RENAL AND ADRENAL FACTORS IN HYPERTENSION: DIAGNOSTIC APPROACHES*

JOHN H. LARAGH

Associate Professor of Clinical Medicine
Columbia-Presbyterian Medical Center
New York, N. Y.

IN MY discussion with you on this occasion I propose to consider the hypertension problem with special emphasis on two causes of secondary hypertension and on the hormonal interaction now known to be involved in these two kinds of hypertension: namely, *adrenal* hypertension caused by primary oversecretion of the salt-retaining hormone aldosterone, and other forms of hypertension in which the adrenal oversecretion of aldosterone is apparently or clearly a *secondary* event.

In the secondary aldosteronism often associated with hypertensive disease, kidney involvement usually preempts and elicits the aldosteronism. In fact, because of this, my discussion necessarily will involve this renal-adrenal interaction, and an exposition of the so-called renin-angiotensin-aldosterone hormonal system.

In deciding what the role of the adrenal gland is in the pathogenesis of hypertensive diseases, it is helpful to appreciate, in the first place, the history and setting in which this implication has been made. As you all know, it has long been appreciated that dietary salt intake has something to do with hypertension, so that a high-salt diet observed in certain populations and produced in experimental models produces a greater incidence of hypertension. Low-salt diets often have a beneficial therapeutic effect in hypertension.

Furthermore, a large body of evidence has accumulated—probably beginning in the time of Richard Bright—to indicate that the kidney plays a central role in many kinds of hypertensive disease. The discovery of renin in 1898, the famous Goldblatt experiment in 1934, and the demonstration of the enzymatic nature of renin by Page and by Braun-Menendez and their associates in 1940 are other landmarks in this area.

*Presented at the *Conference on Arterial Hypertension: Diagnosis and Management* held by the New York Heart Association at The Waldorf-Astoria, New York, N. Y., January 29, 1969.

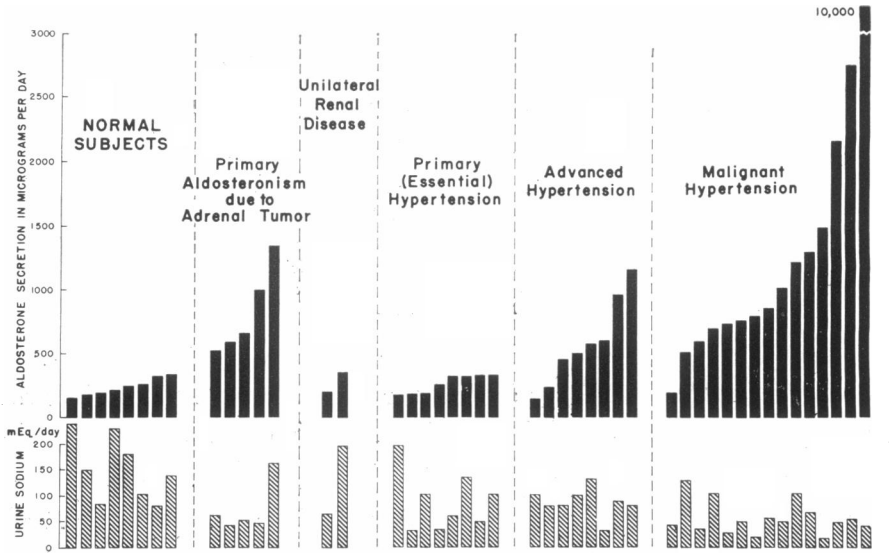

Fig. 1. The adrenal secretion rates of aldosterone in micrograms per 24 hours are presented for 8 normal subjects with primary hypertension, 8 patients with primary hypertension with complications ("advanced" hypertension), and 15 patients with malignant hypertension. For comparative purposes two patients with unilateral renal disease and five patients with primary aldosteronism are presented. The urine sodium content of the corresponding 24-hour urine collection is also shown. There is no evident hypersecretion of aldosterone in primary hypertension. In malignant hypertension marked hypersecretion of aldosterone was found and the values were often higher than those encountered in patients with primary aldosteronism. The patients with malignant hypertension resembled those with primary aldosteronism in that the hypersecretion was not associated with grossly reduced sodium excretion. Reproduced by permission from: Laragh, J. H., Ulick, S., Januszewicz, V., Deming, Q. B., Kelly, W. G. and Lieberman, S: Aldosterone secretion and primary and malignant hypertension. *J. Clin. Invest. 39*:1091-1106, 1960.

Following this, it was also appreciated that total adrenalectomy can prevent or greatly ameliorate experimental renal hypertension.

It has also been known that oversecretion of adrenal steroids can cause hypertension, as Harvey Cushing first demonstrated in the case of Cushing's syndrome in 1963. However it has been appreciated only more recently that the adrenal cortex is really two different endocrine glands secreting two different hormones, cortisol and aldosterone, either of which can cause hypertension, apparently by quite different mechanisms. In animals the hypertension produced by cortisol is independent of dietary salt whereas that produced by aldosterone can be prevented by the deprivation of sodium.

After the discovery of aldosterone, the salt-retaining hormone, in 1953, it was perhaps logical for many people to implicate this new

hormone in common essential hypertension. Thus repeated reports of two groups, one in Ann Arbor and the other in Canada, have claimed that oversecretion of aldosterone is involved in the pathogenesis of from 20 to 44% of patients presenting with typical essential hypertension.

Our own work does not at all support this opinion. We can find no evidence that oversecretion of aldosterone is involved in common benign essential hypertension. We have found that aldosterone secretion and metabolism is usually normal in these patients. Our results therefore provide no indication that oversecretion of this hormone is involved in initiating this condition.

Figure 1 illustrates data from our very early studies, in which secretion rates of aldosterone are plotted in relation to the concurrent rate of excretion of daily urinary sodium. It is apparent that in the eight patients with benign essential hypertension, aldosterone secretion rates are entirely similar to those of the normal subjects. It can also be appreciated that there are two hypertensive disorders in which hyperaldosteronism is the rule. The first is *primary aldosteronism* due to an autonomous adrenal adenoma (Conn's syndrome). Here the values range from 500 to 1,500 micrograms a day. The second condition is *malignant hypertension*, where the values are enormously increased—all the way up to 10,000—in almost all such patients.

One may ask then: What do these two adrenal disorders have in common and how do they differ? Actually the two are quite different. Primary hyperaldosteronism is a benign disorder characterized clinically by mild hypertension of long standing, with potassium wastage as the cardinal physiological defect. Pathologically there is little vasculitis. Furthermore, this condition is completely cured by removal of the offending adenoma of the adrenal cortex.

On the other hand, malignant hypertension is quite a different disorder, both clinically and pathologically; it is characterized by an accelerated course, papilledema, evidences of renal damage, and by necrotizing arteritis. Furthermore, there are no adrenal tumors, and no unique benefits are derived from even a total adrenalectomy.

The Renal-Adrenal Humoral System

All of these observations allow one to suspect that the adrenal oversecretion of aldosterone in malignant hypertension is a secondary response—representing the stimulation of both glands by an extra-adrenal

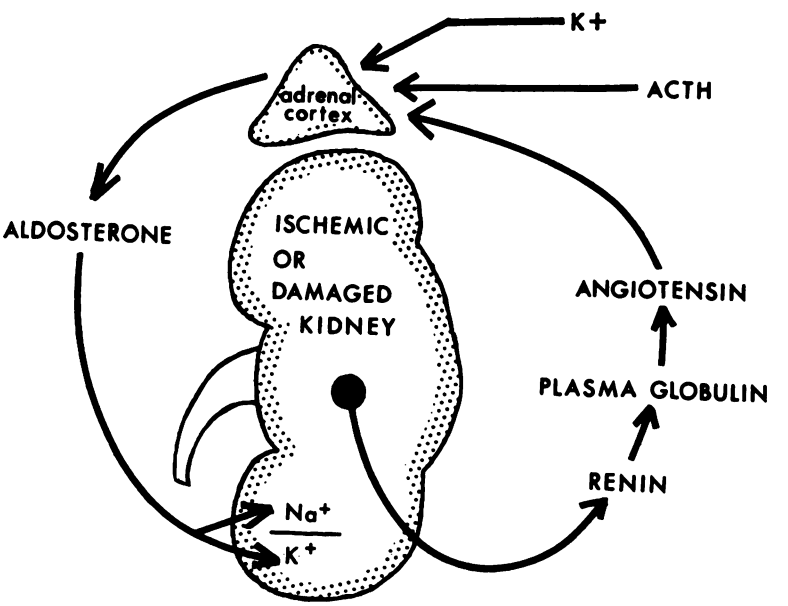

Fig. 2. Renal-adrenal interaction involving angiotensin, aldosterone, and NA^+K^+ metabolism.

source; in fact, it was this sort of reasoning in our laboratory that led us to guess right in one of those rare occasions in medical research. We decided to study the effect of angiotensin, the renal pressor substance, to see whether it was responsible for the hyperaldosteronism of malignant hypertension. Even though this material had become unpopular, we suspected there might be such a connection because, obviously, kidney disease is the cardinal locus of pathological change in malignant hypertension.

The results we obtained are now an old story familiar to most of you. It was possible to demonstrate a renal-adrenal hormonal interaction because, when we infused angiotensin II into normal volunteers, a marked increase in adrenal secretion of aldosterone was produced. The effect was highly selective because cortisol secretion did not increase and because it could not be produced with any other pressor agent.

It therefore appears that this octapeptide, which is the most powerful pressor substance known, also has at least a second function—as a trophic hormone to call forth the adrenal secretion of aldosterone.

These observations thus revived interest in the renal pressor system and pointed to a kidney-adrenal interaction for the regulation of blood

pressure. They allowed us to make a proposal about what is happening in malignant hypertension. Figure 2 presents the hypothesis diagramatically to which we still hold today. In malignant hypertension the kidney develops a critical degree of damage for reasons not fully elucidated. However, when this critical renal damage develops, the syndrome is set in motion: renin is inappropriately secreted into the blood stream in excessive amounts. The renin interacts with the specific circulating plasma globulin (renin-substrate) to release angiotensin II. Angiotensin II, in addition to raising the blood pressure by constricting arterioles, also stimulates the secretion of the aldosterone by the adrenal cortex. The aldosterone, in turn, acts on the kidney to cause sodium retention and in this way to restore renal perfusion.

In normal subjects this feedback loop is closed by the sodium retention, and the increased renin secretion ceases. However, in malignant hypertension, because of the kidney damage, a vicious cycle develops, because the induced aldosteronism cannot turn off the renin secretion, probably because it cannot cause appropriate sodium retention or because the damaged kidney keeps secreting renin. A situation develops in which there is too much angiotensin and too much aldosterone in the blood together at the same time. This vicious cycle, we think, is crucial to the pathogenesis of malignant hypertensive syndrome.

There is a good deal of evidence to support this view. First, the early work of Skeggs and his associates clearly showed there is too much angiotensin in the blood of patients with malignant hypertension. Second, the more recent animal experiments, by Masson and his associates, indicate that when either angiotensin or aldosterone are injected separately into rats no significant pathological changes occur. But when the two agents were given together (either angiotensin and aldosterone or renin and aldosterone) severe and rapidly fatal vasculitis is produced in all of the animals. Furthermore such a malignant syndrome has also been reproduced in the Goldblatt model by tightening the Goldblatt clamps. Here, too, there is evidence for hyperreninemia and hyperaldosteronism which is not observed in milder chronic preparations. This too suggests that chemotropic vasculitis from too much renin and aldosterone is a key pathophysiologic derangement in the pathogenesis of the malignant stages of hypertensive disease.

A large body of evidence has now accumulated to indicate that this renal-adrenal hormonal interaction plays a major role in the day-

to-day regulation of salt balance and blood pressure in all of us. As you know, there are now many studies which indicate that a low-sodium diet in normal subjects produces high plasma renin, and that the high renin caused by the low-salt diet is probably the reason for the hyperaldosteronism (and the renal sodium conservation) of the low-sodium diet that occurs in normal subjects. Conversely, high-salt diets in animals or humans will promptly discontinue the secretion of renin, and this stops the secretion of aldosterone. Dietary salt is thus regulated by these two hormones. Their dynamic changes explain the magnificent constancy of our body weight despite wide fluctuations in diet.

There are certain key implications of these observations for the analysis of various types of hypertensive disease. Obviously if a hypertensive patient has hyperaldosteronism, the next step is to find out why. If he has hyperaldosteronism, and you can measure plasma renin levels, and that is increased, obviously the aldosteronism of the patient is secondary to release of the renin from some sort of a renal disturbance. On the other hand, if a patient has hyperaldosteronism or the clinical signs of it (hypokalemia is the chief clinical sign) and his plasma renin levels are low one can then suspect a hormonal disturbance in which the adrenal is primarily at fault with an autonomous adenoma that causes the retention of salt and suppresses the kidney's secretion of renin.

Thus it is theoretically possible to make judgments about the disturbances in this hormonal system in all hypertensive patients by making these measurements. However this is not logistically feasible. A wide experience throughout the world indicates that it is also probably not necessary in most patients, because in evaluating the clinical situation if one makes repeated measurements of plasma potassium levels (in the absence of thiazide diuretics) one can obtain reliable indirect evidence as to whether or not aldosteronism is present. This is because aldosterone, the sodium-retaining hormone, is also a kaliuretic hormone. Therefore one can expect that almost all patients with aldosteronism will exhibit hypokalemia when on a normal sodium diet (a low-sodium diet can mask this effect by reducing distal tubular sodium supply).

Studies of the Renin-Angiotensin Aldosterone System in Essential Hypertension

As indicated, certain investigators have been very enthusiastic about the possibility that a significant fraction of patients with benign essen-

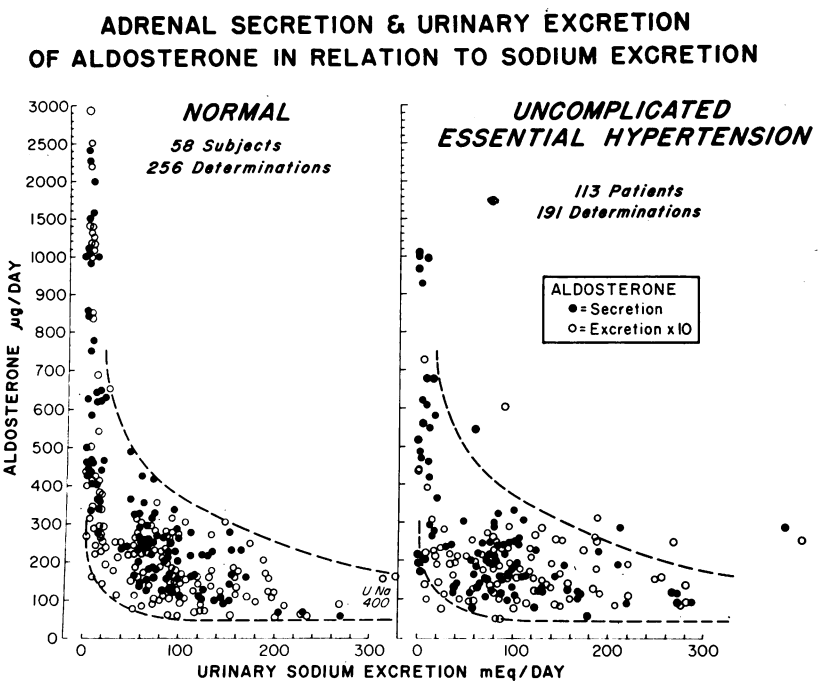

Fig. 3. Adrenal secretion or urinary excretion rate of aldosterone in relation to sodium balance in uncomplicated essential hypertension as compared with a group of normal subjects. Reproduced by permission from: Ledingham, J. G. G., Bull, M. B. and Laragh, J. H. The meaning of aldosteronism in hypertensive disease. *Circ. Res.* Supplement II, *20* and *21:* II-177, 1967.

tial hypertension actually may have oversecretion of aldosterone as the occult cause of their disease. One group has actually proposed and predicted that 20% of this large population actually have primary aldosteronism but have escaped identification because, for some strange reason, they remain normokalemic. This being the case, it has been said that one can identify them only by measuring aldosterone and renin directly.

Because of these claims we have looked into this matter further, and now have amassed some several hundred patients in which these complicated measurements have been made. We have found no gold in this pursuit, and there is no reason for us to change our initial view—that most patients with uncomplicated hypertension have normal rates of aldosterone secretion.

I shall run through these data to give you a feeling for the results you might expect if you were evaluating a hypertensive patient with the aid of these special measurements—at least in the New York City

area. Figure 3 presents some 450 measurements of aldosterone secretion or excretion made in normal subjects and in patients with benign essential hypertension. The only way for such measurements to have any meaning is to relate them to an index of the concurrent state of salt balance. The normal curve, shown on the left, is plotted against the daily rate of urinary sodium excretion. You can see that the relation forms a hyperbola, which suggests a high degree of interdependence between salt balance and the secretion of aldosterone. All measurements of this hormone in disease must be evaluated against this nomogram. Note that normal subjects can secrete enormous amounts of aldosterone—up to 3,000 μg. on a low-salt diet—and that they produce virtually not any on a very high salt diet; thus one must realize the normal can invade far into the pathological range both on the high and low side, depending on salt balance. Any measurement of aldosterone, as arduous as it may be, has very limited meaning unless the simple measurements of urine sodium are made together with it.

With the nomogram of Figure 3 in mind, take a look, on the right-hand panel, at the patients with uncomplicated hypertensive disease. You can see that the large majority of such patients have normal rates of aldosterone secretion. However there are a few, about 4%, that are clearly above normal, as shown here. In these few we measured plasma renin on many occasions. Plasma renins were always high in these few, indicating that the hyperaldosteronism, when it does occur, is always secondary to renal dysfunction. These patients, although we must classify them as benign essential hypertensives, probably have occult renal disease not detectable by the conventional clinical parameters. Taken altogether these data indicate that: 1) hyperaldosteronism is rare in essential hypertension, and 2) when it does occur it is consequent to an increased renin secretion.

Let us look, then, at the second index of this renal-adrenal interaction, the secretion of renin in hypertensive disease. Figure 4 presents data on plasma-renin activity with the normal curve on the left, and the results of uncomplicated cases with benign hypertension on the right. Again, plasma-renin activity depends on salt intake and the concurrent rate of urinary sodium excretion. On the left you can see that the same hyperbolic relation obtains between plasma-renin activity and salt balance in normal subjects.

The hypertensive patients as a group are not as normal with respect

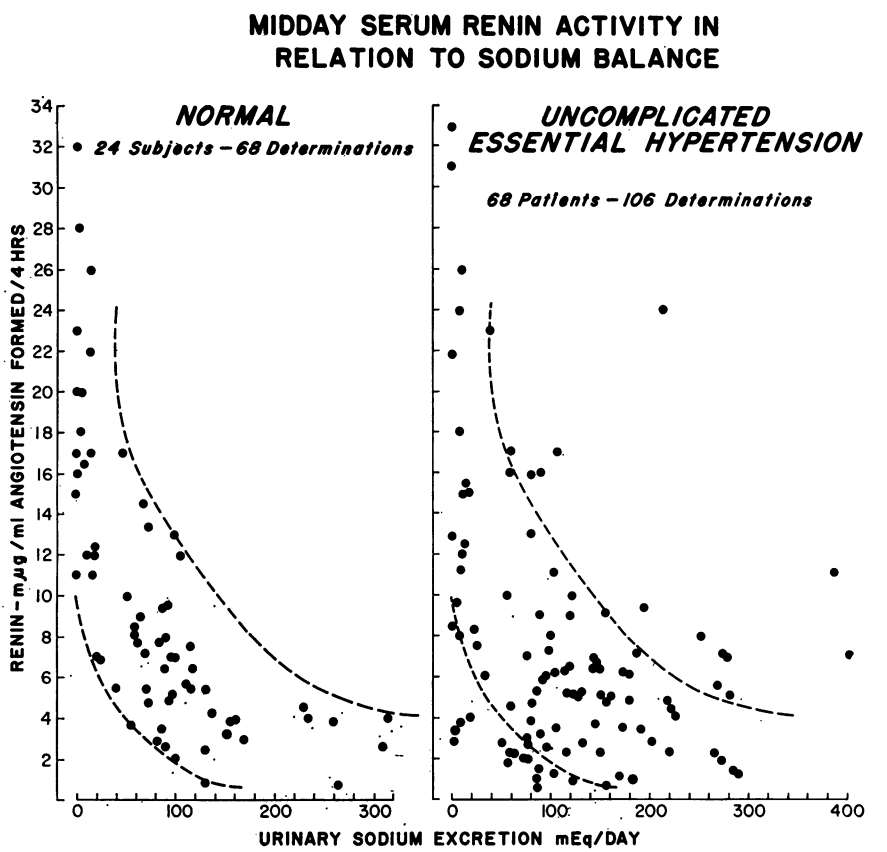

Fig. 4. Mid-day serum-renin activity related to the state of sodium balance in normal subjects and in patients with uncomplicated hypertension. Reproduced by permission from: Ledingham, J. G. G., Bull, M. B. and Laragh, J. H. The meaning of aldosteronism in hypertensive disease. *Circ. Res.* Supplement II, *20* and *21:* II-177, 1967.

to their renin levels as they are with respect to aldosterone. You can see that most patients with uncomplicated hypertension have normal plasma renin levels—but not all. There are minor categories exhibiting derangement here; there is one group that is too low, a group comprising about 10 or 12%. Then there is another group of about 10 or 12% in the series in which plasma-renin activity is clearly higher than normal.

The finding of a high group is not so surprising. One can accept the idea very easily that some patients with essential hypertension really have renal hypertension—perhaps they have some sort of parenchymal renal disease that we cannot identify, which produces occult hyperreninemia. This is not so surprising.

TABLE I. INCIDENCE IN ESSENTIAL HYPERTENSION

I. *Aldosteronism:*
5 of 113 patients *(4.4%)*
all 5—renin increased

II. *Abnormal serum renin:*
A. Increased—9 of 68 *(13.3%)*
1) With aldosteronism, 5
2) Aldo normal, 4 (hypokalemic)

B. Reduced—8 of 68 *(11.8%)*
1) Unresponsive to Na depletion (2)
2) Responsive to Na depletion (6)
} aldo normal or low in all

III. *Increased aldosterone with lowered renin: (0.0%)*

But the fact that you can have established and quite impressive arterial hypertension with subnormal plasma-renin levels is rather surprising. This could be a clue—one that tells us something; nobody knows what.

Low plasma-renin levels in hypertension is something that has intrigued many investigators. In fact this observation led the Michigan group to say that these patients have suppressed renins because of occult primary hyperaldosteronism, and therefore they claimed that this significant fraction of the essential hypertension population really have adrenal tumors and therefore they might all be potentially curable by adrenal surgery.

Our own studies give no support whatever to this reasoning, because we have measured aldosterone secretion in the subnormal renin group of hypertensives many times, and it is always normal or correspondingly low.

Table I recounts and summarizes the salient abnormalities observed in our study of patients with uncomplicated hypertension. Increased secretion of aldosterone was a rare finding; it occurred in about 4% of 113 patients. In every instance it could be attributed to an increase in serum-renin activity. Altogether, abnormal renin levels were observed in 25%. Abnormally high concentrations of renin were observed in nine patients or 13%. The increased renin was accompanied by increased aldosterone secretion unless hypokalemia was present.

Eight patients, or 11.8%, had suppressed renin activity. The cause

of this hyporeninemia was shown not to be hypersecretion of aldosterone because in all of them aldosterone secretion was normal or low.

Among this series of hypertensive patients the diagnostic combination characteristic of primary aldosteronism—low renin activity with high secretion of aldosterone—was not found. In contrast to the reports of the Conn group we have not yet identified an instance of normokalemic primary aldosteronism among our patients with essential hypertension. Accordingly it is our feeling that normokalemic primary hyperaldosteronism is a rare variant of an uncommon disease.

Low Serum Renin in Other Forms of Hypertension With Hypokalemia and Hyperaldosteronism

It should be pointed out here that even in hypertensive patients actually presenting with hypokalemic alkalosis, hyperaldosteronism and a subnormal renin—the triad which one associates with primary aldosteronism—one can no longer be sure of the presence of an adrenal tumor.

Figure 5 presents metabolic data from the case of a woman of 31 who had a blood pressure of 250 over 160. This hypertension had been present for eight years during which she had some seven pregnancies. She exhibited severe hypokalemic alkalosis, and marked oversecretion of aldosterone with suppression of plasma renin, all of which persisted under various conditions of dietary electrolyte manipulation.

Accordingly this patient, we thought, almost certainly had an adrenal tumor causing Conn's syndrome or primary aldosteronism. All of the diagnostic criteria fitted beautifully. And so we explored this woman but could not find any adrenal tumor. Instead there was diffuse bilateral adrenal-cortical hyperplasia involving both glands. We were not quite sure what to do, and we finally decided to do a total adrenalectomy, assuming this must be involved in the causation. A renal biopsy taken at operation revealed atrophy of the juxtaglomerular apparatus —a finding in keeping with the suppressed plasma-renin values.

The only problem with the patient is that her basic disease was not improved by the total adrenalectomy even though, postoperatively, her aldosterone secretion fell to zero and her renin levels came up into the high normal range. Hypertension of a high degree has persisted for three years even without mineralocorticoid replacement, and antihypertensive drugs are relatively ineffective.

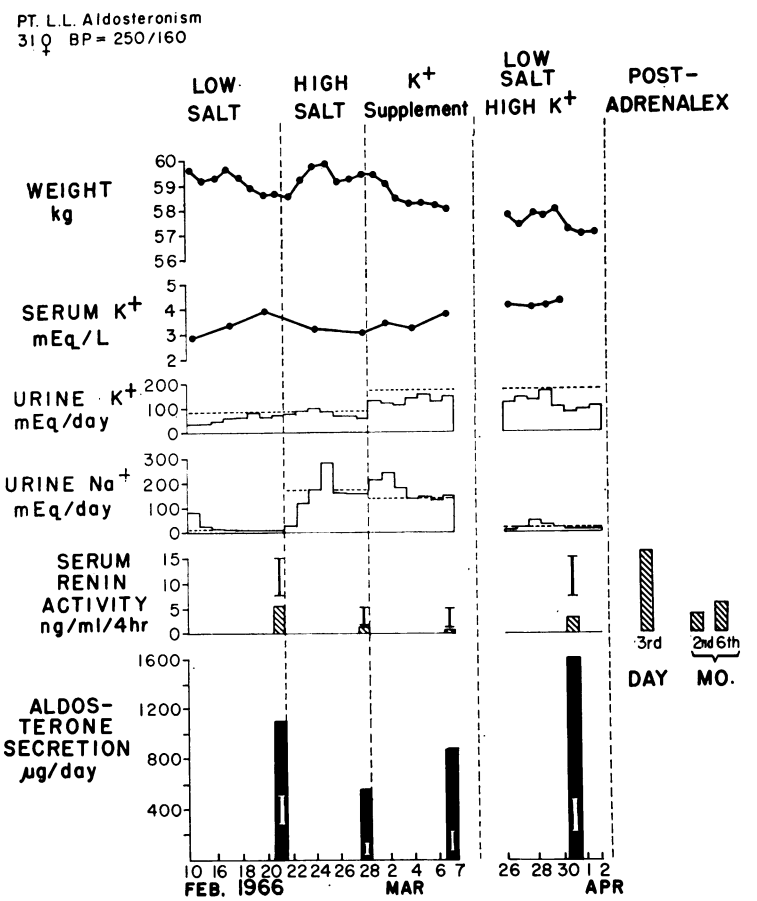

Fig. 5. Metabolism balance study of patient L. L. The dotted lines indicate the intakes of potassium and sodium. The normal ranges for aldosterone secretion and for mid-day serum renin in ambient subjects for each dietary sodium intake are indicated. Aldosterone secretion was always markedly increased and serum-renin levels were abnormally low. The responses of aldosterone and renin to manipulations in sodium intake were blunted. Potassium repletion was more easily accomplished when dietary sodium was reduced. Reproduced by permission from: Laragh, J. H., Ledingham, J. G. G. and Sommers, S. C. Secondary aldosteronism and reduced plasma renin. *Trans. Ass. Amer. Phys. 80*:168, 1967.

If this were just one case, we could say, "Well, it really was primary aldosteronism, but we got the disease too late." But now we have a collection of such patients, who show no benefit whatever from total adrenalectomy. We feel that this condition is biologically different from primary aldosteronism due to an adrenal tumor. We believe that because both glands are involved the adrenal cortex is being driven by an extra adrenal stimulus other than renin, perhaps another hormone.

TABLE II. LOW RENIN SITUATIONS (OTHER THAN PRIMARY ALDOSTERONISM)

A. With increased aldosterone:	
1) *Nonadenomatous adrenal disease*	
2) *Dexamethasone—responsive hypertension**	
3) *High K^+ Intake*	
B. With Normal or Low Aldosterone:	
Essential Hypertension	11.8%

*Laidlaw, Petersen.

Whatever the case, observations of this sort describe one more situation (besides primary aldosteronism) in which established hypertension is associated with very low plasma-renin levels.

CAUSES OF LOWERED RENIN ACTIVITY IN HYPERTENSIVE PATIENTS

Because subnormal renin levels occur in a variety of hypertensive disorders it is pertinent at this point to review the circumstances in which renin levels are low. Table II recapitulates the situations we have observed other than primary aldosteronism, which may be characterized by hyporeninemia. As you can see, serum-renin levels can be depressed whether or not aldosterone secretion is increased. Furthermore, even when the characteristic findings of primary aldosteronism are demonstrable, i.e., increased aldosterone with suppressed serum renin, an adrenal tumor may not always be found. A patient was described above with nonadenomatous adrenal disease who appears to be an example of a syndrome in which the primary abnormality is extra-adrenal. She may be similar to four patients studied by others, all of whom exhibited aldosteronism, hypokalemia, and hyporeninemia.

A high potassium intake can induce elevation of aldosterone secretion with reciprocal depression of serum-renin activity. For this reason, too, this combination of findings can no longer be accepted as a specific indicator of an oversecreting tumor.

However, the nonspecificity of a suppressed serum renin is most clearly defined by the impressive incidence of this abnormality—11.8% —in patients with essential hypertension in whom aldosterone secretion was clearly either normal or low. One must therefore conclude that factors other than aldosterone can depress renin activity in hypertensive patients.

Renal Hypertension

As part of my presentation this morning I should like to consider briefly the clinical problem of renal hypertension insofar as it involves the renal-adrenal hormonal interaction.

Despite intensive study and the development of many angiographic and physiologic tests the cure rates in patients with hypertension associated with unilateral renal disease certainly leave something to be desired. This experience per se suggests that we do not understand fully the pathogenesis of this type of hypertension. Furthermore, as I shall illustrate, there is now a large body of data in both animals and man which suggests that, contrary to expectations, renin levels may not be increased in the chronic stage of this disorder.

Basic Diagnostic Procedures

A typical defect of the Goldblatt kidney is exemplified by its excessive water and sodium excretion or its inability to excrete salt compared with the unaffected kidney. This phenomenon has been studied by many investigators, beginning with White and his associates in dogs. Howard was the first to exploit this characteristic as a diagnostic aid in man.

In our own work, because of the logistical and technical difficulties inherent in such differential renal functional tests, we have turned, as many others have, to the use of timed intravenous pyelography as a basic screening test.

Our experience convinces us that if you do a pyelogram in which the bolus of dye is given rapidly, and then care is taken to time the pictures accurately in the first five minutes one can get a reasonably reliable measure of the glomerular filtration rate in each kidney—probably as accurate as you can with clearance techniques because of the atraumatic approach. With this technique the rate of appearance of the dye in each kidney is related to the GFR, and the concentration of the dye is related to the reabsorption of water. This functional pyelographic test, while imperfect, is amenable to large-scale screening approaches, and it allows us to broaden the search for Goldblatt's phenomenon in man. If such a pyelogram is executed properly and read according to strict criteria, we can get upward of an 80 or 90% correlation with what one can detect by using the more difficult technique of renal arteriography.

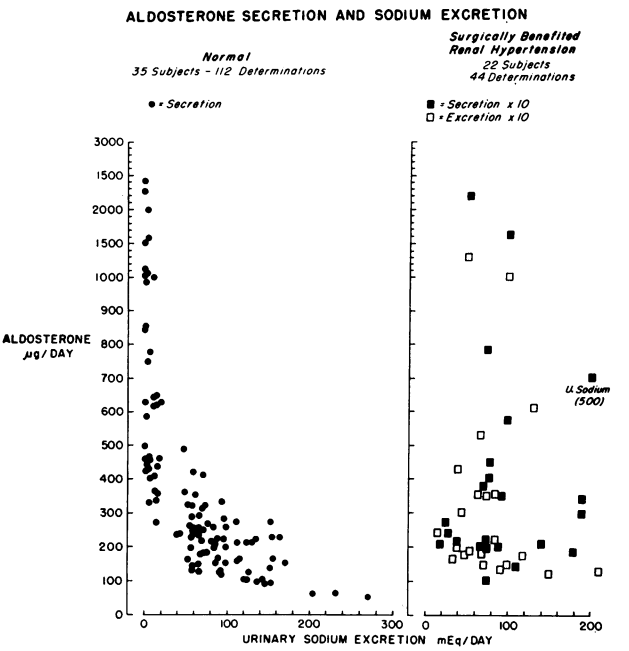

Fig. 6. Aldosterone secretion or excretion and sodium excretion in hypertension of unilateral renal disease. Eighteen of these 22 patients underwent surgery, and in these cases blood pressure was improved a year or more after surgery. The preoperative measurements indicated that the condition often exists with normal aldosterone metabolism. The patients with increased values had more severe hypertension with hypokalemia. See text. Reproduced by permission from: Laragh, John H., Sealey, Jean E. and Sommers, Sheldon C. Patterns on adrenal secretion and urinary excretion of aldosterone and plasma renin activity in normal and hypertensive subjects. *Circ. Res. 18* and *19:* 1-158, 1-174, 1966.

Renin and Aldosterone in Goldblatt's Hypertension

Having found these cases in this way, one can inquire: "How about renin? Classical thinking dictates that renin ought to be increased in all these patients. And how about aldosterone secretion?" It too should be increased. We thought that because aldosterone secretion is such a good index of renin secretion that we should measure aldosterone secretion in renal hypertension. Figure 6 shows you the disappointing results we obtained in a study of 20 surgically corrected cases of hypertension due to unilateral renal disease. You can see that the secretion and excretion of aldosterone is usually normal preoperatively in patients with established Goldblatt hypertension.

This experience bothered us; but it also allowed us to remember that many of the old investigators, going back to Braun-Menendez and Page, Dexter, and others, had repeatedly failed to demonstrate increases in

renin in the blood of animals or patients with Goldblatt hypertension. This was one reason that renin became unpopular for a while.

More recently, with more reliable methods, renin has been restudied by many investigators in Goldblatt's hypertension, and most investigators have reported that a considerable fraction of such subjects do not have increased plasma-renin levels in their peripheral circulations. Combined with our aldosterone results this is perhaps a rather shocking set of observations, because this forces all of us to say: "Does renin cause renal hypertension? Maybe it doesn't." An alternate explanation is that the system has gone through some sort of feedback and normalized renin in the chronic state, but if this be true, one should be able to reveal the fault by an appropriate test to induce increased renin secretion. So far this has not been possible. Some people retain tenaciously the idea that renin causes renal hypertension. However, in my opinion such a view is still unproved. The key problem is really that we do not understand the exact role of renin in the pathogenesis of renal hypertension, and that much more work needs to be done in this area.

The Role of Circulating Renin Substrate: Studies with Oral Contraceptives

The renin-angiotensin aldosterone system is more complicated than other better known endocrine systems. The kidney secretes renin into the blood; then it reacts in the blood with an alpha globulin (a renin substrate) made by the liver to release angiotensin I, a decapeptide. This material is biologically inactive. It is now known that this decapeptide is almost entirely converted to the active substance angiotensin II by enzymes in lung tissue—in one circulation through the lung. Accordingly the lung is potentially an important cofactor in determining the activity of this hormonal system.

Another important cofactor in this hormonal system may be the rate of formation and the concentration of plasma of the renin substrate. This particular aspect has interested us because of the fact that the use of birth control pills, as well as the state of pregnancy itself, are two situations in which one observes enormous increases in the concentration of renin substrate in the blood. This per se could cause large increases in blood angiotensin to occur—in response to normal amounts of renin.

What the full meaning of this abnormality is we do not know, for

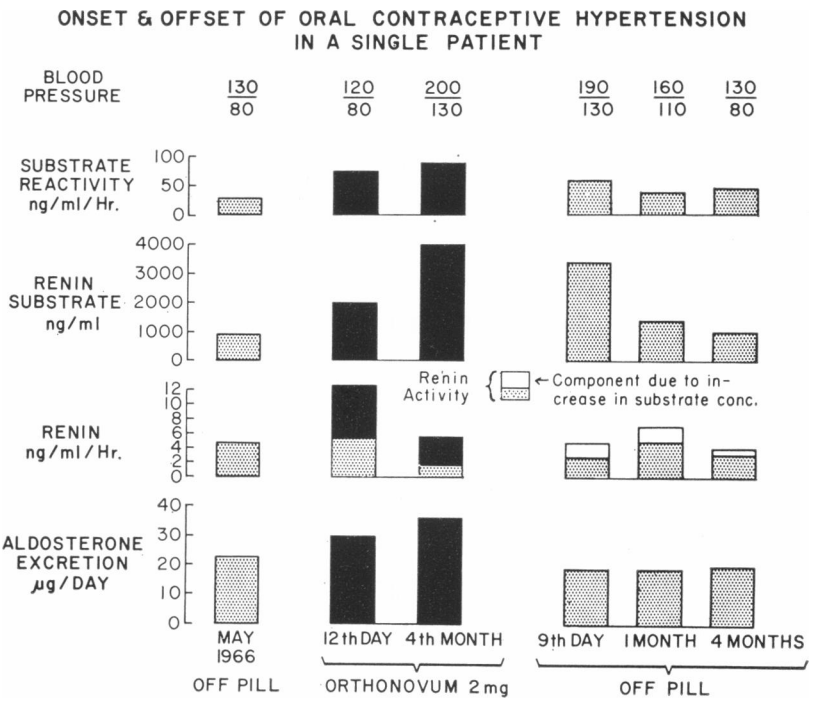

Fig. 7. Oral contraceptive hypertension in a 32-year-old woman in whom hypertension was first discovered after 3 years of oral contraceptive therapy with Enovid 5 mg. Hypertension disappeared after drug withdrawal. It reappeared, as shown here, when treatment was renewed, and then disappeared again after drug withdrawal. The onset and offset of hypertension was associated with concomitant increases and decreases in renin, aldosterone, renin substrate, and reactivity to renin. The data illustrate that in this patient the observed increase in renin activity was largely due to an increase in renin substrate concentration. Reproduced by permission from: Newton, N., Peeler, D. and Newton, M. Effect of disturbance on labor. An experiment with 100 mice with dated pregnancies. *Amer. J. Obstet. Gynec. 101*:1096-1102, 1965.

many patients who take oral contraceptives do not have hyperaldosteronism even though their renin substrate levels are very high. However we have observed some patients who cannot adjust to this deformation of the system.

We have collected more than a dozen such patients, and other investigators are now reporting the same situation all over the world: that the administration of oral contraceptives in certain people can produce hypertension or aggravate markedly preexisting hypertension.

Figure 7 illustrates the case of a woman of 33 whose blood pressure was repeatedly known to be 130/80 who was started on Enovid; 3 years later it was 200 over 130. Associated with this was an enormous rise in the renin-substrate level. The aldosterone secretion increased, and

the renin levels also increased. When the pills were stopped, all of the biochemical abnormalities returned to normal, and so did the blood pressure. Furthermore a rechallenge with Orthonovum produced exactly the same thing—a reappearance of impressive hypertension.

There is, of course, no doubt that oral contraceptives do not cause hypertension in the vast majority of people that take them, but our results suggest to us that in certain susceptible individuals, at least, the deformation of the renin-angiotensin system, which these compounds can produce, may be critically involved in the production of hypertension.

SUMMARY

I should say again that a great deal has been learned about the renin-angiotensin system, and about its involvement in the curable forms of adrenal and renal hypertension.

Because we do not fully understand the true or exact role of renin in renal hypertension, certain reservations must be made in drawing conclusions when using these measurements diagnostically.

It appears that as useful as the measurement of renin is, a subnormal renin may not point to primary adrenal disease, and that a supernormal renin may not point to renal disease—especially if other phenomena, such as oral contraceptives, are interfering with this hormonal system.

REFERENCES

Laragh, J. H., S. Ulick, W. Januszewicz, Q. B. Deming, W. G. Kelly and S. Lieberman. Aldosterone secretion and primary and malignant hypertension. *J. Clin. Invest. 39:*1091, 1960.

Laragh, J. H., Cannon, P. J., Meltzer, J. I., Fleming, R. J. and Stason, W. B. Recent advances in hypertension, combined staff clinic. *Amer. J. Med. 39:*616, 1965.

Laragh, J. H., J. E. Sealey and S. C. Sommers. Patterns of adrenal secretion and urinary excretion of aldosterone and plasma renin activity in normal and hypertensive subjects. *Circ. Res.* (Suppl. I) *18 and 19:* I-158, 1966.

Ledingham, J. G. G., Bull, M. B. and J. H. Laragh. The meaning of aldosteronism in hypertensive disease. *Circ. Res.* (Suppl. II) *20 and 21:* II-177, 1967.

Laragh, J. H., J. G. G. Ledingham and S. C. Sommers. Secondary aldosteronism and reduced plasma renin in hypertensive disease. *Trans. Ass. Amer. Physicians 80* 168, 1967.

Newton, M. A., J. E. Sealey, J. G. G. Ledingham and J. H. Laragh. High blood pressure and oral contraceptives. *Amer. J. Obstet. Gynec. 101:*1037, 1968.