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Current concepts of primary aldosteronism

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CURRENT CONCEPTS OF PRIMARY ALDOSTERONISM

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The identification of aldosterone as a separate adrenal cortical hormone followed the brilliant investigations of Luetscher[23] and Simpson.[56] In 1950, Deming and Luetscher reported the bioassy of a material like desoxycorticosteroid in the urine. Simpson, et. al., in 1952, discovered the secretion of a salt-retaining hormone by the mammalian adrenal cortex. The isolation of this hormone followed improvements in chemical techniques, for the initial chemical methods resulted in destruction of the hormone. Using partition chromatography, which permitted separation of the hormone without excessive loss or damage, a group of experts[57] combined their efforts to identify the unique structure of this substance. It has been called aldosterone.

In 1955, Conn[12] described the first case involving excess secretion of aldosterone by an adrenal cortical adenoma. Since then a tremendous amount of material has been published about aldosterone and the symptom complex which results from its primary hypersecretion. Conn[16] knows of around 200 case reports of the syndrome which now bears his name, however, about 50 of these case reports have not been published in the literature. The amount of information about the chemistry and physiology of aldosterone is even more impressive. To thoroughly review all the literature in this field would be an overwhelming task. Therefore, it will be the purpose of

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this paper to concentrate on the recent articles. Nonetheless, the interesting and unusual cases and the more pertinent research from earlier years will not be excluded here.

In recent years Conn has said, "In retrospect, it was my good fortune to have encountered a classic case of primary aldosteronism as the initial one. Very little, in the way of additional symptomatology or biochemical findings, has been added to the original description. On the other hand, many cases in which some of the classic manifestations have been absent have been recognized as primary aldosteronism by astute clinicians. By means of adrenal surgery such patients have been cured of a disease which we now recognize as potentially lethal. Thus, it is possible to diagnose and treat primary aldosteronism at a much earlier or milder stage in its development. However, the clinician who is armed with a diagnostic awareness of this possibility is quickly beset by a number of difficulties in the differential diagnosis of early cases. In addition, the emergence of a group of patients in whom the complete syndrome (clinically and biochemically) is associated not with tumor but with focal nodular hyperplasia of both adrenals, calls for special considerations by the surgeon at the time of operation."[14] The initial part of the above quotation makes the syndrome sound static. This writer has found the opposite to be true.

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More refined diagnostic methods have been developed; the symptomatology has been more elaborately described; additional biochemical findings and new drugs have aided in the differential diagnosis; and recent developments in regard to malignant hypertension and unilateral renal ischemia have revealed excessive production of aldosterone in these entities, thus, further confusing matters.

There have been several very good articles reviewing the case reports of primary aldosteronism.[10, 15, 24, 47, 55] Most of the presently quoted statistics have been compiled from the 108 cases with adenoma and 18 cases without adenoma Conn[15] reviewed in 1961. This writer has reviewed 23 case reports with adenoma which have been published in the English literature since Conn's excellent presentation. (Table 1.) A few of these cases[11, 43] did not come to operation, therefore, we do not know if there would have been correction of the serum electrolytes and aleviation of the hypertension postoperatively; but the symptomatology and autopsy findings strongly point to primary aldosteronism. Conn prefers not to consider such cases. Five cases[9, 16, 30, 48, 61] of an adrenal carcinoma causing primary aldosteronism have been reported elsewnere in the literature.

Table 2 shows the age and sex distribution of 131 cases of primary aldosteronism due to adenoma. The youngest patient was 15[50] and the oldest 75 years of age.[11] Females with this

disease are $2\frac{1}{4}$ times as common as males, and in both sexes about 71% of the cases occur between the ages of 30 and 49.

CLASSICAL SYMPTOMS*

In its fully developed state the characteristic symptoms of this disease are - headache, polyuria which is mainly nocturnal, polydipsia, episodic weakness, periodic paralysis, manifestations of tetany, and paresthesias. (Table 3.)

1. Headache. Severe headache was found by Delorme[24] to be the most common presenting symptom, and Conn[14] said, "that it has been an almost constant accompaniment of the syndrome." The headache, of course, is the result of arterial hypertension which these patients have. These headaches do not seem to have any distinguishing characteristics.

2. Polyuria. Several factors are probably responsible for this symptom. First, there are changes in the kidney tubules as a result of hypokalemia. (See pathology.) Consequently the kidneys are not responsive to Pitressin and the patient excretes an increased amount of urine at a low specific gravity. Also an increased total body exchangeable sodium may produce polydipsia which secondarily results in polyuria. Water and sodium diuresis have been reported to be exaggerated in the supine position. An explanation for this is lacking.

3. Polydipsia. This seems to be due to an increased total body exchangeable sodium or as vanBuchem[60] puts it, "hypertonic cellular dehydration." Polyuria also tends to drive this

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* Classical, as originally designated by Conn.

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mechanism. Dry mouth has been a prominent symptom in a number of cases.

4. Muscular weakness and paralysis. These patients typically have episodes of muscular weakness which occasionally proceed to flaccid paralysis of the lower extremities and rarely to complete paralysis from the neck down. Delorme[24] noted that the episodes of weakness and paralysis may last from a few hours to several days or weeks. They are more common in cases with adenoma than with hyperplasia.[55] Hypokalemia itself doesn't appear to be the cause of this manifestation, for a patient may have a markedly low serum potassium without weakness. Conn[13] has been impressed with the relative lack of important symptoms at extremely low levels of serum potassium. It appears as though a sudden shift of potassium is more important than the serum potassium level.[60] VanBuchem[59] noted, in a patient with primary aldosteronism and low serum potassium that he studied, no paresis till several days postoperatively suggesting that a sudden marked shift of potassium into the cells is important in regard to paresis. The weakness is more often of the lower extremities. It should be emphasized that the episodes of weakness and paralysis are intermittent with the patient oftentimes recovering after bed rest and without potassium supplement. Again the above picture is the classical one; many patients present only a history of weakness and fatigue. Admittedly these latter symptoms are difficult to evaluate for

they are common complaints. Thiazide diuretics were responsible for precipitating a weak spell in one of the patients reviewed in this paper.[29] This phenomenon has been reported in other cases.

5. Tetanic manifestations. Occasionally these patients will have muscular tetanic manifestations, usually in the upper extremities but sometimes in the lower extremities as well. Delorme[24] noted that the tetanic attacks occurred between episodes of paresis or paralysis. The tetany is due to the insolubility of serum calcium in the more alkaline body fluid in primary aldosteronism. (See laboratory findings.) The serum calcium level is usually reported within normal limits.

6. Paresthesias. Conn[14] described these as, "consisting of prickling and tingling of the face, hands, and feet." They tend to be intermittent and of short duration.[24]

Muscular pain, which was not mentioned by Conn[14] as a classical symptom, has been described in the past,[24] and was prominent in several patients reviewed in this paper. These consist of muscle cramps or ill-defined myalgias.

CLASSICAL PHYSICAL FINDINGS (TABLE 4.)

1. Hypertension. High blood pressure is found in all cases of primary aldosteronism. The mechanism whereby aldosterone causes hypertension is not definitely known. Several investigators[10, 19] believe that the increased blood pressure is related to an increase in the total body exchangeable sodium[7, 18]

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found in this syndrome. VanBuchem[60] noted that postoperatively the normalization of the serum electrolyte concentrations in his patient was not as rapid as the normalization of the blood pressure. He thought that this observation constituted an arguement in favor of a direct effect of aldosterone on blood pressure. The blood loss alone from a major operation of this sort might be responsible for the decreased blood pressure and in some cases the blood pressure falls only slightly postoperatively to become normalized several weeks later after the serum electrolyte concentrations have returned to normal. It is interesting to note that Gross[38] found that aldosterone has a similar inotropic effect on heart muscle as the cardiac glycosides. Orndahl[50] has shown an inverse relationship between the highth of the blood pressure and hypokalemia. Malignant hypertension has occurred in five of nine patients with primary aldosteronism without adenoma,[15] but the hypertension in all cases of primary aldosteronism caused by an adrenal adenoma had been benign until Kaplan[44] reported a case with malignant hypertension in 1963. Carey's third case[10] which is reviewed in this paper may be another case of malignant hypertension associated with an adenoma?

2. The presence of Chvostek and Trousseau signs.

3. Conspicous absence of edema. Conn[14] has stated, "edema is conspicous by its absence" in primary aldosteronism. This statement is no longer absolutely true. August[1] has said, "the presence of edema need not exclude the diagnosis of primary

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aldosteronism." Delorme's[24] review of 31 cases contained three reports of edema without obvious cause and two cases associated with overt cardiac insufficiency. Goldsmith[34] reported a case with prominent peripheral edema where there were no abnormalities of plasma protein or of cardiac or renal function to account for the edema. After removal of an adrenal adenoma the edema disappeared. Several patients presented in this paper had edema without obvious cause. There are many theories explaining the absence of edema in primary aldosteronism. The "escape" mechanism evidenced by normal subjects and those with primary aldosteronism as shown by August[2] is most widely accepted. In these subjects fluid retention in excess of three to five liters is not to be expected unless other disease processes interfere. The mechanism of the "escape" from sodium retention during continued administration of aldosterone is not completely understood. Goldsmith[34] states, "Although sodium retaining steroids, in all probability, increase the tubular transport of sodium, the resultant expansion of extracellular and intravascular fluid volume leads to an increased glomerular filtration rate and an increased filtered sodium load with establishment of a new 'steady state.' Net sodium retention and edema will result only when the secondary increase in the filtered load and consequent 'escape' are prevented." Biglieri[7] also believes that a compensatory increase in glomerular filtration rate may

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explain the lack of edema in these patients. Several investigators have shown an increased glomerular filtration rate preoperatively as opposed to the postoperative value in patients with primary aldosteronism. Gordon[35] said, "It is possible that increased water intake may be of primary importance as a factor causing escape from the salt-retaining effects of aldosterone." It is suggested that the large amount of water ingested by his patient resulted in expansion of the extracellular space sufficient in amount to decrease aldosterone production by the adrenals, and that this resulted in the observed sodium diuresis.

LABORATORY FINDINGS

1. Hypokalemia. Hypokalemia is a constant finding in almost all cases of primary aldosteronism. Since practically all the potassium ingested by the subjects in potassium balance is excreted in the urine (less than 10 milli-equivalents per day is excreted via the intestine), the kidneys play the important role in conservation of this ion. The hypokalemia is the result of excess aldosterone, which probably influences the exchange of potassium ion over that of hydrogen ions for sodium ions in the distal tubules of the kidney. One must be aware that if there is a decrease in the sodium load reaching the distal tubules, as occurs in those individuals on a low sodium diet, this exchange is hindered and serum potassium will rise toward normal levels. Conn[14] studied a patient with primary aldosteronism who complained of some of the symptoms of this syndrome. Although initial

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biochemical study revealed normal levels of serum electrolytes, further study disclosed that hypokalemia was demonstrable in about one-half of a long series of determinations. Therefore, a normal serum potassium shouldn't deter one from further investigation. In his initial articles Conn stated that the low serum potassium level was not affected by dietary potassium supplementation. Since then various clinicians[25, 26, 32, 3] have not found this to be always true.

2. Hypernatremia. The serum sodium is usually elevated, but may be normal or even decreased.[24] Excess aldosterone, which promotes the reabsorption of sodium ions in the distal tubules of the kidney, is responsible for the hypernatremia.

3. Metabolic Alkalosis. This is due mainly to the shift of hydrogen ions from the extracellular fluid to the interior of the cells as a result of potassium deficiency.[27] The majority of patients with primary aldosteronism have an elevated carbon dioxide-combining power or content, or blood pH. In the 23 patients reviewed here, two cases[40, 49] had values falling within the normal range, and another had a metabolic acidosis.[43] The latter case had been vomiting for several days prior to admission, and only the admission chemistry was given.

4. Elevated Urinary Aldosterone Level. This finding is a great help in establishing the diagnosis of primary aldosteronism, but at the present time urinary aldosterone determinations are

are difficult to perform and not readily available. Values
within normal ranges do not speak against the diagnosis, and
one must be cautioned for serial determinations may be necessary
since hypersecretion of aldosterone is frequently intermittent.
The secretion of aldosterone is not under the control of the
pituitary to the extent that is true for the other adrenal
cortical hormones. Many factors have been found to influence
aldosterone output. Detailed discussions of these factors can
be found elsewhere.[1] In general, the factors causing increase in
aldosterone secretion are sodium deprivation, decrease in extra-
cellular volume and potassium loading. Sodium loading, increase
in extracellular volume, and potassium deprivation decrease
aldosterone secretion. Thus the diagnosis in a patient on a
high sodium diet may be obscurred. The site of mediation
appears to be the juxtaglomerular cells of the kidney where
renin is secreted. "Some hemodynamic alteration secondary to
a decrease in pressure and flow through the kidney leads to
release of renin by the juxtaglomerular cells. Available data
indicates that angiotension II acts on the zona glomerulosa of
the adrenal cortex to promote aldosterone production."[21] This
latter factor is out of line with the findings of zona fasciculata
in the majority of aldosteronomas (See pathology), but it is still
a debatable point whether aldosteronomas are subject to physiologic
control[7, 35] or are autonomous.[4, 26] In the past, unchanged

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aldosterone in the urine has been calculated and this accounts for only a small percentage of that secreted, i.e. about ten micrograms per day. It has been recognized that the measurement of urinary excretion of unchanged hormone may not accurately reflect significant changes in adrenal secretion of aldosterone. During the past several years a method has been devised which provides an estimate of the amount of aldosterone which is actually produced by the adrenal glands.[58] The technique involves the injection of a trace amount of tritiated aldosterone and the determination of the specific activity of a urinary metabolite of aldosterone in the subsequent 24 hour urine. The difference between the specific activity of the injected hormone and that of the urinary metabolite is considered to be a measure of the endogenous production of aldosterone and, as such, permits the estimation of the daily secretion rate. With this method it has been found that the average patient secretes 250 micrograms of aldosterone per 24 hours. Sodium deprivation will increase the secretion to 1000 micrograms, whereas, sodium loading decreases the rate to 50 micrograms per 24 hours.

5. Normal Values for 17-hydroxycorticosteroids and for 17-ketosteroids. This does not hold true for adrenal cortical carcinoma producing primary aldosteronism. To date, those reported have shown abnormally large quantities of the above steroids. Also Delorme[24] has reviewed two cases, and Crane[18]

has reported one case of adrenal cortical adenoma where there were increases in the two steroids in the former case and only of the 17 ketosteroids in the latter.

6. Persistently Alkaline or Neutral Urine. The greater majority of cases of primary aldosteronism have an alkaline urine. This is due to the increased excretion of potassium ion in the urine with a concomitant diminution in excretion of hydrogen ion.[51, 60] Several criteria need to be satisfied in order to have excessive potassium excretion. First, an adequate amount of sodium ions has to be delivered to the distal tubules in the kidney for exchange with potassium ions since most of the filtered potassium is reabsorbed in the proximal tubule. Second, the competition between hydrogen ions and potassium ions in the distal tubular cells for exchange with sodium ions is governed by the concentration of these ions in the cells;[61] a higher concentration of an ion favors its exchange. The first criteria is generally satisfied unless the patient is receiving a low sodium diet. The second criteria, unless nullified, would favor hydrogen ion excretion in primary aldosteronism since hydrogen ions enter body cells (including the distal tubular cells in the kidney) and potassium ions leave cells in potassium deficient states. Therefore, it must be postulated that aldosterone stimulates specifically the exchange of potassium ions for sodium ions or inhibits hydrogen exchange, thereby, accounting for the alkaline

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urine. This does not explain the increased excretion of ammonia observed in some patients.[31] Gross[39] states that aldosterone does not influence simply the sodium-potassium exchange mechanism in the distal tubule, but may act separately on sodium ion reabsorption and potassium ion elimination. In patients who are on a low sodium diet, or who have secondary aldosteronism, either due to congestive heart failure or cirrhosis, further administration of aldosterone causes almost complete sodium reabsorption but does not necessarily increase potassium excretion indicating that sodium is not exclusively reabsorbed by direct exchange against potassium.[38] Patients with primary aldosteronsim also have difficulty acidifying their urine after being give ammonium chloride.

7. Persistent or Intermittent Albuminuria of Mild Degree. This finding can be explained on the basis of the renal lesions to be mentioned later.

8. Large Urine Volumes of Low Specific Gravity Responsive to Neither Water Restriction Nor Administered Pitressin. (See Pathology.)

9. Excessively High Urine Potassium at Exceedingly Low Levels of Serum Potassium. This is a significant finding with the daily excretion of potassium generally exceeding the normal range of 25 to 75 milliequivalents per day. Potassium clearance has been calculated in several reports, and it has been

constantly higher preoperatively than postoperatively.

10. Variable Degrees of Decreased Renal Function. "In patients with primary aldosteronism, renal function can be modified by three main factors: prolonged hypokalemia resulting in the production of vacuolar nephropathy; pyelonephritis, the occurrence of which is enhanced by prolonged potassium depletion; and arterial hypertension of long duration giving rise to arteriolar lesions in the kidneys. It is difficult therefore to attribute a change in renal function to any given factor..."[24] For this reason it seems to be unnecessary to draw any conclusions about specific renal function tests in primary aldosteronism.

11. Abnormally Low Levels of Sodium in Thermal Sweat and Saliva. Initially this determination was considered to be of some value, but it has now fallen into disreput. Salivary sodium ion to potassium ion ratio usually fall well below one, however, because of their variability, these ratios may not be entirely reliable.[52] In Zimmerman's[61] experience, the salivary sodium ion to potassium ion ratios have not been helpful diagnostic measures.

12. Electrocardiographic Changes Typical of Hypokalemia. The majority of patients with primary aldosteronism have electrocardiographic changes consistent with hypokalemia. The importance of this is now becoming apparent because asymptomatic patients are being discovered to be hypokalemic because

an electrocardiogram suggested the need for a determination
of serum potassium. In hypokalemic states one sees lowering
of the T wave and rising of the U wave with an apparently
prolonged QT interval. In their patient with primary aldoster-
onism, vanBuchem[59] noted that it took five weeks after surgery
for the electrocardiogram to become normal again, though the
serum potassium level had reverted to normal earlier. This
suggests that intracellular rather than extracellular potassium
is of primary significance in the etiology of the electro-
cardiogram changes. Also in hypokalemic states, one sees
morphologic changes in the myocardium but not in skeletal
muscle.[59]

13. Diabetic Glucose Tolerance Test. This finding has
been noted in cases of primary aldosteronism before.[24] Three
patients[36, 40, 49] reviewed in this paper demonstrated a
diabetic glucose tolerance test, which became normal postoper-
atively. This phenomenon appears to be due to impeded intra-
cellular glucose metabolism resulting from potassium depletion.

14. Increased Plasma Volume (decreased hematocrit).
Biglieri[7] studied five patients with primary aldosteronism and
four control patients with particular reference to measurement
of plasma volume. He found that there was an increase in the
total blood volume, while the red cell volume was essentially
normal in those patients with primary aldosteronism. This
is such a recent finding that I have found no other reference

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to this in case reports of primary aldosteronism. Nonetheless, Conn[16] has now listed the increased plasma volume among the other characteristic findings in his table of biochemical and functional alterations observed in primary aldosteronism.

15. Hypomagnesemia. A low serum magnesium level has been reported in some cases[5] of primary aldosteronsim, but most case reports have not listed or have not gotten a serum magnesium level. The magnesium level may prove in the future to have greater significance than the serum calcium in tetany.

16. Hypophosphatemia. Gordon[35] studied a patient with primary aldosteronism who had persistent hypophosphatemia associated with a high phosphate clearance. The large quantities of bicarbonate excreted by this patient suggested that the excess presented to the kidney tubules for reabsorption may have competed with phosphate for a transport system resulting in decreased phosphate reabsorption. One case report[42] that was reviewed in this paper had a low serum phosphate level.

PATHOLOGY

1. Adrenal Glands. At present it is difficult to assign a percentage value to the cases of primary aldosteronsim due to adenoma, carcinoma, and hyperplasia.* In 1961, Conn[15] reviewed 108 cases with adenoma, 13 with bilateral hyperplasia, and five with normal glands. I have reviewed 23 cases with adenoma which were not included in Conn's 1961 study, but in 1963, Conn[16]

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* Conn considers those cases with hyperplasia secondary aldosteronism.

reported 135 cases with adenoma. Since he did not list the authors of the additional 27 cases, there is no way of knowing if they include any of the 23 cases reviewed here. As stated before, five cases of primary aldosteronism due to adrenal cortical carcinoma have appeared in the literature. Bilateral adenomata have been reported in a small number of cases. "Although the numbers are still too small to be certain, it begins to appear that left-sided adenomas are more common than right-sided ones. Of the tumors reported in grams 68 per cent have weighed less than 6 grams, and of those reported in centimeters 73 per cent have measured less than 3 centimeters in diameter. It is worthy of emphasis that the great majority of these tumors are small and that failure to visualize them by the various techniques now in vogue does not exclude their presence."[16] The various techniques referred to include-intravenous pyelography, tomography, and presacral oxygen or carbon-dioxoide insufflation. Table 5 shows the site of adenomas in 23 cases reviewed in this paper.

Grossly the adenomata of primary aldosteronism are not unusual; they are generally encapsulated and may be yellow in color. Whereas in animals there is evidence that aldosterone is produced by the zona glomerulosa only, cells of adenomata from cases of primary aldosteronism have usually resembled those of the zona fasciculata or those of both these layers. Data from

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Table 6 seems to indicate that the tumorous tissue is generally zona fasciculata and that, maybe, the zona glomerulosa in normal adrenal tissue is responsible for producing aldosterone and is being suppressed in primary aldosteronism by the excess secretion of this hormone by the tumor resulting in its atrophy. Delorme[24] came to the conclusion that adrenal histology does not enable one to predict the function of these tumors.

"In virtually all cases in which an analysis of the tumor has been made the aldosterone content has been greatly elevated. Studies of in vitro secretion of aldosterone by tumors from patients with primary aldosteronism also indicate increased secretion of aldosterone. Some tumors from cases of primary aldosteronism in addition to secreting excessive amounts of aldosteronism have been shown to produce increased amounts of corticosterone. Other cases have not, and they have had precisely the same clinical and laboratory manifestations."[15]

2. Kidney. It has been experimentally proven that potassium depletion results in characteristic renal lesions.[54] Conn,[14] who found these changes in patients with primary aldosteronism, was the first to call this "kaliopenic nephropathy." He described a vacuolization mainly in the proximal tubules but sometimes extending into the distal tubules. Relman,[54] who has studied kidney changes in various potassium depletion states, also found that the most striking lesion is vacuolization of the tubular epithelial cells confined chiefly to the convoluted

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tubules. He lists the less specific alterations in potassium depleted states as, "...granularity or foamy swelling of cytoplasm, necrosis and sloughing of cells, dilatation of tubules with atrophy of epithelium, and even calcification of cells."[54] In addition, a high incidence of pyelonephritis exists in patients with primary aldosteronism. There is some evidence to suggest that chronic kaliopenia decreases the resistence of the kidney to infection. This explains why this disease was called "potassium-losing nephritis" before its true pathology became clear. As stated before, various degrees of arteriolosclerosis have been observed in primary aldosteronism.

The most consistent functional defect associated with potassium depletion nephropathy is to be found in the tubules, with pitressin-resistant isosthenuria as the chief characteristic. The absence of significant lesions in the collecting tubules is noteworthy in this respect. Antidiuretic hormone also acts on the distal convoluted tubules, where lesion have been found; and a defect here would allow the urine to enter the collecting ducts in a hypotonic state instead of being isotonic. Then, even with maximal ADH stimulation, i.e., a four-fold concentration, a urine of 50 osmolarity when entering the collecting ducts would still not be isotonic when it reaches the kidney pelves.

DIAGNOSIS

Conn[14] has stated, "...that if we insist on all the classic findings, we will be able to diagnose only about 30 per cent of

the cases of primary aldosteronism." Thus it is important to think of this syndrome in any patient with hypertension. This is being done by some clinicians and is resulting in the diagnosis of asymptomatic cases. As the emphasis in the past has been on the diagnosis of pheochromocytoma in hypertensive patients; in the future it should be on Conn's Syndrome, for the great increase in the number of cases recently shows that it probably is a more common cause of hypertension than pheochromocytoma. Laxity in the search for potentially cureable forms of hypertension is not wise, for a considerable number of middle aged patients[41] with a non-malignant form of hypertension due to primary aldosteronism have succumbed from cerbrovascular accidents before coming to surgery.

All patients with hypertension should have the benefit of having a serum potassium done. As said before, a single normal value for serum potassium does not exclude the disease in a hypertensive patient. "While it is probably too early to expect acceptance of the following suggestion, a better screening procedure would be the ingestion by the hypertensive patient of 200 milliequivalents of sodium per day for a week, the last three days of which a daily determination of serum potassium is made. In addition, a test based upon administration of chlorothiazide as a screening procedure might be a sensitive one, since it has been our experience, and that of others, that

the development of severe muscular weakness during the first week of chlorothiazide administration often ends with the demonstration of an aldosteronoma."[16]

Table 7 divides into seven categories the various conditions in which hypertension and hypokalemia due to renal loss of potassium may coexist. Group I has already been defined. "From a numerical point of view category III is important since a majority of hypertensive patients are currently treated with some form of thiazide compound. These drugs are capable of producting renal loss of sodium and thus a secondary increase in aldosterone production. It has been estimated that at least 25 per cent of hypertensive patients who are receiving thiazide therapy develop significant hypokalemia. Why the remainder do not is an intriguing question. How many of the patients who do develop hypokalemia upon administration of thiazides have primary aldosteronism is not known but an increasing number of patients with aldosteronomas are being discovered in this way."[16]

Group II includes patients with bilateral adrenal hyperplasia or normal appearing glands, and has been temporarily designated as congenital aldosteronism. It is frequently associated with malignant hypertension, and is generally found in younger individuals. Conn believes that this is a form of secondary aldosteronism which may have its origin in abnormal function of the juxtaglomerular apparatus of the kidney. "A diabetes insipidus-like picture

or tetanic manifestations can be traced all the way back to very early childhood."[16] Total adrenalectomy results in prompt cure. "That something besides excessive production of aldosterone is involved in this group of patients is indicated by their exquisite hypersensitivity to mineralocorticoids following adrenalectomy."[16] "Polyuria and polydipsia, unresponsive to administration of vasopressin, in a child with hypertension is most likely to be congenital*aldosteronism. All cases of so-called nephrogenic diabetes insipidus should be reviewed with the possibility of primary aldosteronism in mind."[14]

The problem of distinguishing malignant hypertension (Group IV), presumably due to unilateral or bilateral renal ischemia, from primary aldosteronism has recently become more complex. As stated before, the first proven case of aldosteronoma causing malignant hypertension has just been reported (December, 1963).[44] The role of the adrenal cortex and of aldosterone in particular in the pathogenesis of hypertensive disease remains obscure, but evidence is rapidly accumulating to indicate that it is involved. Dawson[22] has found a much higher incidence of adrenal cortical hyperplasia at postmortem in patients who during life had had either essential hypertension or renal hypertension than in people who had been normotensive.

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* Changed from primary to congenital (newer terminology).

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It is certain that renal ischemia is capable of producing secondary aldosteronism,[37] and it is likely that this same mechanism is at work in malignant or accelerated hypertension. In 14 of 15 patients in the malignant phase of essential hypertension, Laragh[45] found extremely high levels of aldosterone secretion. If four of these cases adrenal cortical nodular hyperplasia was observed. On the other hand, normal rates of secretion of aldosterone were found in all their eight subjects with benign hypertension. Most of the malignant hypertensives also had mild hypokalemia. Cortes[17] postulated that long term stiumlation of the aldosterone producing cells may lead to adenomata formation in a manner similar to the production of nodular thyroid hyperplasia in chronic iodine deficiency.

Gowenlock[37] has recently reported six patients with hyper-aldosteronism and renal ischemia. Renal ischemia has usually involved the whole of one kidney, but segmental lesions were described. Segmental lesions are especially difficult to diagnose and it is possible that such patients have in the past been mistaken for cases of primary aldosteronism. The only way to differentiate primary aldosteronism from aldosteronism secondary to renal ischemia then is by renal arteriography, and this may not be satisfactory in segmental lesions. It should be mentioned that hyponatremia[16] has frequently been associated with malignant hypertension and should be a warning

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that one is not dealing with primary aldosteronism.

There has been much written about the use of spironolactones in diagnosing primary aldosteronism. It is worth mentioning that when hypokalemic alkalosis is produced by excessive activity of aldosterone (whether induced by primary aldosteronism or secondary to severe renal disease) administration of spironolactone is capable of reversing the metabolic abnormality toward normal. This procedure, therefore, cannot be used to distinguish these two types of aldosteronism. All that the spironolactone test can prove is that the hypokalemic alkalosis is due to excessive activity of a salt-active compound on the renal tubule.

The entities under Group V are not difficult to differentiate from primary aldosteronism. The most important differential points are that in these conditions acidosis, hyponatremia, hypovolemia and decreased total body exchangeable sodium stand out in contrast to alkalosis, hypernatremia, hypervolemia and normal or increased total body exchangeable sodium observed in primary aldosteronism. It must be recognized that in these potassium-wasting renal diseases sodium also is being wasted. This may produce a state of secondary aldosteronism which could contribute to increased renal loss of potassium. However, potassium depletion tends to minimize the secondary aldosteronism normally induced by sodium loss.

Conn believes that there is always a normal level of 17 hydroxycorticosteroids in primary aldosteronism. This makes the separation of primary aldosteronism from those states caused by excess production of cortisol (Group VI) easy. One must remember that hypertension and hypokalemic alkalosis can be produced by excess production of cortisol. Yet a few proven cases of primary aldosteronism reviewed by this writer have had elevated levels of 17 hydroxycorticosteroids (See laboratory findings), therefore, the differential diagnosis of primary aldosteronism from mild clinical cases of excess production of cortisol is not always easy.

For the more rare situations listed in Group VII, one is referred to Conn.[16] Nonetheless, it is worthwhile mentioning a small group of patients with benign hypertension who have given all the requirements for a diagnosis of aldosteronoma, but at operation have failed to disclose one (Group VIIa). In most of these cases, total or subtotal adrenalectomy has not produced significant reductions in blood pressure. Some of these cases probably represent examples of renal hypertension mediated via the renin-angiotensin system. At the time of operation when no tumor is found subtotal adrenalectomy has been recommended.

OPERATION AND PROGNOSIS

There is no universally accepted operative approach to an aldosteronoma; transabdominal and paravertebral incisions are

both used. What should be stressed is that both adrenal glands and the renal vasculature must be thoroughly inspected at the time of operation. Also the patient should not come to surgery until his serum potassium deficit has been partially or totally corrected. The importance of normal electrolyte and fluid balance preoperatively is known by all. In primary aldosteronism it is even more important to have normal levels of serum electrolytes since several investigators[10, 24, 31] have noted a synergistic effect of potassium depletion and curare-like compounds. In regard to preoperative preparation Osborne[51] recommends 200 milligrams of spironolactone and 40 to 60 milliequivalents of potassium in liquid form every six hours for one week preoperatively increasing the spironolactone dosage if necessary. This preoperative plan seems to be the most effective, although, prior to the discovery of spirolactones, 150 to 300 milliequivalents of of potassium for a week or two raised the serum potassium level to normal in most cases. If subtotal or total adrenalectomy is anticipated because of failure to demonstrate adenomata with pneumography, the standard coverage with cortisone or hydrocortisone is indicated. It does not seem necessary to perform a total adrenalectomy in cases of bilateral hyperplasia since cures are produced by leaving 20 per cent of one adrenal gland.

Conn[14] has noted that in about two-thirds of the patients the blood pressure returns to normal within three months after operation and remains there indefinitely. In about one-fourth

of the patients the blood pressure falls in the postoperative period to levels significantly lower than before operation but not to normal values. In a third group of patients, about 15 per cent, the blood pressure may fall for several seeks or months and then gradually rise again to its preoperative level. This may be due to irreversible renal damage (arteriolosclerosis or pyelonephritis), misdiagnosed renal ischemia, or a missed adenoma at operation. Only one-half or 10 of 21 cases reviewed in this paper (See Table 1) have had normalization of the blood pressure postoperatively. In all cases the metabolic defect in electrolyte metabolism has been completely corrected by the operation-usually within several days or a week following the operation.

It is worth mentioning that with renal damage in primary aldosteronism, the decreased glomerular filtration rate which accompanies a lower blood pressure in the immediate postoperative state usually results in elevation of the blood urea nitrogen. Some people have also reported hypoaldosteronism as a postoperative complication.

SUMMARY AND CONCLUSIONS

In 1955, Conn described the first case of a symptom complex resulting from the excess secretion of aldosterone by an adrenal cortical adenoma. In the short time since then over 150 cases of primary aldosteronism have appeared in the literature. The majority of these cases have been due to adrenal cortical adenomas (aldosteronoma), but carcinomas, bilateral adrenal cortical hyper-

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plasia and normal appearing glands have been reported.

The pathophysiology of this disease entity has been stressed in this paper. The symptoms as well as the signs have been separately covered. Similarly, individual attention has been given to each laboratory finding and to the pathology, differential diagnosis, and surgical aspects of primary aldosteronism.

One of the main purposes of this paper has been to emphasize the newer concepts of primary aldosteronism. To achieve this objective 23 of the more recent case reports have been thoroughly reviewed and presented in chart form. Discussion of recent developments, such as, the angiotensin-renin mechanism, malignant hypertension in a case of aldosteronoma and the increased secretion of aldosterone in cases of renal ischemia and malignant essential hypertension are also included here.

It appears to this wrtier that the increasing number of cases of primary aldosteronism diagnosed during the last several years indicate that this entity will assume greater importance in the differential diagnosis of hypertension in the future.

TABLE 1

REFERENCE	AGE	SEX	SYMPTOMS*	BLOOD PRESSURE		POSTOP	MO	SERUM PREOP.				ALDOST*	ALB	Rx	URINE	ADENOMA*	IVP	INSUFFL
				PREOP*	POSTOP		MO	Na+	K+	Cl-	CO$_2$*	ALDOST*	ALB	Rx	CONC	ADENOMA*	IVP	INSUFFL
1. Carey	39	F	H, NE, W, N	200/120	120/83		9	145	2.6	94	31.5	16(18)	1+	Alk	1.021	RS 1.5 cm.	N	–
2. Ibid.	47	F	N, PO	220/120	150/90		16	143	2.6	100	30.8	24(18)	1+	–	1.021	LS 2 cm.	N	–
3. Ibid.	47	M	W, H, N, F	250/150	128/82°		6	148	3.1	96	39	elevated on one occasion	1+	–	1.021	RS 1.8 cm.	N	–
4. Brill	28	M	Loss of visual acuity	190/130	138/85		10	150	2.8	–	–	76(15)	–	Acid Alk	–	LS –	N	N
5. Case from Mass. Gen.	75	F	PO	210/95	–		–	150	2.7	104	32	–	3+	–	–	RS 1.5 cm.	–	–
6. Davignon	35	F	PD, PO, H tired, T	220/140	145/105		15	140	2.3	–	–	58(-)	–	Alk	1.027	LS 1.6 cm.	–	–
7. Elkman	40	F	Dec. strength H, N, leg edema, SOB	220/110	160/100		12	155	2.3	96	33	15(8)	tr.	Acid Alk	1.020	RS 2.0 cm.	N	–
8. Flanagan	36	M	numbness in arm	230/140	160/100		12	148	2.6	–	Inc.	–	–	Alk	1.013	LS .6 cm.	N	N
9. Ibid.	50	M	H	230/130	150/100		4	147	2.6	–	Inc.	–	–	Alk	–	LS 3.5 cm.	–	–
10. Ford	34	F	W, carpo-pedal spasm, ankle edema, PD, N, H	235/140	110/90		12	143	2	99	34.7	30(-)	2+	Alk	1.006	LS 1 cm.	N	N

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TABLE 1 Continued

#	Name	Age	Sex	Symptoms													
11.	Gilbert	48	M	W, N	170/120	144/104°	12	165	2.4	98	37	normal	neg	Alk	1.010	LS 1.6 cm.	N	+
12.	Gordon	49	F	H, W	170/110	normal	-	-	2.5	98	35	140(20)	-	-	-	LS -	-	-
13.	Halprin	42	F	W, leg pain numbness rt. hand	190/110	125/80	-	140.5	2.5	103	35.7	450(100)	tr.	Alk	1.008	LS 2.5 cm.	N	-
14.	Ibid.	43	F	W, H	220/115	170/105	-	143.7	2.9	105	25.1	59(-)	1+	Alk	1.010	RS 2 cm.	+	-
15.	Jacobson	36	F	W, PA, MAP, ankle edema	210/110	120/80	18	151.3	2.9	108	33.2	20(12.5)	tr.	Alk Neut	1.007	RS 1.6 cm.	-	+ (false)
16.	Jakobson	41	F	Fatigability and nausea and vomiting	210/90	-	-	142	2.9	101	9	23(-)	-	Acid	-	RS 3 cm.	-	-
17.	Kaplan	42	M	H, W, N, PO, PD	190/120	150/100	10	145	2.8	95	31	25(15)	-	Alk	1.008	LS 1.5 cm.	-	-
18.	Liang	22	M	H, albumin-uria	220/140	160/90	-	157	3.2	120	31.5	28(-)	tr. 4+	-	-	LS 2 cm.	N	+
19.	North (Sayres)	36	F	W, PA, NP, gun barrel vision	160/110	120/80	3	145	2.7	99	26.8	normal	-	Neut	1.022	LS 2 cm.	N	+
20.	Osborne	32	M	W, H, PD, PO, N	230/130	120/70	2	138	3	101	34	12(11)	1+	Alk	-	RS 2.5 cm.	-	+
21.	Ibid.	52	F	W	240/130	115/70	-	149	1.4	103	42	13(11)	tr. 4+	Alk	-	LS 3.3 cm.	N	+
22.	Playoust	36	F	P, H	190/140°	160/100	12	146	2.3	93	Inc.	-	neg	Neut	1.012	LS 2 cm.	N	+
23.	Simpson	37	F	H, W, PD, N, ankle edema	210/120°	200/100	-	146	1.9	83	Inc.	50(20)	tr.	Alk	-	LS 3 cm.	N	+

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TABLE 1 continued

* Code

    Symptoms: W (muscular weakness), N (nocturia), PD (polydipsia), T (tetany)
                 PA (paralysis), P (paresthesias), H (headache), MA (muscular aches)
                 PO (polyuria), F (fatigue), Dec. (decreased), NE (nervousness)

    Blood Pressure (Preop.): O (on hypertensive drugs)

    Serum Preop. (CO_2): Inc. (increased)

    Urine (Aldost.): normal values are withing parentheses

    Adenoma: R (right), L (left), S (single)

TABLE 2

Age and Sex Distribution of 130 Cases of
Primary Aldosteronism Due to Adenoma*

AGE	FEMALE		MALE		TOTAL	
15-20	4		1		5	
20-30	6		7		13	
30-40	28		9		37	
40-50	39	72%	17	66%	56	71%
50-60	9		4		13	
60-70	4		1		5	
70-80	2		-		2	
TOTAL	92		39		131	

* Adapted from Conn[15] with 23 of my own case reviews added.

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TABLE 3[*]

Symptoms in 103 Cases of Primary Aldosteronism

	FEMALE 76	MALE 27	TOTAL 103
Muscular weakness	54 (71%)	21 (78%)	75 (73%)
Polyuria (nocturia)	53 (70%)	21 (78%)	74 (72%)
Headache	41 (54%)	12 (44%)	53 (51%)
Polydipsia	34 (45%)	13 (48%)	47 (46%)
Paresthesias	23 (30%)	2 (7%)	25 (24%)
Visual disturbance	16 (21%)	6 (22%)	22 (21%)
Intermittent paralysis	18 (24%)	3 (11%)	21 (21%)
Tetany	20 (26%)	1 (4%)	21 (21%)
Fatigue	17 (22%)	3 (11%)	20 (19%)
Muscle discomfort	13 (13%)	3 (11%)	16 (16%)
No symptoms	4 (5%)	2 (7%)	6 (6%)

* From Conn[16]

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TABLE 4[*]

Physical Findings in 103 Cases of Primary Aldosteronism

	FEMALE	MALE	TOTAL
Hypertension	76 (100%)	27 (100%)	103 (100%)
Retinopathy	34 (45%)	17 (63%)	51 (50%)
Cardiomegaly	28 (37%)	13 (48%)	41 (41%)
Positive Trosseau	16 (21%)	2 (7%)	18 (17%)
Tetany	9 (12%)	-	9 (9%)
Positive Chvostek	9 (12%)	-	9 (9%)
Paralysis	4 (5%)	-	4 (4%)

* From Conn[16]

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TABLE 5

Site of Adenomas in 23 Cases Reviewed in This Paper

Single adenomas	Right	Left
Female	6	9
Male	2	6
Multiple adenomas	-	-

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TABLE 6

Adrenal Histology in Primary Aldosteronism:
12 Cases Reviewed in this Paper

REFERENCE	TUMOR	REST OF CORTEX	CONTRALATERAL GLAND
Brill	Zona fasciculata	Normal	-
Case from Mass. Gen.	-	Atrophy of zona fasciculata	-
Davignon	Zona fasciculata	-	-
Ford	Report was not specific	Atrophy of zona glomerulosa	-
Gilbert	Sharply outlined lipid cells in nests and cords	-	Normal
Jacobson	Zona fasciculata	Narrow zona glomerulosa	-
Jakobson	-	-	Zona glomerulosa was atrophic
Kaplan	Clear cells containing foamy cytoplasm	-	-
Liang	The tumor miniced no specific zone	Narrow zona glomerulosa	-
Osborne #1	Zona fasciculata	-	-
Ibid #2	Zona fasciculata and zona glomerulosa	-	-
Playoust	Zona fasciculata and less numerous cells of zona glomerulosa	Narrow zona glomerulosa	-

TABLE 7[*]

Etiological Classification of Coexisting
Hypertension and Hypokalemia

I. Primary Aldosteronism (tumor)

II. Congenital Aldosteronism (bilateral hyperplasia)

III. Diuretic Therapy in Hypertensive Patients

IV. Accelerated ('Malignant') Hypertension

V. Potassium-Wasting Renal Disease

  (a) Fanconi Syndrome

  (b) Renal Tubular Acidosis

  (c) Advanced Chronic Nephritis

  (d) Chronic Pyelonephritis

VI. Conditions Associated with Large Production of
Hydrocortisone

  (a) Cushings Syndrome

    1. Adrenal hyperplasia or tumor

    2. Corticotropin producing pituitary tumor

  (b) Neoplasms Producing Corticotropin-like Compounds
      (lung, thymus, pancreas, gallbladder)

VII. Miscellaneous

  (a) A Few Benign Hypertensives with all the Characteristics
      of Aldosteronism but no Tumor

  (b) Aberrant Aldosteronoma (Howard)

  (c) Factitious (pseudo-primary aldosteronism)

    1. Chronic ingestion of licorice (four cases)
       (subnormal aldosterone excretion and secretion)

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[*] From Conn[16]

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