In 1952 Simpson, Tait and their associates detected biologically, and isolated chromatographically, from the "amorphous fraction" of adrenal cortex extract a compound which caused intense retention of sodium and great diuresis of potassium when administered to adrenalectomized rats (Simpson & Tait 1952; Grundy et al. 1952; Simpson et al. 1953). The potency of this material was so great [30 times greater on sodium retention and 5 times greater on potassium diuresis than deoxycorticosterone (21-hydroxy-pregn-4-ene-3,20-dione)] that these investigators realized at once that they were not dealing with any of the known corticosteroids or with any combination of them. They, as well as Farrell & Richards (1953), demonstrated the existence of this material in adrenal venous blood of monkeys and dogs. This constituted good evidence that the substance in question was a normal secretory product of the adrenal glands. Tentatively, the material had been given the name "electrocortin". Within a surprisingly short time electrocortin was isolated in pure crystalline form and shortly thereafter was identified chemically as the 18-aldehyde of corticosterone (11β, 21-dihydroxy-3,20-dioxo-pregn-4-ene-18-al).

In October, 1954 we described and designated as primary aldosteronism an intriguing clinical syndrome which is completely curable by surgical removal of an adrenal cortical adenoma (Conn 1955). Since that time 56 cases have been reported and many more are either now in press or being prepared for publication. The author has been made aware of more than 100 unpublished cases together with their clinical and laboratory manifestations. It is with this background of information on approximately 150 well documented cases of primary aldosteronism that this discussion will be based.

In retrospect, it was our good fortune to have encountered a most classical
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 classical 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 very 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 cases with the complete syndrome (clinically and biochemically) associated not with tumour but with focal nodular hyperplasia of both adrenals, calls for special considerations by the surgeon at the time of operation. I propose to discuss against a background of the full-blown disease, some of these newer developments as well as the variations in clinical expression of primary aldosteronism which have evolved during the past five years.

DEFINITION

Because a good deal of uncritical thought has crept into the literature regarding what does and what does not constitute primary aldosteronism, I wish to re-emphasize our original definition, especially since all of the cases which I shall discuss fall into this category. Primary aldosteronism is a syndrome of mineralocorticoid excess (the symptoms, signs and biochemical findings of which are described below) induced by adrenal cortical elaboration of excessive quantities of aldosterone and characterized by (a) abnormally large amounts of urinary aldosterone and (b) normal amounts of urinary 17-hydroxycorticoids and 17-ketosteroids. In connection with this definition it must be cautioned that in primary aldosteronism excessive amounts of aldosterone in urine may not be detectable on all days. Multiple determinations may be required to demonstrate that hyperaldosteronuria is present.

SYMPTOMATOLOGY OF PRIMARY ALDOSTERONISM

The classical symptoms of this disease in its full-blown state are as follows:

1. Frequent episodes of severe muscular weakness which occasionally proceed to flaccid paralyses of the lower extremities and rarely to complete paralysis from the neck down.

2. Muscular tetanic manifestations, usually in the upper extremities but sometimes in the lower extremities as well. Positive Chvostek and Trousseau signs may be present.
3. Polydipsia and polyuria with increasingly frequent nocturia. Nocturnal polyuria contributes a disproportionately great fraction of the daily urine volume.

4. Severe headache has been an almost constant accompanyment.

5. Paraaesthesias consisting of prickling and tingling of the face, hands and feet.

The classical physical findings are as follows:

1. Hypertension. This has varied from mild, benign hypertension to malignant hypertension with marked papilloedema and haemorrhagic retinopathy.
2. Positive Chvostek and Trousseau signs.
3. Cardiac enlargement may or may not be present.
4. Oedema is conspicuous by its absence in a situation where gross oedema would be expected.

LABORATORY FINDINGS

The characteristic laboratory findings of primary aldosteronism are as follows:

1. Hypokalaemia.
2. Hypernatraemia.
3. Alkalosis (elevation of CO₂ combining power as well as blood pH).
4. A moderate to great increase in urinary aldosterone.
5. Normal values for 17-hydroxycorticosteroids and for 17-ketosteroids.
6. Persistent or intermittent proteinuria of mild degree.
7. Persistently alkaline or neutral urine with an inability to respond normally to an ammonium chloride load.
8. Large urine volumes of low specific gravity responsive neither to water restriction or to exogenous pitressin.
9. Excessively high U/p ratio for potassium at very low levels of serum potassium.
10. Variable degrees of decreased renal function from very mild to severely disturbed. Frequently the decrease in tubular reabsorption of water is disproportionately greater than any other measureable decrease in renal function.
11. Abnormally low levels of sodium in thermal sweat.
12. EKG changes typical of hypokalaemia.

CHANGING DIAGNOSTIC CRITERIA WITH INCREASING EXPERIENCE

In a situation the diagnosis of which must lead to surgery, one desires infallible pre-operative diagnostic criteria. The lists of symptoms, signs and laboratory findings given above provide such criteria and form the basis
from which points of departure may be possible. Experience during the past five years has taught us that if we insist on having all of the classical findings we will diagnose only about 30% of the cases. Undoubtedly this figure will drop much further as we increase our ability to diagnose primary aldosteronism at an earlier and/or milder stage of its development. While more time and experience are needed before all of the variations can be tabulated, and the diagnostic criteria further sharpened, nevertheless one already observes a spectrum anchored on one end by the classical syndrome, and exhibiting on the other some of the mildest forms of this syndrome which have so far been capable of detection. In this area, for example, are proven and cured cases which pre-operatively were completely asymptomatic but were known to be hypertensive. They were detected by routine testing of serum potassium in hypertensive individuals. On the other hand, we have studied a patient who complained of some of the symptoms of primary aldosteronism but whose initial biochemical study revealed normal serum electrolytes, normal urinary aldosterone and no other biochemical aberrations. Further study disclosed that hypokalaemia could be demonstrated in about half of a long series of determinations of fasting serum potassium. Further, urinary aldosterone was elevated in some but not in all of the specimens tested. An 8 gram aldosteroma was removed with an excellent clinical result. All gradations from these more difficulty detected cases to the full-blown disease have been observed. For mild cases newer testing procedures such as the response to potassium loading, to administration of aldosterone antagonists and to compounds of the chlorothiazid type are being studied but definitive answers are not yet available.

THE ADRENALS IN PRIMARY ALDOSTERONISM

To date, about 70% of the cases have disclosed a single, benign, well-encapsulated adrenal cortical adenoma. These have varied in weight from \( \frac{1}{2} \) g to 87 g. The usual weight is 1 to 3 g. It is the small size of these tumours which needs to be emphasized. Failure to visualize them by the various roentgenographic techniques does not exclude their presence. Their very small size also suggests the probability that some of the many, small so-called nonfunctioning cortical adenomas which are seen at the autopsy table may, in fact, have been producing excessive amounts of aldosterone during life.

Fifteen percent of the cases have shown more than one adenoma in the removed adrenal gland when it has subsequently been dissected. This suggests the possibility that in some cases the contralateral adrenal gland may also contain small adenomas. Recurrent adenomatous primary aldosteronism is a situation which will probably occur in some cases in the future following unilateral adrenalectomy for removal of one or more aldosterone-producing tumours.
Nine percent of the cases have revealed bilaterally enlarged adrenal glands due to cortical hyperplasia. Usually the hyperplasia has been nodular but not invariably. The hyperplastic zone has usually resembled the fasciculata but sometimes it has resembled the glomerulosa alone or a combination of the two types of architecture. One interesting aspect of the cases showing bilateral hyperplasia is their age. A large majority of these cases have occurred in children or young adults. The same type of lesion, however, has been found as late as the 5th decade of life. Total or sub-total adrenalectomy has produced amazingly rapid reversal of the disease. Polyuria and polydipsia, unresponsive to pitressin, in a child with hypertension is most likely to be primary aldosteronism. All cases of so-called nephrogenic diabetes insipidus should be reviewed with the possibility of primary aldosteronism in mind.

The remaining 6% have shown adrenal glands of normal size. The architecture has appeared either normal or has shown focal nodular hyperplasia. The clinical picture has been typical and large amounts of aldosterone have been found in the urine of such patients. Again, total or sub-total adrenalectomy has resulted in disappearance of the clinical and biochemical manifestations of primary aldosteronism. From this analysis it is clear that in most cases of primary aldosteronism the surgeon will be obliged to expose and inspect both adrenal glands before attacking either one. Furthermore, it will be necessary that the pre-operative diagnosis have sufficient support that there will be no hesitation in removing 90% of the adrenal tissue when tumour or hyperplasia fails to materialize at the time of adrenal exploration. Until future results can be evaluated we believe that sub-total rather than total adrenalectomy is the procedure of choice in cases showing no tumour.

Undoubtedly there will occur an occasional adrenal cortical carcinoma which produces exclusively an excess of aldosterone. To date, those reported to us have shown, in addition, abnormally large quantities of urinary 17-hydroxycorticosteroids and 17-ketosteroids. Such mixtures of excessive steroidal excretion along with varied clinical manifestations are to be expected in adrenal cancers. Although the major clinical expression in some of these cases may be that produced by excessive mineralocorticoid activity, they are by definition not cases of primary aldosteronism.

THE KIDNEYS IN PRIMARY ALDOSTERONISM

The renal defect in tubular reabsorption of water which is resistant to administered pitressin, as well as the inability to acidify the urine normally are due to the effects of chronic depletion of body potassium upon renal function and renal architecture. For descriptive purposes we have suggested that this lesion be called kaliopenic nephropathy. The lesion consists of a vacuolar nephropathy mainly in the proximal tubules but sometimes ex-
tending into the distal tubules. In severe cases there are scattered areas of tubular necrosis with occasional spots of calcification. Various degrees of arteriolosclerosis have been observed. Much of the tubular lesion is reversible by potassium repletion but functional recovery is likely to be slow but definite. In severe and long standing cases of kaliopenic nephropathy a variable degree of irreversible damage may be present.

Kaliopenic nephropathy is a renal lesion of metabolic origin. In addition, however, a high incidence of pyelonephritis exists in patients with primary aldosteronism. This accounts for the reason that this disease was called “Potassium-losing nephritis” before its true pathological physiology became clear. There is some evidence to suggest that chronic kaliopenia decreases the resistance of the kidney to infection.

All of these considerations point up the importance of early diagnosis and treatment before irreversible renal damage has occurred.

**THE POST-OPERATIVE RESPONSE IN PRIMARY ALDOSTERONISM**

Removal of the source of excess aldosterone production results in very dramatic disappearance of the entire syndrome in the vast majority of cases. The usual response consists of a prompt internal rearrangement of electrolytes, urinary diuresis of sodium, a retention of variable quantities of potassium, and return of the CO₂ combining power and blood pH to normal. These electrolyte and acid-base shifts are usually complete by the third post-operative week. All of the symptoms including the polyuria and polydipsia disappear abruptly.

In about two-thirds of the patients blood pressure returns to normal within three months after operation and remains there indefinitely. In about one-fourth of the patients blood pressure falls similarly in the post-operative period to levels significantly lower than before operation but not to normal values. In a third group, about 15 %, blood pressure may fall for several weeks or months and then gradually rise again to its pre-operative level. It is very significant that in all of the cases (regardless of blood pressure response) the metabolic defect in electrolyte metabolism has been completely obliterated by the operation. Thus, hypertension which was initially of steroid origin and which was associated with a marked aberration of sodium and potassium metabolism can return in the presence of normal metabolism of these electrolytes and in the presence of normal secretion of aldosterone, presumably on the basis of a secondary renal lesion produced in the course of chronic primary aldosteronism. Nevertheless, since kaliopenic nephropathy is at least partially reversible and since the biochemical aberration disappears in all cases one is obliged to advise operation in all cases even when severe renal damage can be demonstrated.
The occasional occurrence of two complications in the immediate post-operative period are worthy of mention. Where severe renal damage is present the decreased glomerular filtration rate which accompanies a lower blood pressure in the immediate post-operative state may intensify the degree of uraemia. This has proven to be temporary and has disappeared as renal function has improved over the ensuing months. More experience is needed in this regard.

A second post-operative complication is the occasional presence of temporary or prolonged aldosteronopenia following removal of an aldosteroma. This situation is easily treated but must be recognized.

On the basis of the accumulating information it is my opinion that primary aldosteronism will prove to be a much more common disease than we think it is today.

REFERENCES