle cramps, weakness and recently tetany in addition to polydipsia and polyuria. Blood pressure was 210/140. Trousseau sign was present. CO_2 was 42 mEq/L; K: 20; Cl: 93, Na: 151; urine pH was 7.0. After extensive evaluation of electrolyte balance on various diets, she was given a period of high potassium intake and subjected to surgical exploration on November 4, 1957. Since no tumor was found the right adrenal and ⅔ of the left were removed. Eventual recovery was complete and adrenal replacement has not been required. An extensive description of the clinical findings and the above-mentioned balance studied has been made and will not be included in detail here.[38]

Patient 3. J. P. (UH #928904), a 38-year-old woman, was admitted to the University Hospitals on June 3, 1958 with a history of hypertension of 2½ years' duration, 2 episodes of tetany, polyuria and nocturia and muscular weakness occurring predominantly in the morning. A year previously she was hospitalized for pneumonia and a large pneumotocoele was present in the right lung. Admission blood pressure was 200/130. Trousseau sign was present, serum sodium was 145 mEq/L; K: 2.1; CO_2: 35; urine pH: 6–7; salivary Na/K ratio: 0.21.

On admission the right kidney was palpable and 10 days later she developed right flank pain and a fever of 101°. Following this the mass in the flank was more prominent. Intravenous urogram showed a depressed right kidney. This clinical picture suggested hemorrhage into a suprarenal mass, and steroid excretion studies which are discussed below were also suggestive of a sudden change in the status of a functioning tumor.

After a period of potassium loading, exploration was carried out through a right thoracoabdominal incision and a 583 Gm. tumor removed which was adherent to the liver and invaded the inferior vena

cava, a portion of which was removed. The tumor was a carcinoma of the right adrenal which contained some blood and necrotic material. The postoperative course was stormy and blood pressure fell requiring use of hydrocortisone and vasopressor substances. She developed a lung abscess and evidence of gram-negative bacteremic shock but recovered and was discharged on August 23, 1958 with blood pressure of 144/110 and normal blood chemistry. Blood pressure gradually fell to 128/90, but subsequently rose over ensuing months to 190/125. Pulmonary metastases became apparent. She was re-admitted for study on several occasions. At one point (February 1959) metabolic alkalosis also recurred with CO_2: 36 mEq/L; K: 3.4. Metastasis to the thoracic spine became manifest.

Patient 4. V. C. (St. Barnabas #3816–1957), a 43-year-old woman, was first seen in August 1958, with a 3-month history of hypertension. She complained of "tiredness and tightening in the hand muscles" which had interferred with knitting and of urinary frequency. On examination, blood pressure was 225/138, there were grade II arteriolar retinal changes and Trousseau sign was present. EKG showed left axis deviation and ST segment changes suggestive of potassium deficiency. CO_2 combining power was 29.6–32.8 milliequivalents per liter, chloride: 107–110; Na: 150–156; K: 2.4–2.7; urine pH: 5.5. After preoperative potassium loading she was operated upon and a 1.8 cm. adenoma of the left adrenal cortex removed. Postoperatively she did well and electrolyte balance has been normal though hypertension of 165–170/110 has persisted.

Patient 5.* A 44-year-old obese woman was seen in September 1957, with a history of difficulty in swallowing, severe weakness and difficulty in speaking above a whisper. Blood pressure was normal: 120/90 but sodium was 154 mEq/L; K: 3.1; CO_2: 43 mEq/L; Cl: 90; urine pH was 6.0. This patient improved progressively on potassium supplementation and despite clearly elevated aldosteronism excretion values (below) has declined surgical exploration.

Methods

Urinary 17-ketosteroids were measured colorimetrically employing the usual m-dinitrobenzene reaction. The total 17,21-dihydroxy-20-ketosteroids in the urine were measured following enzymatic hydrolysis with glucuronidase by modification of the method of Silber and Porter and electrolytes were determined by common laboratory methods.[46]

Aldosterone in Patient #1 was measured by biological assay following chloroform extraction and chromatographic separation; a method which was previously used in this laboratory before a purely chemical method was developed.[6, 52] In the remaining patients, the determination of aldosterone 3-oxo-conjugate was carried out by the following technique: Twenty-four hour urine specimens were adjusted to pH 1.5 with concentrated HCl, extracted with 0.1 volume of $CHCl_3$ and extracted again after standing 24 hours at 25° C., four times with 0.1 volume of $CHCl_3$. After the extracts were combined and washed with cold .1 N NaOH and cold distilled water the material was brought to dryness *in vacuo* at 40° C. The residue was subjected to chromatography for 36 hours in the prophylene-glycol toluene system [3] following which the region of the chromatogram which included a cortisone standard and a section of paper 10 cm. below it was eluted with 95% ethanol. This in turn was divided into aliquots of one-tenth and nine-tenths and chromatographed in the iso-öctane-tertiary butanol-water (E_2B) system.[15] Color reactions were carried out by dipping in a blue tetrazolium-NaOH solution for 25 minutes at 80° and examined under ultraviolet light as described by Neher and Wettstein.[41] Aldosterone being the only substance between the starting point and the cortisol standard which gives both blue tetrazolium reduction and soda fluorescence, the identity of the compound was assumed if these two reactions gave products of equal intensity. A detailed analysis of the method has been presented elsewhere.[39]

Since the clinical association of hypertension and hypokalemic alkalosis is not restricted to aldosteronism, a reliable deter-

* This patient was originally studied by Dr. Ernest Reiner of Tampa, Florida, to whom we are indebted for the opportunity to carry out the urinary steroid studies which are herein reported.

TABLE 1. *Major Steroid Components*

Patient	Diagnosis	Aldosterone (mcg./24 hr.)	17-Hydroxy-corticoids (mg./24 hr.)	17-Ketosteroids (mg./24 hr.)
1. J. B.	Adenoma	720 mcg. DCA (see text)	7.8	5.2– 5.6
2. A. P.	Hyperplasia	22–23	6.0	9.7– 9.8
3. J. P.	Adrenal carcinoma	17–180	4.7–5.0	29.2–37.5
4. V. C.	Adenoma	8	6.1–6.7	7.4– 8.4
5. K. S.	Undetermined	60	10.6	2.0

mination for aldosterone is extremely important. The method described here in which initial separation is carried out by chromatographic methods also allows identification of a large number of other steroids which may be of considerable theoretical interest.

Steroid Excretion Patterns

Normal output of aldosterone 3-oxo-conjugate (or more properly perhaps: "acid labile conjugate") by the method described is around 2–5 mcg. per 24 hours or less, and rarely exceeds 8 mcg. in the absence of adrenal stimulation. The first patient with a small adenoma was studied by the older method in which activity of the refined extract was compared to desoxycorticosterone. The value given in Table 1 corresponds to about 13 mcg. of aldosterone, but the material was obtained by enzymatic hydrolysis which yields only one-fourth to one-third the amount of active hormone as the acid method of hydrolysis now used. This would, therefore, represent around 40 mcg. of aldosterone if analyzed by the present technic. The excretion of the major steroid groups in this and the other patients is shown in Table 1.

A significant finding was that patients with aldosteronism could excrete variable amounts of aldosterone from day to day, so that, as they are followed, a few values may fall within the normal range. It is important therefore, to carry out multiple determinations.

On inspection of ultraviolet prints of the chromatograms prepared from the urinary extracts of patients suffering from this disease there appears to be a rather characteristic pattern which can be recognized even before quantitative determinations are completed. For some reason the large number of commonly seen metabolites other than aldosterone appear to be reduced in amount and aldosterone stands out sharply. Seventeen-hydroxy-corticoids were normal in these patients and 17-ketosteroids were normal except in the patient with adrenal carcinoma who excreted 30 mcg. per 24 hours. This confirms the general impression that malignant tumors are more likely to secrete steroids of multiple functional categories than benign ones.

The tetrahydro-metabolite of Substance S (11-desoxy-17-hydroxy-corticosterone) was determined in the carcinoma patient and found to be less than 20 mcg. per 24 hours —a finding which is in contrast to that reported in other types of adrenal carcinoma in which the production of substance S is commonly increased.[29]

Responsiveness of Adrenal Steroids

A matter of current interest pertains to the mechanisms by which the adrenal secretion of aldosterone is regulated. Sodium restriction is a potent stimulus to aldosterone production [31] and a great deal of investigation has delineated the importance of circulating fluid volume in this connec-

tion.[28] The role of potassium ion in the control of aldosterone secretion has also been studied and there has been some question as to whether potassium acts directly on the adrenal or indirectly by production of negative sodium balance.[27, 30, 48] Recent evidence for a direct effect of potassium on aldosterone output comes from experiments in this laboratory showing that elevation of serum potassium causes an increased aldosterone concentration in adrenal vein blood of experimental animals.[40] Farrell has shown that centers in the diencephalon are involved in the mediation of the circulating-volume stimulus to the release of this hormone and that this effect is probably mediated through a humoral trophic substance produced in these areas.[17] Although the role of hypophyseal corticotrophic activity in this regard has been debated it is now agreed that, even though aldosterone output can be mobilized in the absence of the pituitary gland, administered ACTH does stimulate aldosterone release.[17] In the light of these known factors, it was of great interest to study the response of patients with abnormally high aldosterone production to various stimuli. The important question of autonomy of hormone production in aldosteronism has been considered by others and much remains to be learned about it.[1, 25]

Figure 1 illustrates the response of aldosterone and the other steroids to a two-day course in which 40 mg. ACTH were given intravenously over an eight-hour period each day to the 18-year-old patient with adrenal hyperplasia. Aldosterone excretion rose from 23 to 60 mcg. with concomitant elevations of 17-hydroxy-corticoids and 17-ketosteroids. The second part of Figure 1 shows a similar study done after five-sixths of the adrenal tissue had been removed. It will be noted that, although she is now entirely able to maintain electrolyte balance without replacement therapy, aldosterone output is extremely low and does not respond to ACTH stimulation. Figure 2 shows a similar experiment carried out in the patient with adrenal carcinoma. The very striking increase in aldosterone excretion from 17 to 173 mcg./24 hours was somewhat unexpected. It should be mentioned that the level in this patient immediately preceding ACTH administration was low compared to the extremely high output at the time of admission. The subsequent fall was apparently associated with hemorrhage and necrosis in the tumor which occurred a few days after the initial determinations were run. Since the output fell again after ACTH, it seems valid to ascribe the response to corticotrophic stimulation. Figure 2 also shows the subsequent course of steroid excretion in this patient with adrenal carcinoma. Although she developed evidence of extensive recurrence of tumor associated with unsustained reappearance of some hypertension and alkalosis, aldosterone excretion has not returned to extraordinarily high levels. Seventeen-hydroxy-corticoid, and 17-ketosteroid levels have risen moderately since operation. Measurement of aldosterone has become increasingly difficult because of the appearance in the urine of large amounts of interfering substances and in an attempt to surmount these difficulties additional stages of chromatography have been utilized. Such determinations done in February indicated that she could still respond to ACTH by a several-fold increase in aldosterone output. This was less apparent in March, during which time patient was under treatment with Amphenone B.

In Figure 3 are depicted the aldosterone excretion values on three patients (#2, #4, #3) before and during periods of high potassium intake. In the patient with hyperplasia and the one with adenoma, there was a significant increase in output under the latter circumstance. Of particular interest is the response of the adenoma patient (V. C.) since her basal value was relatively

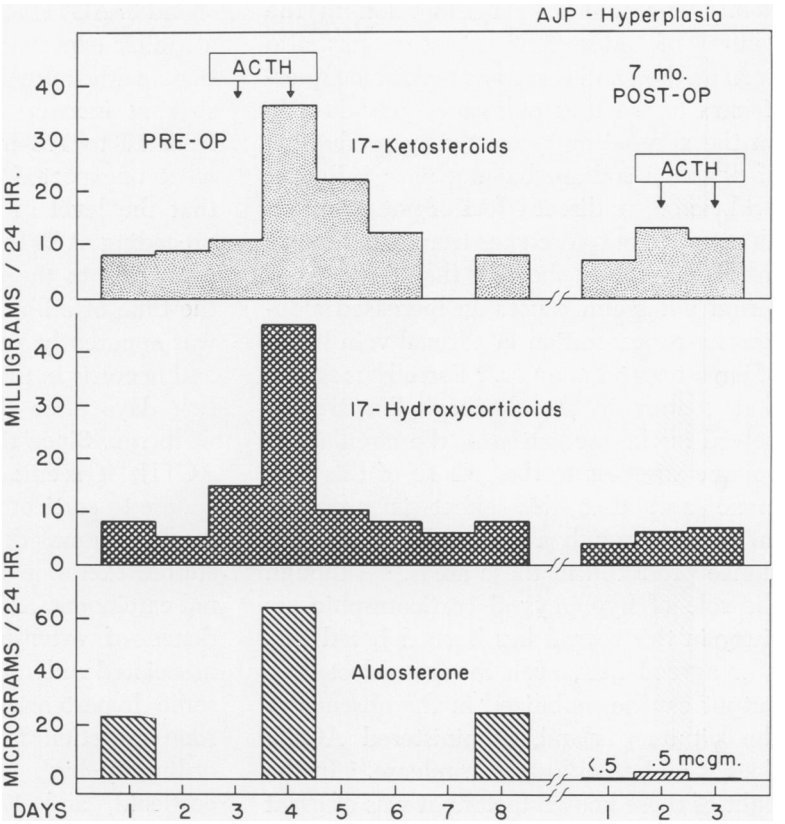

FIG. 1. Steroid excretion and response to ACTH in Patient #2 before subtotal adrenalectomy and 7 months later.

low and the experiment suggests that moderate elevation of potassium intake may put patients with marginal aldosterone excretion into the clearly diagnostic range. There was no evidence for such a response in the patient with carcinoma.

Preoperative Preparation with Potassium

In the first patient who was operated upon in 1956 an adequate effort was not made to restore the potassium deficit prior to operation and it was felt that this deficiency played an important part in the postoperative difficulties and ensuing death. Since then we have become convinced from subsequent patients and the experience of others that it is always possible and extremely important to effect potassium balance in the presence of aldosteronism even though further mobilization of aldosterone may be stimulated. Figure 4 shows portions of extended balance studies which were carried out on Patients 2 and 3. They illustrate the production of positive potassium balance associated with immediate reduction of CO_2 combining power and elevation of serum potassium with intakes in the neighborhood of 300 milliequivalents daily. It is apparent that failure to do this constitutes an unnecessary surgical hazard.

Anesthesia and Technical Considerations

As has been mentioned, the earliest patient succumbed following surgery. She had previously undergone a thoracolumbar sympathectomy. Pentothal-curare anesthesia was utilized and K+ repletion had not been adequate. Respiratory paralysis and irreversible shock in this individual emphasized the synergistic effect of potassium deficiency and curare-like compounds and suggested that muscle relaxants should not

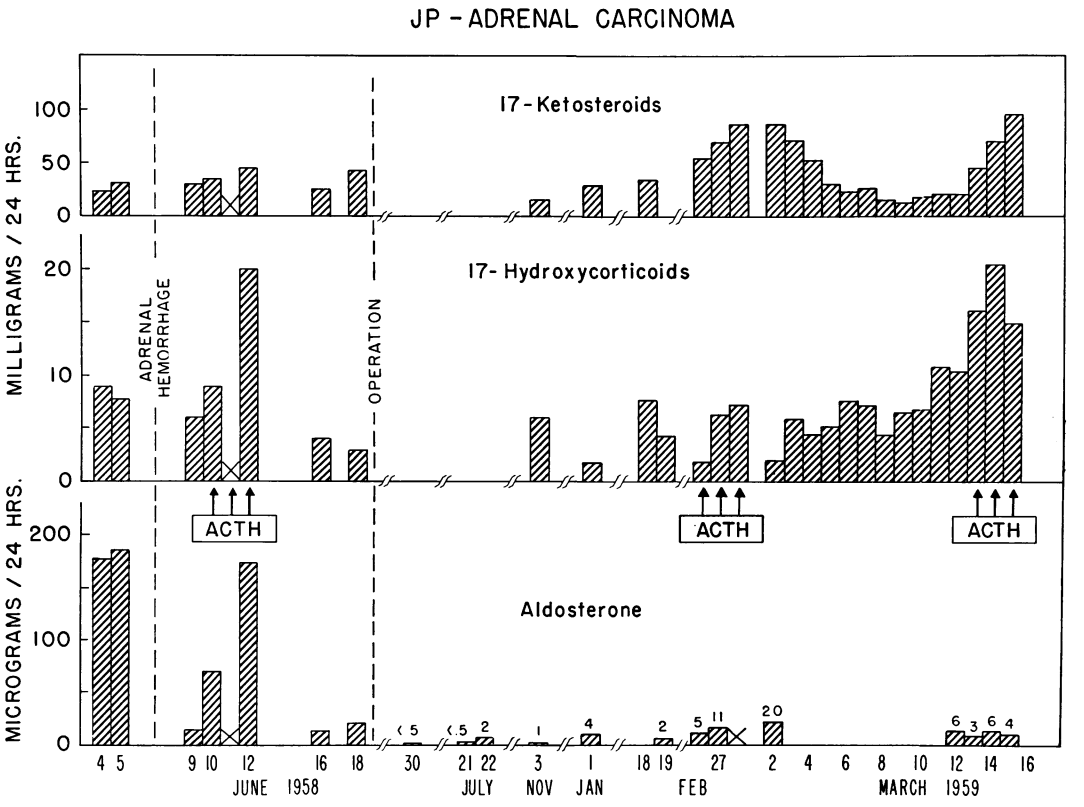

FIG. 2. Steroid excretion and response to ACTH in Patient #3. Aldosterone was extremely high (170–180 mcg./24 hr.) on admission. After episode of adrenal hemorrhage this fell to much lower but still abnormally high values (17 mcg./24 hr.). Preoperatively aldosterone responded vigorously to ACTH. After removal of malignant tumor aldosterone values remained low despite clinical evidence of recurrence. In February, ACTH again produced aldosterone response.

be used. We feel that this is an important precaution even though others have used these agents without apparent ill effects.[21]

Cortisone, 100 mg. has been given the night before and the day of surgery although it is by no means clear that this would be necessary simply for the removal of a functioning tumor. The availability postoperatively of a potent synthetic mineralocorticoid such as 9-α-fluoro-hydrocortisone would seem to be a valuable precaution.

Aldosterone producing tumors may be very small and there is no evidence for the type of contralateral atrophy which is seen in Cushing's disease. For this reason, a transabdominal approach is to be recommended with thorough exposure of both adrenals before any excision is attempted. In the case of adrenal carcinoma in which a very large tumor had been demonstrated preoperatively a right thoracoabdominal approach was used. This greatly facilitated the extirpation of an extensive malignant growth which was adherent to the liver and vena cava and in close relationship to the hepatic veins.

Management of Aldosteronism Without Adrenal Tumors

It is difficult at the present time to reach a final conclusion regarding the optimum surgical procedure in patients in whom an adrenal tumor is not found, a circumstance which is apparently much more likely to be seen in patients under 21 years of age. In a

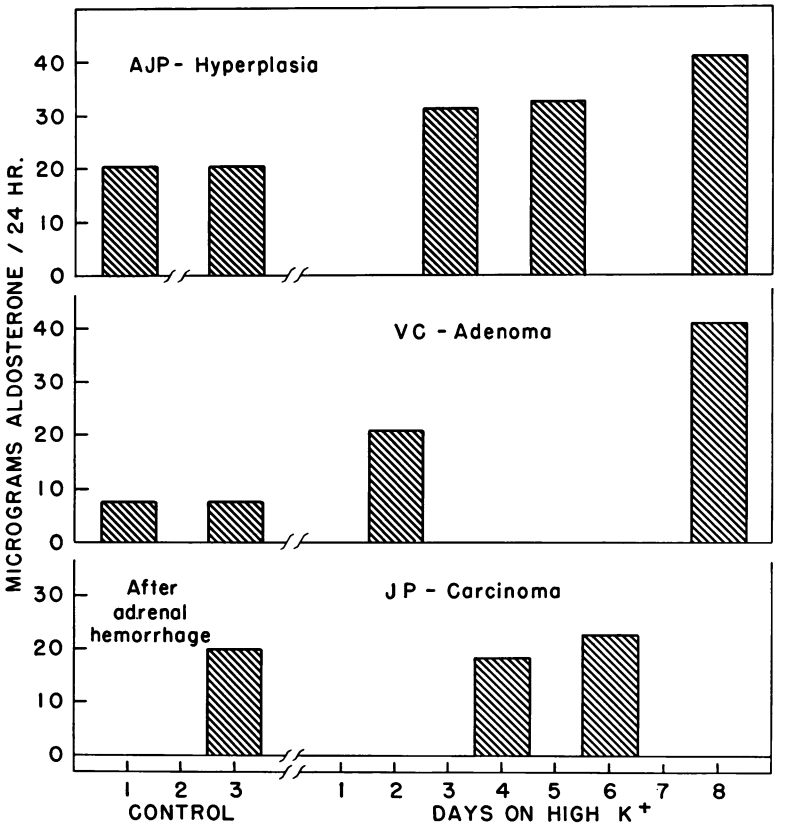

FIG. 3. Aldosterone output in three patients before and during potassium loading.

case reported by Bartter the right adrenal and four-fifths of the left were removed with a good result.[26] In the patient of Holten *et al.* only one gland was removed following which the electrolyte pattern returned to normal but hypertension persisted.[26] In a similar situation van Buchem *et al.* recorded a satisfactory result following removal of one adrenal and nine-tenths of the other but replacement medication was required.[50] Similarly in a child studied by Mellinger, bilateral total adrenalectomy was carried out with excellent control of the hypertension and electrolyte disturbance but replacement steroids were obviously necessary.[36] In Case 2 presented here, removal of one adrenal and two-thirds of the other produced complete clinical remission without the necessity for adrenal replacement. Until evidence appears that the syndrome can recur following such a procedure, subtotal adrenalectomy would appear to be adequate.

What Is Not Aldosteronism?

Since hypertension is common and there are other mechanisms which can occasionally be responsible for hypokalemic alkalosis, an erroneous diagnosis of aldosteronism is sometimes made. This is illustrated by 2 cases in whom the opportunity was afforded to carry out steroid studies.

The first such case (M. M., UH #930612) was a 57-year-old woman with known hypertension (220/120) for 6 months and symptoms of "tingling" in her face and extremities. Carbon dioxide combining power was 41 mEq/L; K: 2.6; Na: 136; Cl: 81. Urine pH was 7.0 and salivary Na/K was (less than 10)/37. Aldosteronism was strongly suspected, but the aldosterone excretion was only 2 micrograms per 24 hours.

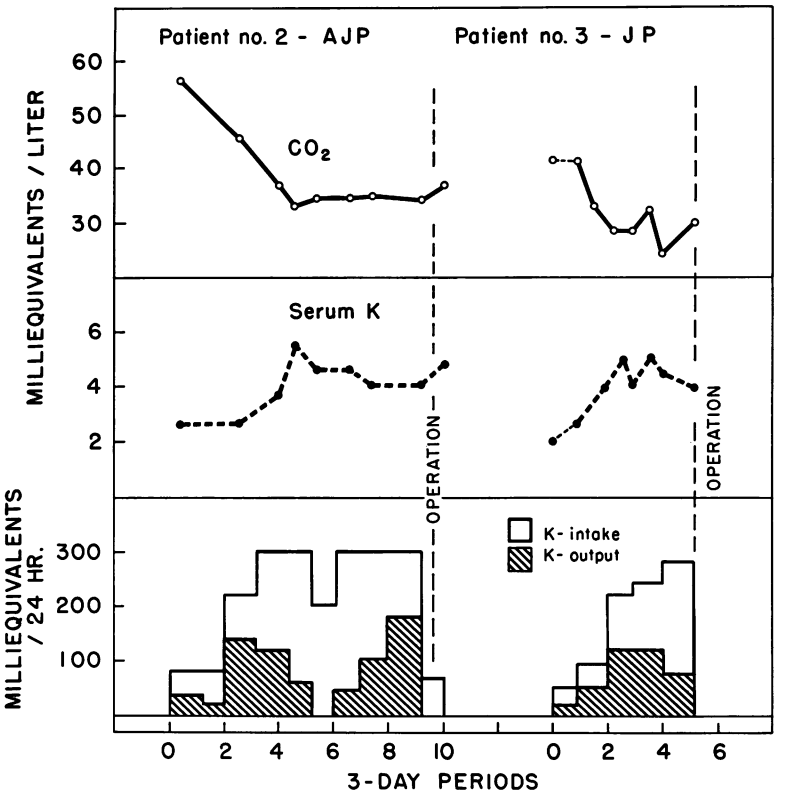

FIG. 4. Response of serum potassium, CO_2 and potassium balance in two patients during preoperative preparations on high K intake.

After this finding was made a very thorough investigation revealed that she had been treated with chlorothiazide as a diuretic, a drug which she initially denied having taken. Her subsequent course has indicated that this in all probability was the cause of her hypokalemic alkalosis and it is well recognized that this diuretic causes profound potassium loss in occasional individuals.[12] A second aldosterone determination done 6 months later revealed a 24-hour excretion of 6 micrograms.

A second case aroused the suspicion of aldosteronism. Patient C. B. (UH #937408), a 69-year-old woman, first complained of weakness just two years prior to admission. This was periodic and within 6 months before admission there had been two episodes of paresis involving mainly the upper extremities and approaching actual paralysis. This patient was not hypertensive, but CO_2 combining power was 32 mEq/L; K: 2.3 and Na: 168. Urine pH was 5.0 and salivary Na/K was (less than 10)/19. Again aldosteronism was suspected but excretions during two separate 24-hour periods were 1 and 2 micrograms respectively. This woman turned out to be a chronic user of cascara sagrada which she had taken as a cathartic for many years. Her history and findings were strikingly similar to those reported by Schwartz and Relman in 1953 in an article describing the syndrome of hypokalemic alkalosis associated with the chronic overuse of laxatives.[45]

In this connection it is significant that save for the results of actual aldosterone determinations, there were no chemical findings in the aldosteronism cases which differed significantly from other situations characterized by metabolic alkalosis. The frequent failure of patients with metabolic alkalosis to produce an alkaline urine is well recognized,[50] but this would appear to

apply to patients with aldosteronism as well as to individuals suffering from gastro-intestinal losses of chloride or potassium. Although low salivary Na/K ratios have been considered indicative of excessive mineralocorticoid activity, depressed ratios were seen in the two patients mentioned above who suffered from other forms of potassium loss as well as the one with aldosteronism (Patient #3, J. P.) in whom it was measured.

Summary and Conclusions

1. Of the five cases discussed here four were operatd upon. In the fifth the diagnosis of aldosteronism seems adequately proved by the finding of aldosterone excretion of about 10 times the normal range. Two cases had benign tumors, one carcinoma and one spontaneous hyperfunction without tumor. Basal aldosterone excretion ranged from 8 micrograms per 24 hours in one patient with adrenal adenoma to 180 in the presence of a metastasizing adrenal carcinoma.

2. In two cases in which ACTH was given, the treatment caused striking elevation of aldosterone excretion. Although it has been suggested that the response to ACTH might be used to differentiate "hyperplasia" from tumor,[25] this experience would seem to refute such a concept since a ten-fold increase was produced by ACTH in a patient with a highly malignant tumor.

3. In two patients of three studied, addition of potassium to the diet caused an increase in aldosterone output. This may be of some diagnostic value in patients such as #4 in whom the basal level is in the borderline range.

4. Despite the mobilization of aldosterone which is occasioned by potassium administration, it is possible to produce positive potassium balance in these patients with quite rapid reversal of alkalosis, hypokalemia and electrocardiographic changes. Failure to reconstitute potassium balance before operation permits an unnecessary surgical hazard.

5. Since aldosterone-producing tumors may be very small and there is no evidence for the type of contralateral atrophy which is seen in Cushing's syndrome a transabdominal approach is suggested for exploration. Because of the possibility of incompletely restored potassium balance, curare-like drugs should not be used in conjunction with anesthesia.

6. Other mechanisms can cause hypokalemic alkalosis in the presence or absence of hypertension and thereby present diagnostic problems. The two cases which have been presented illustrate the occasional effects of chlorothiazide and of chronic abuse of cathartics in the genesis of clinical potassium depletion. Urine pH and salivary Na/K ratio have not been helpful. Such cases emphasize the necessity for specific aldosterone determinations done by a reliable chemical method. The method described here, though rather elaborate and cumbersome, has sufficient specificity for clinical and experimental purposes.

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Discussion

Dr. Victor Richards: I express my admiration for this excellent paper and excellent work by Dr. Zimmermann.

We have been fortunate in having four such cases at Stanford, largely due to the fact that Dr. Leutscher, of our medical staff, was one of the first men to work with and discover aldosterone. Three of these cases have been operated on. Each had an adenoma of the type that you saw in Dr. Zimmermann's illustration. The outstanding clinical feature of all these cases was hypertension associated with a low blood potassium.

Dr. Bailey, working with Dr. Leutscher, has done some interesting studies on incubation of the adrenal tumors that we removed. I discussed this with him yesterday, and he tells me that these tumors on incubation produce an excessive amount of aldosterone. They also produce an excessive amount of hydrocortisone and corticosterone on adrenal incubation.

Response to ACTH stimulation occurs in the adrenal incubates, but this may be a nonspecific response, since the same response is produced by the administration of any protein substance.

The method for assay that they have used for aldosterone is a biological one in adrenalectomized rats, and we have had no experience with the method of assay that Dr. Zimmerman has reported. We, too, have felt that the best approach is an anterior abdominal approach, and in the three instances a small tumor was found which