CLINICAL AND PATHOLOGICAL ASPECTS OF PRIMARY ALDOSTERONISM

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Aan Els,
Maartje, Gijs, Imke en Meike

Aan mijn ouders

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INLEIDING

Met de studies van Kloppenborg over „De secretiesnelheid van aldosteron onder normale en pathologische omstandigheden" (Thesis, 1966) en van Benraad over de „Bepaling van aldosteron met behulp van een dubbel-isotoop methode" (Thesis, 1966), werd het beslag gelegd voor de totstandkoming van dit proefschrift. In de Kliniek voor Inwendige Geneeskunde te Nijmegen bestond echter reeds langer belangstelling voor de water- en zouthuishouding bij de mens, met name door de oorspronkelijke waarneming van Majoor over de remming van de secretie van aldosteron onder invloed van heparine in 1955, tevens het jaar waarin Conn het syndroom „primair aldosteronisme" wereldkundig maakte. Het is dan ook niet verwonderlijk, dat het syndroom „primair aldosteronisme" in de Nijmeegse Interne Kliniek, de belangstelling van velen heeft genoten, zoals mede tot uiting is gekomen in de proefschriften van Casparie (1968), Driessen (1969) en Drayer (1975). Een toenemend aanbod van patienten met primair aldosteronisme en ontwikkelingen in diagnostiek en behandeling, waarmee de laatste jaren ervaring werd opgedaan, hebben geleid tot studies, waarvan de resultaten in dit proefschrift werden neergelegd Deze ontwikkelingen waren:

1. De bepaling van aldosteron in plasma. Hiermee werd het mogelijk de regulatie van aldosteron bij patienten te bestuderen en tevens na te gaan in hoeverre het gedrag van aldosteron bij patienten met primair aldosteronisme met en zonder bijnieradenomen, verschillend was
2 Scintigrafie van de bijnieren Het lokaliseren van aldosteron-producerende adenomen langs niet invasieve weg, leek een aantrekkelijk en voor de patient weinig belastend onderzoek, waarmee het succes van een operatie aanzienlijk zou kunnen worden vergroot.
3 Medicamenteuze behandeling met spironolacton of amiloride. De waarneming dat amiloride bij sommige patienten een bruikbaar medicamenteus alternatief is voor spironolacton, heeft geleid tot een vergelijkend onderzoek naar het werkingsmechanisme van beide medicamenten

Het hier bovengenoemd onderzoek werd vooral gestimuleerd door de wetenschap, dat patienten met primair aldosteronisme zonder bijnieradenoom (idiopathisch aldosteronisme) over het algemeen niet gunstig reageren op een operatieve behandeling Het was daarom nodig om over betrouwbare diagnostische methoden te beschikken om deze patienten preoperatief te identificeren en te beschikken over optimale medicamenteuze behandelingsmethoden.

CHAPTER I

REVIEW OF DATA IN THE LITERATURE ON PRIMARY ALDOSTERONISM

I.1. History and classification

In 1955 Conn gave a description of a woman aged 34 years with a clinical picture of intermittent tetany, paresthesia, periodic severe muscular weakness and paralyses, polyuria, polydipsia, hypertension and absence of edema. There was a severe hypokalemic alkalosis, that could not be corrected permanently by administration of potassium, hypernatremia and a renal tubular defect in the reabsorption of water. In the urine an excess of a sodium retaining corticoid was found, that 2 years later, after a method for its determination had become available, could be identified as aldosterone (Conn 1967). Operative removal of an adrenal adenoma 4 cm in size led to disappearance of the complaints and a normalization of the blood pressure (Conn 1955b; Conn and Louis 1956). The syndrome was given the name of "primary aldosteronism" by Conn. As early as 1956 12 cases of primary aldosteronism were known to Conn (via "personal communication"). A rapidly increasing number of publications made it possible for Conn in 1964 to describe the clinically characteristic features of the syndrome on the basis of 145 cases that up to that time had been published (Conn et al. 1964a). Most of the patients were 30 to 50 years old; there were fully 2.5 times as many women as men. The adenomas, the greater proportion of which were localized in the left adrenal were solitary in 91% of the cases, weighed less than 6 grams and were smaller than 3 cm. In 70% of the cases the blood pressure became normal on removal of the adenoma. The "classical symptoms" were certainly not present in all of the patients and some patients (5%) manifested no symptoms whatever. Later on it was found from various case reports that an adenoma of the adrenal was not revealed at operation in every patient who fulfilled all the criteria for making the diagnosis. At operation in such cases a bilateral adrenal hyperplasia was established while, in some patients, no anomalies were encountered in the adrenals. At first Conn was of the opinion that 2 groups of patients with "primary aldostero-

nism"* without adrenal adenoma could be distinguished (Conn 1961): one group with so-called "congenital aldosteronism" – young adults and children often with malignant hypertension in whom the blood pressure in the majority of cases responded well to a (sub)total adrenalectomy (van Buchem et al. 1956, Therien et al. 1959, Kretchmer et al. 1959, Moran et al. 1960), and another group – adults in whom in general the blood pressure did not respond favourably to a (sub)total adrenalectomy (only in 1 of the 9 patients who werd diagnosed up to 1961 did the blood pressure fall after operation). Later on, no more cases of "congenital aldosteronism" have been reported in the literature. It is possible that these first publications were, in fact, dealing with patients with a secondary hyperaldosteronism (renin determinations were not available at that time). Adult patients in whom no adrenal adenoma was found became continually better known at the end of the sixties, probably because of the extension of the diagnostic possibilities (Davis et al. 1967, Katz 1967, Salti et al. 1969). The studies of Biglieri et al. and Baer et al. that were published simultaneously in 1970 showed that this form of "primary aldosteronism" was not so rare as was thought at first: in 11 of the 23 patients who from 1959 to 1969 were operated on in the Presbyterian Hospital in New York City on account of "primary aldosteronism", no adrenal adenoma was found (Baer et al. 1970); and the same is true for 14 of the 49 patients operated in the San Francisco General Hospital (Biglieri et al. 1970a). A second important discovery in both studies was that the patients with and without an adrenal adenoma could not be distinguished from each other preoperatively although the degree of aldosteronism and the metabolic consequences it entailed in patients with an adrenal hyperplasia were, in general, less severe. The fact that patients with and without adrenal adenoma could not be differentiated on clinical and biochemical grounds was, however, not of merely theoretical importance: in patients without adrenal adenoma the effect of an operation (unilateral or (sub)total adrenalectomy) remained limited to a correction of the metabolic aberrations. In none of these patients was there a normalization of the blood presure, in contradistinction to a "cure rate" of 83% (Baer et al. 1970) and 60% (Biglieri et al. 1970) in patients with adenomatous primary aldosteronism. The discoveries that both adrenals of a great proportion of the patients were hyperplastic and the disappointing results of the adrenal surgery raised doubt about the "primary" character of the diagnosis of "primary aldosteronism" in these patients. For this reason Baer et al. (1970) suggested the name "pseudo-primary aldosteronism", and by Biglieri et al. (1970) the expression "idiopathic aldosteronism" was advised, a denomination that was first used by Liddle in 1962 and that nowadays is used

* Conn reserved the name "primary aldosteronism" for the cases with an adenoma.

almost generally for the definition of patients with primary aldosteronism in whom no aldosterone-producing adenoma is found The findings of Baer et al and of Biglieri et al are supported by the publications of Distler et al (1969) and George et al (1970), who found no adenoma at operation in 50% and 32% of patients with primary aldosteronism, respectively, while the blood pressure in general did not return to normal values after the performance of (sub)total adrenalectomy Also, from recent review articles (Ferriss et al. 1978a, Weinberger et al. 1979) it is clear that idiopathic aldosteronism exists relatively frequently Thus, in the group of patients with primary aldosteronism examined by Ferriss et al in 14 out of 64 of the operated patients (21%) no adenoma was found, whereas Weinberger et al reported the absence of an adenoma in 11 of 51 patients (21%) The fact that idiopathic aldosteronism not rarely occurs has from the beginning of the seventies led to the development of methods and techniques that make possible a pre-operative differentiation between idiopathic and adenomatous aldosteronism, the objective of which is to save patients with the first mentioned form of primary aldosteronism from an unnecessary operation

Besides the 2 most frequently occurring forms of primary aldosteronism – adenomatous and idiopathic – 2 more, but less frequently occurring subgroups of the syndrome are distinguished, namely ."glucocorticoid remediable aldosteronism" and "primary aldosteronism as the sequel of an aldosterone-producing carcinoma" Glucocorticoid remediable aldosteronism is a very rare form of primary aldosteronism, that has been found up till today in 5 patients, while research among the members of the families of these patients brought to light more cases in 4 of the 5 families (Sutherland et al 1966, New et al 1973, Miura et al 1968, Giebink et al 1973, Grim et al 1980) It is a familial affection that is inherted autosomal dominantly (New et al 1980) The affection is characterized by. a slight hypertension, suppressed renin activity, a moderate aldosteronism, a complete suppressibility of the aldosterone excretion within 24 hours after the administration of 1 mg of dexamethasone, and a normalization of the blood pressure after 10 to 14 days of treatment with low doses of glucocorticoids In general the opinion is that for these reasons patients with primary aldosteronism should receive a trial of dexamethasone treatment for 14 days. The adrenal lesion in these patients is a bilateral adrenal hyperplasia (Sutherland et al 1966)

The aldosterone-producing adrenal carcinoma is a rare affection, that was first reported by Foye and Feichtmeir (1955). Apparently up till today less than 20 cases have been reported in detail in the literature. For a general review of this subject we refer the reader to chapters VIII 6. and IX of this thesis.

I.2. Diagnosis of primary aldosteronism and differentiation between idiopathic and adenomatous aldosteronism

I.2.1. *Clinical diagnosis*

The clinical features of the syndrome mostly contribute little to making of the diagnosis, in view of the fact that in many patients – and above all in patients with idiopathic aldosteronism – these may be partially or entirely absent. In the review published by Conn in 1964 muscular weakness (73% of the patients), polyuria and nycturia (72% of the patients), headache (51% of the patients) and polydipsia (46% of the patients) belonged to the most frequently occurring symptoms. The presence of a raised blood pressure proves to be no absolute precondition in view of the recent report in the literature of 3 patients with primary aldosteronism and a normal blood pressure (Snow et al. 1976, Zipser and Speckart 1978, Kono et al. 1980). At first it was thought that the hypertension only rarely induced vascular complications or the development of a malignant hypertension (Kaplan 1963). But it has now become evident that patients with primary aldosteronism are not exempt from the complications of hypertension (Kloppenborg et al. 1974, Beevers et al. 1976). Thus, Beevers et al. (1976) reported that 2.9% of patients with primary aldosteronism developed malignant hypertension, while 22.8% acquired vascular complications.

I.2.2. *Biochemical diagnosis*

The diagnosis of primary aldosteronism is based on the demonstration of an inappropriately raised aldosterone production and a suppression of the plasma renin activity in patients with hypertension (Conn 1964b). For the detection of patients with primary aldosteronism the demonstration of a spontaneous and persistent hypokalemia is a simple aid. In 1966, however, Conn reported the presence of persistently normal plasma potassium concentrations in a few patients with histologically confirmed primary aldosteronism, which caused him to suggest that probably a considerable proportion of patients (± 20%) with essential hypertension in fact may suffer from primary aldosteronism. This suggestion was also based by him on the following considerations:
1. The occurrence of a suppressed plasma renin activity in primary aldosteronism (Conn 1964b) and in 21% of unselected hypertensive patients (Brown et al. 1964).
2. A disturbed carbohydrate tolerance, a frequent finding in patients with primary aldosteronism, may – conversely – also be an indication of

primary aldosteronism in patients with "essential hypertension" (Conn 1965).
3. The occurrence of so-called "non-functioning adrenal adenomas" in 20% of autopsy patients with essential hypertension (and only in 1.8% of patients without hypertension (Shamma et al. 1958)). In this respect Conn proceeded from the notion that the "non-functioning" character of these adenomas is dubious.
These propositions were for many research workers an inducement for setting up research on the incidence of primary aldosteronism, the occurrence of normokalemic hyperaldosteronism and the aldosterone and renin values in the total hypertensive population. From these studies the following conclusions were drawn:
1. Primary aldosteronism is a rare affection, the incidence of which is probably much lower than 1% of the hypertensive population (Kaplan 1969, Gifford 1969, Tucker and Labarthe 1977).
2. Recent review studies (Ferriss et al. 1978a, Weinberger et al. 1979) show that intermittently or persistently normal plasma potassium values in both adenomatous and idiopathic aldosteronism are frequently found. The percentages mentioned by Ferriss et al. (28%) and Weinberger et al. (22%) are in good agreement.
3. The aldosterone production in patients with essential hypertension and a suppressed plasma renin activity was usually found to be normal (Ledingham et al. 1967). Most investigators agree that the incidence of low renin essential hypertension in an unselected hypertensive population is between 20 and 30 percent (Ganguly and Weinberger 1979).

I.2.3. *The demonstration of an inappropriately raised aldosterone production*

Most authors agree that for the demonstration of a raised aldosterone production, use must be made of one of the suppression tests that will be described here later on. The principle is based on the demonstration of an insufficient suppressibility of aldosterone after the performance of certain procedures (administration of salt and/or mineralocorticoids) with which an expansion of the plasma volume is accomplished. The excretion of aldosterone in the urine is not seldom entirely normal in patients with primary aldosteronism, if the determination is made while the patients use a diet with a normal salt content. Thus Weinberger et al. (1979) reported that in 31% of 32 patients with primary aldosteronism an excretion of aldosterone was found that was less than 20 μg/24 hours, during a diet of normal salt content. Biglieri et al. (1967) showed that excretions of aldosterone in the urine may display considerable variations from day to day, and occasionally even normal aldosterone

values may be found. In addition, Cain et al. (1972) found that the values of aldosterone secretion determined during a salt-free diet did not show any differences as between normal persons and patients with primary aldosteronism. The following suppression tests were described in the literature:

1. Dietary salt loading. To a salt-free diet is added, for 3 to 5 days, 200 mmol Na^+/day (Cain et al. 1972, Demanet and Vrijens 1971) or 300 mmol Na^+/day (Collins et al. 1970) and the secretion rate of aldosterone is determined before and during the giving of salt. Cain et al. (1972) found a percentile fall of the aldosterone secretion of 40% in patients with primary aldosteronism, and of 80% in normal control persons.
2. Intravenous administration of salt: Espiner et al. (1967) and Christlieb et al. (1971) found that giving 2 l physiological salt for 4 hours on 2 successive days, caused a fall of 83% in the aldosterone secretion rate in normal test persons and of only 16% in patients with primary aldosteronism. The test was carried out during a saltless diet. Kem et al. (1971) reached the same results after simplification of the test: plasma aldosterone determined at 08.00 hours in the morning during a normal salt-containing diet (after 2 hours of ambulation) fell in normal test persons by 84% after administration of 2 l physiological salt given intravenously within 4 hours. In patients with primary aldosteronism the fall was 25%.
3. Desoxycorticosterone acetate (DOCA). Bilglieri et al. (1967) showed that administration of DOCA 10 mg/12 hours intramuscularly for 3 days during a normal salt-containing diet in patients with primary aldosteronism, did not cause the aldosterone excretion in the urine to decrease (there was, in fact, a rise of 14%), in contrast to what was found in normals (−70%) and patients with essential hypertension (−61%).
4. 9-alpha-fluorohydrocortisone (Fludrocortisone). Oral administration of fludrocortisone for 3 days at a dose of 0.4 mg/day (Biglieri et al. 1970b), 0.8 mg/day (Padfield et al. 1975) or 1.2. mg/day (Horton et al. 1969, Lund and Nielsen 1980) is a simple test for policlinical use. From the study of Horton et al. (1969) it emerges that the plasma aldosterone concentration (during a normal diet) falls off by 82% in normals and by 15% in patients with primary aldosteronism. Padfield et al. (1975), however, found after adminstration of fludrocortisone a definite overlap between the plasma aldosterone values of patients with essential hypertension and those of patients with primary aldosteronism. The results of the study by Lund and Nielsen (1980) are convincing and show that after administration of fludrocortisone the excretion of tetrahydroaldosterone falls off by 67% in normals, by 51% in patients with essential hypertension, and by 11% in patients with primary

aldosteronism (n=24). The aldosterone values of the first 2 groups were also, without exception lower than those of the last mentioned group.
5. Albumin. George et al. (1970) found that the aldosterone excretions of patients with both idiopathic and adenomatous aldosteronism (determined during a salt-free diet) underwent almost no change after infusion of 50 to 100 grams of human serum albumin for 4 days, while, in normals a diminution of the aldosterone excretion of 55% was found.
All of the tests mentioned are, in the majority of cases, sufficient for the detection of patients with primary aldosteronism, as in the remaining forms of hypertension the aldosterone values lie within the normal distribution area after performance of the suppression test. But an exception to this is the form of primary aldosteronism that was denominated as "indeterminate aldosteronism" by Biglieri et al. (1972). In this form of primary aldosteronism all the characteristic features of the syndrome are present, except the insuppressibility of aldosterone after administration of DOCA.

I.2.4. *Differential diagnosis of adenoma and hyperplasia*

The importance of the differential diagnosis between adenomatous and idiopathic aldosteronism has been set forth previously. In ± 20% of patients with primary aldosteronism the affection is caused by a bilateral adrenal hyperplasia. Because of the fact that an operative treatment (total or subtotal adrenalectomy) mostly does not yield the desired fall of blood pressure, a number of diagnostic methods that make recognition of this form of primary aldosteronism possible, have been developed. In what follows we shall, therefore, discuss the value of the various diagnostic procedures.

I.2.4.1. Mathematical methods

Aitchison et al. (1971) described the so-called "quadric analysis": a method in which, with the aid of statistical analysis of 8 variables (plasma sodium, potassium, bicarbonate, renin, aldosterone, systolic and diastolic blood pressure and age) a distinction can be made between patients with primary aldosteronism with or without adrenal adenoma. The method makes use of the fact that the biochemical aberrations in patients with idiopathic aldosteronism are less severely disturbed, while blood pressure and age of these patients are commonly higher than in patients with adenomatous aldosteronism. The method

was applied retrospectively in 5 series of patients that were published in the literature (a total of 105 patients) and in 95% of the patients a correct diagnosis was made. Another statistical method, the multiple logistic analysis (Luetscher et al. 1974) makes use of analysis of 3 variables (plasma renin, aldosterone and potassium). Both statistical methods are reliable but make a computer analysis necessary. Biglieri et al. (1972) were able on the basis of a linear discrimination analysis of the aldosterone values after administration of DOCA for 3 days, and of the basal plasma renin values in the recumbent patient, to make a correct diagnosis in thirteen patients (11 adenomas and 2 hyperplasias). This method is simpler, but is also considered to be less reliable. From the researches by Biglieri et al. (1972) and also by Padfield et al. (1975) it becomes evident that the suppressibility of aldosterone by administration of mineralocorticoids in patients with adenomatous aldosteronism is not different from the suppressibility in patients with idiopathic aldosteronism. A suppression test is therefore not usable for the differential diagnosis.

I.2.4.2. The influence of body posture on the plasma concentration of aldosterone

In 1973 Ganguly et al. showed that in patients with adenomatous aldosteronism (APA) the plasma aldosterone concentration does not, as in normals, increase after ambulation in the morning from 08.00 a.m. to 12.00 noon (Ganguly 1973a, 1973b). Both during use of a diet with 300 mmol Na^+, and during a salt-free diet the plasma aldosterone concentration was found to diminish, in contradistinction to patients with idiopathic aldosteronism (IHA) in whom the plasma aldosterone concentration after ambulation during the morning displayed an obvious increase. The findings of Ganguly et al. were confirmed by Biglieri et al. (1974, 1979a), who, however, also showed that on the basis of this test no absolute distinction between patients with adenomatous and idiopathic aldosteronism could be adduced: in 25% of the patients with APA a rise of the plasma aldosterone concentration was seen, although this rise (+25%) was considerably less than what was seen in patients with IHA (+153%). An explanation for the paradoxical decrease of plasma aldosterone to the stimulus of "ambulation for 4 hours in the morning" in patients with APA was given by Schambelan et al. (1976), who showed that the regulation of aldosterone in these patients, even in the upright posture, is predominantly under the influence of ACTH and not of the renin angiotensin system. On the other hand, in patients with IHA, Schambelan et al. (1976) found that aldosterone is primarily regulated via the renin angiotension system. But 2 questions remained:

1 Why is it that in some patients with APA there is a rise of the plasma aldosterone concentration after the stimulus of "ambulation"?
2 Why is it that, in patients with IHA, after "ambulation" a definite rise of aldosterone is seen, while the plasma renin activity is suppressed, and shows only a small rise in response to "upright posture" (Schambelan et al 1976)?
From recent studies it seems that the renin angiotensin system is not entirely excluded from having an influence on the aldosterone regulation in patients with APA Vaughan et al (1981) have shown that after a rigorous suppression of the renin angiotensin system with 300 mmol Na^+/day and fludrocortisone 0 5 mg/day for 3 days, plasma aldosterone in all patients with APA decreased after ambulation, in contradistinction to what was found before this volume expansion was applied Furthermore, it turns out from the study of Wenting et al. (1978) that aldosterone in patients with APA may show a considerable interindividual variability for exogenous administration of increasing doses of ACTH and (Asp^1-val^5) angiotensin II. Brown et al (1980) showed with in vitro studies that in aldosterone-producing adenomas angiotensin receptors are present but that these qualitatively, and possibly quantitatively, differ from angiotensin II receptors in normal adrenal tissue. But the in vitro response of aldosterone was much more sensitive for an increase of the ACTH concentration than for an increase of the angiotensin II concentration in the medium An answer to the second question can be found in the studies of Wisgerhof et al (1978) and Brown et al (1979) who showed that the sensitivity of the adrenal for the giving of low doses of angiotensin II to patients with IHA, is considerably greater than that which is found in normals On the other hand is was found that patients with APA had a diminished sensitivity for exogenously administered angiotensin II

I 2.4 3 Frequent blood sampling for 24 hours for the determination of the diurnal and episodic variations of aldosterone, cortisol and renin activity

From recent researches on the diurnal rhythm of aldosterone and renin in patients with adenomatous aldosteronism, the following data have become known.
Cain et al. (1972) demonstrated that the plasma concentrations of aldosterone in patients with APA are higher in the morning than in the evening Moreover they found that plasma aldosterone displays a circadian rhythm that is parallel to that of cortisol, which facts were confirmed by studies by Kem et al (1973), Vetter et al (1973) and Schambelan et al (1976) The plasma aldosterone values show a peak

value between 04.00 hr and 08.00 hr a.m. and a lowest value between 06.00 hr and 12.00 hr p.m. By means of frequent blood sampling during the night hours, Vetter et al. (1974, 1978) and Kem et al. (1976) showed that in patients with APA synchronous "secretory bursts" of aldosterone and cortisol occur. The circadian rhythm of plasma aldosterone was found not to be influenced by salt loading or bodily posture, but was influenced by the administration of dexamethasone (Ganguly et al. 1973b, Schambelan et al. 1976). The circadian rhythm of aldosterone was not found during use of dexamethasone (Kem et al. 1973, Ganguly et al. 1973b) nor the "secretory bursts" of aldosterone (Vetter et al. 1974, Kem et al. 1976). However, there is less agreement in the literature about the degree to which the aldosterone values are reduced by administration of glucocorticoids (Newton and Laragh 1968, Slaton et al. 1969, Kem et al. 1973, Katz et al. 1975). Ganguly et al. (1977) showed that dexamethasone in patients with APA has only a temporary suppression of aldosterone production as its sequel. Within 24 hours after the beginning of dexamethasone a falling-off of the aldosterone values was observed, while on the second and third days of dexamethasone administration the aldosterone values rose again to the initial level. This transient effect probably accounts for the conflicting reports in the effectiveness of dexamethasone in lowering plasma aldosterone in APA, because the results are dependent on the duration of dexamethasone treatment. But it is also necessary to take into consideration the fact that the degree of the influence of ACTH on the aldosterone production can present a considerable interindividual variability. Thus Wenting et al. (1978) described a subgroup of APA patients with ACTH-dependent aldosteronism. These patients manifested a suppression of aldosterone to subnormal values after 1 day's treatment with dexamethasone. In contradistinction to patients with glucocorticoid remediable aldosteronism (Sutherland et al. 1966), the aldosterone values displayed a tendency to return to the pretreatment level within 8 days of treatment.

Less is known about the diurnal variability of the plasma renin activity in patients with APA. This is partially ascribable to the fact that in a number of studies (Vetter and Vetter 1975, Schambelan et al. 1976) renin values are suppressed to values beneath the threshold of detection. With the aid of a determination of renin, the sensitivity of which was magnified by prolongation of the incubation period, Modlinger et al. (1976) showed that renin in APA patients also displays a circadian rhythm with peak values between 04.00 and 08.00 hr a.m., as in normal test persons in recumbency (Gordon et al. 1966). In 6 patients with APA, Siebenschein et al. (1979) found typical short-duration secretion periods of the renin activity during the early hours of the morning. The influence of these renin variations on the diurnal rhythm of aldosterone

is probably small. Kem et al. (1973) found no correlation between the diurnal rhythm of renin and aldosterone in recumbent patients with APA, while Schambelan et al. (1976) detected under comparable circumstances only a weak correlation between the two hormones. Also on frequent blood sampling during the nocturnal hours, no synchronous secretion bursts of aldosterone and renin were observed (Kem et al. 1976).

After this review of the diurnal and episodic variations of aldosterone, renin and cortisol in patients with APA, we shall compare the data with what is available in the literature about the diurnal variability of the same hormones in patients with IHA. Ganguly et al. (1973b) could not demonstrate any diurnal rhythm of aldosterone in the recumbent patient, while Schambelan et al. (1976) did, it is true, show a diurnal rhythm, parallel to that of cortisol, but with small variations in the aldosterone concentrations. It emerges from frequent blood sampling during the night-time that also in patients with IHA, episodic periods of secretion of aldosterone occur, which are correlated with those of cortisol (Kem et al. 1976, Vetter et al. 1978). In patients with IHA there was found, in contradistinction to patients with APA, an important influence of the bodily posture on the plasma aldosterone concentrations during the day: the plasma aldosterone values were throughout the whole day higher than the values during recumbency (Schambelan et al. 1976). During ambulation the aldosterone values were no longer correlated with cortisol, but with the plasma renin activity (Ganguly et al. 1973b, Schambelan et al. 1976). Treatment with dexamethasone caused the disappearance of the nightly secretory bursts of aldosterone (Kem et al. 1976, Vetter et al. 1978), but had no influence on the rise of aldosterone during the day under the influence of the upright posture (Schambelan et al. 1976).

It may be said in summary, that the aldosterone production in patients with primary aldosteronism takes place autonomously only to a partial degree. The aldosterone secretions are found to be subject to modulations that are brought about via ACTH and the renin angiotensin system.In patients with adenomatous aldosteronism ACTH plays a predominant role in the regulation of aldosterone, while the influence of the renin angiotensin system is apparently of lesser importance. In patients with IHA the renin angiotensin system plays a predominant role in the regulation of aldosterone during the erect position, whereas during the lying down an influence of ACTH on the diurnal aldosterone variations is recognizable. The regulation of aldosterone in patients with IHA proceeds not otherwise than in normal test persons (Katz et al. 1972, Vagnucci et al. 1974, Armbrurster et al. 1975, Lightman et al. 1981) although at a higher level of aldosterone production. The abovementioned data from the literature about the regula-

tion of aldosterone in both forms of primary aldosteronism, have been the point of departure for the studies on which a report is made in chapters IV and V of this thesis.

I.2.4.4. Determination of other adrenal steroids than aldosterone

In the literature there are several studies about the secretion of other adrenal steroids in patients with primary aldosteronism: the zona glomerulosa steroids deoxycorticosterone (DOC), corticosterone and 18-OH-corticosterone (18-OH-B), and the zona fasciculata steroid 18-OH-11-deoxycorticosterone (18-OH-DOC). It is claimed by a few authors that determination of these steroids could contribute to the differentiation of adenomatous and idiopathic aldosteronism. Biglieri et al. (1968) found raised secretion values of DOC and corticosterone in, respectively, 4 out of 23, and 7 out of 23 patients with APA. Recently, Biglieri et al. (1979) reported that the plasma values of 18-OH-B, determined at 08.00 hr in the morning, in patients with APA (n=9) were higher than 100 ng/100 ml, while the values in patients with IHA (n=14) were lower than 50 ng/100 ml. The conversion of 18-OH-B into aldosterone takes place under the influence of 18-dehydrogenase (type 2 methyl-oxydase). The activity of this enzyme is probably dependent on the potassium concentration. In view of the fact that in patients with APA the potassium values were lower than in patients with IHA, an explanation is forthcoming for the presence of higher ratios of 18-OH-B/aldosterone in patients with APA than in those with IHA (Biglieri et al. 1979). The 18-OH-11-deoxycorticosterone (18-OH-DOC) is a weak mineralocorticoid that is synthesized in the zona fasciculata. It is almost exclusively dependent for its secretion on ACTH (Melby et al. 1972). The 18-OH-DOC may possibly play a role in certain forms of experimental and human hypertension (Melby and Dale 1976, Ulick 1976). Melby et al. (1971) found normal excretion values of 18-OH-THDOC in 10 patients with primary aldosteronism. An increase of the secretion rate of 18-OH-DOC in vitro and in vivo was shown by Ulick (1976) in 1 patient with APA, while 2 patients with IHA had normal secretion values. We found no confirmation of this finding in the literature later on. In connection with our research on the influence of ACTH on the regulation of aldosterone, determinations were made of the plasma concentrations of aldosterone, cortisol and 18-OH-DOC, after which the reciprocal correlations between these 3 hormones were calculated. The plasma 18-OH-DOC concentrations were not significantly different in the 3 groups examined by us (chapter IV).

I 2 5 *Lateralization procedures*

The following procedures were developed for the preoperative localization of an aldosterone-producing adrenal adenoma

1 Adrenal phlebography and adrenal venous sampling
2 Adrenal scintigraphy
3 Adrenal computerized tomography

In general the diagnosis of "idiopathic aldosteronism" is arrived at, if a lateralization procedure has not led to the revealing of a unilateral adrenal lesion, in view of the fact that the chance of a bilaterally localized adrenal adenoma being present, is negligibly small

I 2 5 1. Adrenal phlebography and adrenal venous sampling

Arteriography of the adrenals has turned out to be not a suitable method for the demonstration of aldosterone-producing adrenal adenomas, because these tumors are relatively avascular. Selective adrenal arteriography is a cumbersome examination (Khan et al. 1971) as the arterial blood supply to the adrenal runs along 3 sides (superior, middle and inferior suprarenal arteries). As the venous drainage of the adrenals on both sides runs mostly via one vein only (on the right towards the vena cava inferior, and on the left towards the vena renalis) adrenal phlebography is the best method for showing up the adrenal angiographically An adrenal adenoma is manifested by a distorsion of the veins that lie alongside the tumor The right adrenal vein is difficult to catheterize as it is short and can at various levels flow into the vena cava inferior. Perforation of adrenal veins and intra-adrenal hemorrhages and infarctions occur in 5% of the catheterizations (Bayliss et al 1970) Remission of primary aldosteronism after phlebography has been described (Fisher et al 1971) Adrenal adenomas smaller than 0 8 cm are not shown up (Nicolis et al 1972) These limitations are of much less significance if the catheterization of the adrenal veins is being done for determination of adrenal steroids in adrenal venous blood. Only a small amount of contrast medium is given for controlling the way the catheters lie. The ratio of aldosterone/cortisol in blood samples from the right and left adrenal veins, is compared with the ratio that is found in the vena cava inferior According to some authors (Scoggins et al 1972, Fukuchi et al 1975, Lund et al 1980), this lateralization procedure is not less accurate if only the aldosterone/cortisol ratios of the left adrenal vein and the vena cava inferior are compared Dunnick et al. (1979a) and Weinberger et al (1979) are of the opinion that artefacts that are the sequel of the episodic secretion of aldosterone, can be prevented when the examination is carried out during the

administration of ACTH. The table I-1 gives a general survey of the literature on the results of adrenal phlebography and adrenal venous sampling. From the percentages it appears that adrenal venous sampling is a good method for localization of adrenal adenomas and for their differentiation from bilateral adrenal hyperplasia. From these figures it is also apparent that the performance of an adrenal phlebography has become superfluous to a considerable degree. The fact that the method is invasive is, however, a disadvantage that does not apply to adrenal scintigraphy and computerized tomography.

Table I-1.

Diagnostic accuracy of adrenal phlebography and adrenal venous sampling in patients with primary aldosteronism

	number of patients	surgery		adrenal venous sampling	venography
		adenoma	hyperplasia		
Melby 1967	7	7	0	100%	29%
Cerny 1970	17	17	0	–	70%
Kahn 1971	20	14	6	85%	70%
Horton 1972	14	14	0	100%	71%
Nicolis 1972	7	7	0	100%	57%
Scoggins 1972	11	11	0	91%	33%
Fukuchi 1975	18	18	0	100%	–
Dunnick 1979a	10	10	0	100%	–
Weinberger 1979	44	36	8	91%	66%
Vetter 1980	30	21	9	71%	57%
Lund 1980	16	16	0	100%	–

I.2.5.2. Adrenal scintigraphy

In 1970 Beierwaltes reported the first successful visualization of human adrenals in vivo by means of adrenal scintigraphy. For this use was made of ^{131}I-19-Cholesterol, synthesized in 1969 by Counsell et al. This radiocholesterol compound is, after intravenous administration at a dose of 2 mCi, concentrated in the cortex of functioning adrenal tissue, and the adrenals are visualized scintigraphically about 7 days later. In 1975 the development of a new adrenal scanning agent, the ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol was described simultaneously by Bas-

madjian et al. and by Kojima et al. The latter compound is more rapidly and intensively concentrated than the ^{131}I-19-Cholesterol, so that disturbing background activity is reduced. The first successful localization of an aldosterone-producing adenoma by means of adrenal scintigraphy was described by Conn et al. in 1971. Hogan et al. (1976) confirmed the value of adrenal scintigraphy with ^{131}I-19-Iodocholesterol in patients with primary aldosteronism with regard to localization of adenomas and the preoperative differentiation between adenoma and hyperplasia: in 10 of the 12 patients who had an aldosterone-producing adenoma on biochemical grounds, an asymmetrical uptake of radioactivity was found in the adrenals, while this was found only in 1 of the 13 patients in whom the diagnosis of idiopathic aldosteronism was made on biochemical grounds. Only a slight asymmetry in the uptake of activity was, however, established in small adrenal adenomas and in adrenals with macronodular hyperplasia (Seabold et al. 1976). So, to increase the specificity of the examination, the dexamethasone suppresion scan was developed by Conn (Conn et al. 1972, 1976). Dexamethasone at a dosage of 2 mg/day for 48 hours before administering ^{131}I-19-Iodocholesterol gave almost complete suppression of the normal adrenal. The accuracy with which the adenoma was lateralized was found to be 88%, and 71% when no dexamethasone was given. The dexamethasone suppression scan was found to be of particular value in the differentiation between tumor and hyperplasia. The suppression scan in 6 patients with histologically proven adrenal hyperplasia showed no – or practically – no accumulation of activity, whereas, without the use of the dexamethasone, the diagnosis of adenoma would have been made in 2 out of the 6 patients on the grounds of an asymmetric distribution of the activity. On the other hand, 2 of 17 patients with an adenoma, that was correctly lateralized on the suppression scan, would have been incorrectly classified as having hyperplasia on the basis of a symmetrical activity distribution in scintigraphy without dexamethasone. Since ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol has become available the use of dexamethasone has proved to be of special importance because of the intense uptake of this compound into the adrenals. But there is still insufficient clarity in the literature about the dose and duration of dexamethasone treatment preceding the administration of this new radiocholesterol compound. In Conn's study (1976) it was found that also in the normal adrenal accumulation of activity can occur, beginning 5 to 6 days after administration of ^{131}I-19-Iodocholesterol in spite of the continued use of dexamethasone. This was confirmed for the new radiocholesterol compound by the prospective research of Gross et al. (1979), among healthy volunteers. Uptake of radioactivity, although weak, was seen 3 to 5 days after giving the tracer during the use of high doses of dexamethasone (8 mg) beginning

48 hours before the examination The uptake into the adrenals was delayed ± 2 days if dexamethasone at a dose of 4 mg was given, beginning 7 days before the examination It remains unexplained why during the use of dexamethasone and suppression of the steroid production, concentration of radioactivity still takes place in the normal adrenals From the research of Gross et al (1979) it can be deduced that long-lasting pretreatment with dexamethasone causes a more effective suppression of the normal adrenal and therefore can contribute to a more optimal lateralization of adenomas Experiences with the ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol in the diagnosis of primary aldosteronism have been reported in a number of studies (Sarkar et al. 1977, Freitas et al 1979, Miles et al 1979) If the results of these studies are taken as a whole it will be seen that 22 of 23 adenomas were correctly localized, while in 6 out of 7 adrenal hyperplasias a correct diagnosis was made These results concern only those patients in whom the scintigraphic diagnosis was verified histologically We have left out the 20 patients in these studies in whom no operation was done Dexamethasone was started 2 days (Freitas et al 1979, Miles et al 1979) or 7 days (Sarkar et al 1977) before the examination, at a dose of 2 mg/day (Miles et al 1979) or 4 mg/day (Sarkar et al. 1977, Freitas et al 1979) The dose of the radiocholesterol compound given in these 3 studies was comparable and varied from 1 to 2 mCi The scintigraphic diagnosis could be made within 5 days after its administration, which is considerably shorter than the 7 or more days with the use of ^{131}I-19-Iodocholesterol. Uptake of radioactivity, unilaterally or bilaterally, within 5 days after administration of the radiocholesterol during the abovementioned dexamethasone suppression schemes, was in agreement with, respectively an aldosterone-producing adrenal adenoma or a macronodular hyperplasia. There are indications that scintigraphy in micronodular hyperplasia in essence yields the same results as in normal adrenals, that is to say, an image of both adrenals later than 5 days after administration of the dose (Sarkar et al 1977) In conclusion it may be said that the adrenal scintigraphy of recent years has turned out to be an important acquisition in the diagnosis of primary aldosteronism. The accuracy with which adenomas are localized and unilateral and bilateral adrenal affections are differentiated approximates to the results of the adrenal venous sampling technique, that has always been regarded as the "gold standard" in the diagnosis. For the future the following developments in adrenal scintigraphy are desirable.

1 Reduction of the dose of radioactivity given, thus making less the dose of irradiation of the gonads

2 Optimalization of the dexamethasone suppression schemes.

I.2.5.3. Computerized tomography of the adrenal glands

Montagne et al. in 1978 described the visualization of the human adrenals by means of computerized tomography. The left adrenal is depicted as an inverted V or Y, mostly in the section just above the top of the left kidney. The right adrenal has a linear form or that of an inverted V, the posterior arm of which is longer than the lateral arm, and is laid in the section above the top of the right kidney, immediately behind the vena cava inferior. By this time 3 studies have appeared in which the value of CT scanning in the diagnosis of primary aldosteronism has been evaluated. If we take the results of the 3 studies (Linde et al. 1979, Dunnick et al. 1979b, White et al. 1980) together, it emerges that of the aldosterone-producing adenomas that were removed, 24 adenomas (80%) were detected preoperatively by CT scanning. The tumors that were localized, varied in size from 1.1 to 6 cm, while the 6 adenomas that were not localized had the following diameters: 0.9 - 1.0 - 0.5 - 1.0 - 1.0 and 2.0 cm. In the study by White et al. (1980) 6 patients with primary aldosteronism, on the basis of absence of a demonstrable adenoma, were classified under the diagnosis of idiopathic aldosteronism. However, histological confirmation of this diagnosis was not forthcoming. The conclusion for the time being is that CT scanning is a usable and rapid method for the localization of adenomas that are greater than 1.0 cm. According to the review of the literature by Conn et al. (1964) the percentage of adenomas greater than 1 cm amounts to 92%. If in the future CT scanners become available with a greater resolving power, the diagnostic accuracy can be further promoted (Linde et al. 1979).

I.3. Medicamentous treatment

I.3.1. *Spironolactone*

After it had been shown by Salassa in 1958 that short-lasting administration of spironolactone caused the metabolic anomalies of primary aldosteronism to disappear, Laidlaw found in 1961, that prolonged administration of this aldosterone antagonist brougth about a fall in the blood pressure of 2 patients with APA to normal values. In the studies of Spark and Melby (1968) it then was found that spironolactone at a dose of 400 mg for 3 to 5 weeks normalized the blood pressure in 20 patients with APA, in contradistinction to the absence of a hypotensive effect in 20 patients with hypertension and secondary aldosteronism. Correction of the electrolyte disorders, however, occurred both in patients with primary and with secondary aldosteronism, after a few

days of treatment. Furthermore a remarkable fact was that the body weight fell with this treatment in patients with APA by 3.6 kg and in patients with secondary aldosteronism by only 0.9 kg, thus giving evidence of an expansion of the extracellular volume under the influence of aldosterone in patients with APA, but not in patients with hypertension and secondary aldosteronism. The effect of spironolactone on the blood pressure, however, turned out to be not specific for primary aldosteronism (Crane and Harris 1970): in 32 out of 43 patients with an essential hypertension and a lowered PRA a normalization of the blood pressure occurred after 3 weeks of treatment with spironolactone, 400 mg per day. Therefore, the hypotensive effect of spironolactone was found to be unusable for the tracing of patients with primary aldosteronism (Crane and Harris 1970), but proved useful for the prediction of a fall in blood pressure by adrenal surgery (Spark and Melby 1968). The results of long-lasting treatment of patients with primary aldosteronism by spironolactone were reported fully by Brown and colleagues (Brown et al. 1969, Brown et al. 1972, Brown et al. 1975), whereas more recent experiences of the Glasgow group were described by Ferriss et al. (1978c). These results can be summarized as follows:

1. Normalization of the blood pressure occurred in 46% of patients with APA (n=37) and in 50% of patients with IHA (n=14).
2. A highly significant correlation was worked out between the lowering effect on blood pressure of spironolactone and that of operation, in patients with APA (systolic $r=0.86$, $p<0.001$, diastolic $r=0.75$, $p<0.001$, $n=34$). In patients with IHA this correlation was only weakly positive.
3. Correction of the plasma electrolytes occurred in all patients, independently of the hypotensive effect.
4. Spironolactone caused the following metabolic effects: a significant lowering of the plasma sodium, total exchangeable sodium, total body water, extracellular volume, plasma volume and plasma total CO_2 concentration. There was a significant increase of the plasma potassium, total exchangeable potassium, urea, renin and angiotensin concentration. The plasma aldosterone concentration did not change significantly. Ganguly et al. (1973) found a rise of renin and aldosterone during treatment with spironolactone, that was greater in patients with IHA than in patients with APA. This finding could not be confirmed by Ferriss et al. (1978c).
5. The occurrence of side effects in the dosage of spironolactone used (50 to 400 mg/day, in most cases 300 to 400 mg/day, on the average for 9.7 months) led to stopping of the medication in only 3 patients, but the percentage of patients with side effects was not mentioned. To these side effects were reckoned: fatigue, upper abdominal pain, Raynaud's

phenomenon, gynecomastia, menstrual disorders, impotence, excessive sweating and pigmentations of the skin. From the study by Crane and Harris (1970) it was found that at a dosage of 400 mg/day about half of the patients showed side effects, while Ferriss et al. (1978c) wrote only that "the drug has been well tolerated in the great majority".

The mechanism of action of spironolactone on the blood pressure and the metabolism of aldosterone is still partially clarified. Although spironolactone was introduced as a competitive antagonist at the site of the aldosterone receptors in the distal tubuli of the kidney (Kagawa 1960) it was found in in vitro studies of Erbler (1972 and 1973) that this substance is also active at the level of the adrenal. Spironolactone, that has a chemical structure related to the adrenal steroids, is subject to an extensive metabolism, in which hydroxylating adrenal enzymes play a role. It is probable that competition with the 11 beta- and 18-hydroxylases, that are concerned in the adrenal in the conversion respectively of DOC into corticosterone (B) and B into 18-OH-B, cause a diminution of the synthesis of aldosterone in vitro. The effects in vivo were studied by Abshagen et al. (1976), who, after giving spironolactone to normal test persons, found signs of an initial inhibition of the aldosterone synthesis, that after a few days was compensated by activation of the renin angiotensin system. These findings were not confirmed in the studies of Gaillard et al. (1980). In vivo a restraining effect on the synthesis of aldosterone can be camouflaged because antiregulation mechanisms (renin, ACTH, potassium) are called in. In patients with primary aldosteronism it was found from the study of Spark and Melby (1968) that the rate of secretion of aldosterone rises. But it was noticeable that this rise (with a factor of 1.5) was clearly behindhand in the rising of the plasma renin activity (by a factor of 12!). A single case report (Sundsfjord et al. 1974) related a lowering of aldosterone during treatment with spironolactone. Conn and Hinerman (1977) found in patients with primary aldosteronism a falling-off of aldosterone excretion during the first weeks of spironolactone treatment and, at the same time an increase of the number of "spironolactone bodies" in the glomerulosa zone of adrenals that were removed in this period (see chapter VIII). After, on the average, 6 weeks, there occurred an increase of the excretion of aldosterone to above the values before the treatment. Thus, the data indicate that spironolactone also in patients with primary aldosteronism has an inhibiting influence on the synthesis of aldosterone. Because the renin angiotensin system in these patients is suppressed it lasts longer than in normals, before the production of aldosterone begins once more to rise. From these data it is not clear whether an inhibition of the biosynthesis of aldosterone contributes to the antihypertensive effect of spironolactone. The hypotensive action of spironolactone in patients with mineralocorticoid hypertension is

ascribed to a non-specific diuretic effect (Bravo et al. 1973) as well as to a specific antimineralocorticoid effect (Spark and Melby 1971, Spark et al 1974, Benraad et al 1978)

I.3 2. *Amiloride*

Amiloride is a weak diuretic that diminishes the potassium secretion and sodium reabsorption in the distal kidney tubules independently of the presence or absence of aldosterone (Baer et al. 1967). Braren et al. reported in 1968 that amiloride given at a dose of 20 to 40 mg per day for 10 days, to a patient with an aldosterone-producing adenoma, normalized the plasma sodium and potassium concentrations Lowering of the blood pressure was not observed. But an antihypertensive effect was, indeed, observed by Kremer et al. (1973a) after 6 weeks treatment with amiloride 40 mg per day in a woman with primary aldosteronism in whom the spironolactone medication had to be stopped because of a duodenal ulcer. In the subsequent studies of Kremer et al. (1973b and 1977) the antihypertensive effect of amiloride in 19 patients with primary aldosteronism was confirmed, although the hypotensive effect was less than with spironolactone or with operation (Kremer et al 1977, Ferriss et al 1978c). Amiloride was well tolerated and only in few patients did transitory upper abdominal complaints occur From a comparison of the tables in the study by Ferriss et al. (1978c) it turned out that the effects of amiloride on the concentration of sodium in the plasma, the exchangeable sodium, the plasma potassium concentrations and the exchangeable potassium, are comparable with those of spironolactone Furthermore it will be noticed that the plasma aldosterone concentration after treatment with amiloride rises significantly, but does not essentially change after treatment with spironolactone. This is remarkable because the renin and angiotensin concentrations after spironolactone display quite clearly a greater rise than after amiloride. Although Ferriss et al. (1978c) do not interpret the findings as such, one can find likewise an indication for a diminution of the aldosterone synthesis by spironolactone, as described above Amiloride seems to be a suitable alternative for spironolactone for the treatment of patients with primary aldosteronism in whom unacceptable side effects occur from spironolactone.

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PATIENTS AND RESEARCH METHODS

In the appendix of this thesis and in chapter IX a description is given of the clinical and pathological histories of 28 patients with primary aldosteronism, who were referred to the department of internal medicine in the period 1961 to 1979. The clinical, diagnostic and therapeutic data are reported for each patient, insofar as these are relevant for the clinical picture. For simplification each clinical history is divided into headings 1 to 8, in which the following subjects are discussed:

1. General clinical data
2. The diagnosis of "primary aldosteronism"
3. The day and night rhythm of the plasma aldosterone concentration
4. Adrenal scintigraphy
5. Medicamentous treatment
6. Operation
7. Pathology of the adrenals
8. Clinical follow-up

The headings are summarized in chapter III (headings 1, 5, 6, 8), chapters IV and V (headings 2 and 3), in chapter VI (heading 4), chapter VII (heading 5) and chapters VIII and IX (heading 7). The reason for discussing each case individually as well, is in accordance with the plan of this thesis, in which we endeavour, in addition to the more scientific aspects, to give practical information about the patient with the relatively rare syndrome of "primary aldosteronism". Furthermore, in many patients more or less exceptional findings are recorded and these may be easily overlooked in a somewhat brief survey. The patients were selected with reference to the following criteria:

1. The demonstration of a raised aldosterone secretion rate and a low plasma renin activity, virtually unresponsive to stimulation by a salt-free diet.
2. The histological confirmation of the diagnosis of "primary aldosteronism" after anatomicopathological examination of adrenal tissue obtained by operation or at autopsy. In 3 patients (T, v E-v U, C-J) no histological material was available, but the results of adrenal scintigraphy made it probable that these patients had an adrenal hyperplasia,

or, rather, had no aldosterone-producing adenoma as the cause of their primary aldosteronism.
In this chapter we describe the methods by which the data were collected for each of the headings 1 to 8, as mentioned above. It will be clear that not each of these headings applies to every patient, in view of the fact that some methods of research have only quite recently come into usage (for instance the determination of the plasma concentration of aldosterone and adrenal scintigraphy).

II.1. General clinical data

Under this heading we go into the question of what symptoms and signs have in the end led to the setting up of search for the presence of "primary aldosteronism". Then scores are given for the presence of the following complaints: headache, visual symptoms, nycturia, polyuria, polydipsia, paraesthesias, muscular weakness, muscular paresis or paralysis, and edemas. The duration of the hypertension, the presence of the hypertension of pregnancy and the time lag between the diagnosis of "hypertension" and of "primary aldosteronism" are potentially important factors in the assessment of the results of the medicamentous or operative treatment. The relevant data of physical examination are: the blood pressure at the first consultation and during the stay in the clinic, edemas, central venous pressure, size of the heart, abdominal vascular murmurs and fundoscopy. The laboratory examination is mostly limited to the examination of the urine and the values of the plasma electrolytes, creatinine and urea, as found at the first consultation. The electrocardiogram was interpreted according to the presence of signs of left ventricle hypertrophy, myocardial ischemia and hypokalemia. The following radiological examinations were considered to be relevant: a chest film for estimation of the size of the heart, intravenous pyelography for exclusion of renal hypertension, renal arteriography for exclusion of renal artery stenosis. In the latter examination attempts were frequently made to show up both adrenals. Adrenal phlebography (combined or not with determinations of venous adrenal aldosterone) and presacral insufflation of gas were done in only a few patients; and this applies also to computerized tomography of the adrenals.

II.2. The diagnosis of "primary aldosteronism"

All patients were admitted into the clinic for determinations of the aldosterone secretion rate (ASR) under standardized conditions. In the

majority of the patients, for this purpose the antihypertensive medication was stopped for a considerable time before admission (2 to 4 weeks). The aldosterone secretion rate measured in urine collected during 24 hours of bed rest, was determined before and after salt loading in order to find out the suppressibility of the aldosterone secretion under the influence of increasing salt intake. All of the patients throughout the whole of their stay in the clinic used a salt-free diet, to which no, 6 grams or 18 grams of extra salt were added. Measurements of the aldosterone secretion rate were done when equilibrium in the ingestion and excretion of salt was reached i.e. after 4 to 5 days of constant ingestion of salt. The aldosterone secretion rate was initially measured with a double isotope dilution derivative assay (Benraad and Kloppenborg 1965) and from 1972 onwards with a radioimmunoassay of aldosterone acetylated to 21-monoacetate, after hydrolysis at pH 1 (de Man and Benraad 1977). The values obtained according the first method showed good agreement with those obtained according to the second method. The aldosterone secretion rate measured in healthy adults, varies from 200 to 500 μg/24 hr during the taking of a salt-free diet; from 80 to 180 μg/24 hr while taking a diet with 6 grams of salt and from 40-80 μg/24 hr while taking 18 grams of salt. The plasma renin activity (PRA) was determined after 5 days of salt-free diet, at 11.30 a.m. after 3 hours of ambulation. The PRA was at first measured by a bioassay (Boucher et al. 1964) with modifications (Driessen 1969) and from 1973 onwards by a radioimmunoassay (Drayer and Benraad 1975). The results of both methods of determination were in good agreement with each other (Drayer and Benraad 1975). The PRA measured after 5 days of salt-free diet and 3 hours of ambulation, varies in healthy adults from 115 to 595 ng/10 ml/3 hr.
The diagnosis of "primary aldosteronism" was made when in patients with hypertension the aldosterone secretion rate was raised and was not, or insufficiently, suppressible by loading with salt, while the plasma renin activity after the usual methods of stimulation yielded a value lower than normal. At the same time as the measurement of the aldosterone secretion rate, determinations were made of sodium, potassium and creatinine in plasma and urine. The ingestion of potassium with the diet was estimated to be 50 to 70 mmol/24 hr and the patients obtained no extra potassium.

II.3. The day and night rhythm of the plasma aldosterone concentration

In chapter I a general survey is given of studies of the circadian rhythm of aldosterone, the episodic variations of aldosterone, the correlations

between the plasma levels of aldosterone and cortisol, and between those of aldosterone and renin, the influence of body posture, and the effect of giving dexamethasone on the concentration of plasma aldosterone in patients with primary aldosteronism. As explained, probably ACTH plays an important rôle in the regulation of the aldosterone production in patients with an aldosterone-producing adrenal adenoma. In patients with an idiopathic aldosteronism the relative importance of the various regulating mechanisms (ACTH and renin) is still insufficiently known. Also so far there is no uniformity in the literature reports on the effect on the plasma level of aldosterone of giving dexamethasone to patients with adenomatous or idiopathic aldosteronism. It was on the basis of these considerations that the protocol of the study described later on (II.3.2.) was formulated.

II.3.1. *Patients*

The study was carried out in 12 patients with primary aldosteronism. Eight patients (S-R, S-Kr, H-S, K-H, H, M-G, N-M, P-R) proved later on at operation to have an aldosterone-producing adenoma. In one patient (K) at autopsy a bilateral adrenal hyperplasia was found, and in 3 patients (T, v E-v U, C-J) the diagnosis of "idiopathic aldosteronism" was made after no indications of an adenoma were found on the adrenal scintigram. Furthermore, 7 patients (F, vd V, O-K, vd K-M, K-H, M-G, N-M) were examined after removal of an aldosterone-producing adenoma. Three of these patients (K-H, M-G, and N-M) were also examined preoperatively. The postoperatively examined patients had after operation a normal or low secretion of aldosterone, with the exception of the woman M-G, who had developed a recurrent primary aldosteronism as the sequel of an aldosterone-producing adenoma in the contralateral adrenal. The results of the examination of patients with primary aldosteronism are discussed in chapter V, while in chapter IV these results are compared with those in patients after removal of an aldosterone-producing adenoma.

II.3.2. *Methods*

Figure II.-1. shows a diagrammatic representation of the study protocol. During the study the patients took a salt-free diet, to which 6 grams of salt were added per day. The potassium ingestion with the diet varied from 50 to 70 mmol/day. The patients took the diet for at least 3 days before the beginning of the study. The antihypertensive medication was stopped 3 weeks before admission to the clinic. During their

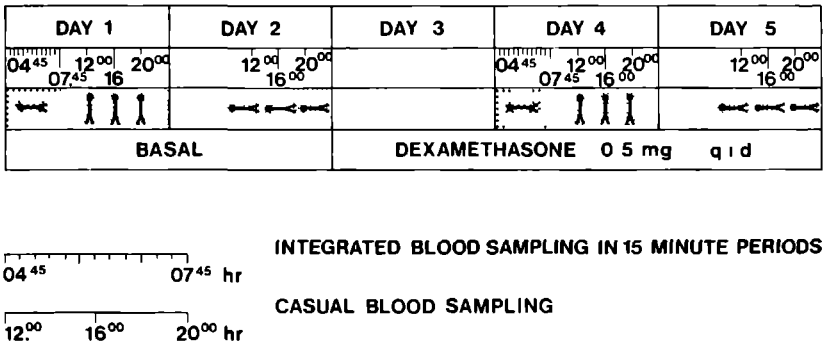

Figure II-1. Design of the study protocol

stay the patients took no medicines, and especially no supplementary potassium. The urine was collected during the 5 days of the study for determination of the 24 hours excretion of sodium, potassium, creatinine and the aldosterone-18-glucuronide The blood samples were examined as to the concentrations of aldosterone, cortisol and 18-hydroxy-11-deoxycorticosterone (18-OH-DOC). The blood samples taken at the points of time 12.00 hr, 16 00 hr and 20 00 hr were also examined as to the activity of plasma renin. The blood was collected in 2 different ways during the last part of the night (from 04 45 to 07 45 hr) use was made of a method that will be described later on (II 3 3) It is in essence a continuous collection of blood specimens ("integrated samples") During the day (12 00, 16.00 and 20.00 hr) blood samples were collected by repeated punctures of veins ("casual samples") The time interval of 04 45-07 45 hr was chosen because, during these hours the circadian rise of ACTH-activity occurs Frequent blood sampling during this period makes it possible to work out correlations between the plasma concentrations of the 3 hormones mentioned above In view of the fact that cortisol and 18-OH-DOC are almost entirely dependent for their secretion upon ACTH, one would expect to find a significant correlation between the plasma concentrations of both hormones. One can obtain an impression of the influence of ACTH on the plasma concentrations of aldosterone by comparing the correlation coefficients between the plasma concentrations of aldosterone and cortisol and of aldosterone and 18-OH-DOC with those between cortisol and 18-OH-DOC. Correlation calculations are done of the values during the night period (n=12) and of the values during the night, day 1 and day 2 (n=18). The influence of body posture on the plasma concentrations of aldosterone is investigated by contrasting the values at the time

points of 12.00 hr, 16.00 hr and 20.00 hr of day 1 (during ambulation) with the concentrations at the same time points of day 2 (during supine position). Further, the influence of changing body posture on the plasma aldosterone concentrations is studied, by comparing the values found on day 1 at 07.45 hr with the values at 12.00 hr after 4 hours of ambulation. The time points for blood sampling during the day (12.00 hr, 16.00 hr, and 20.00 hr) were so chosen that any influence of the meal on the plasma aldosterone concentrations was eliminated as far as possible. The samples of blood at 12.00 hr and 16.00 hr were taken before the meal, and those of 20.00 hr about 3 hours after the meal. Dexamethasone 2 mg/day was given in 4 divided doses of 0.5 mg, spread over 24 hours. On days 4 and 5 of the study protocol (the second and third day of dexamethasone medication) the examination was repeated in a manner identical with the procedure described above.

II.3.3. *Description of the method for continuous collection of blood ("integrated blood sampling")*

Continuous blood collection for several hours calls for the necessary measures for the prevention of coagulation in the collecting system. For this, use was made of commercially available non-thrombogenic venous catheters (Cormed Inc., Middleport, USA). The catheters acquire their non-thrombogenic property from a coating of the wall of the catheter lumen with heparin as described by Grode et al. (1969). The clinical utility of this catheter was demonstrated by Kowarski et al. (1971). The non-thrombogenic catheter was connected to a fraction collector, that was adapted for the purpose of this study by the Technical Service Department of the Sint Radboud Hospital. For reception of blood, use was made of heparinized tubes of 0.1 ml calibre, 24 of which can be placed in the fraction collector. A continuous blood flow is maintained by means of a vacuum that is created via a rotating pump (see figure II-2.). The periods within which the fractions are collected (in this study it was always 15 minutes), can be determined by a time clock mounted on the fraction collector, or by hand. The apparatus needed was placed on a trolley table at the head end of the bed and near the patient. The non-thrombogenic catheter was at 24.00 hr inserted into an antecubital vein and connected with a 50 cc syringe by which, via an infusion pump with a rate of 5 cc/hour, 5 % glucose was infused. At the start of the continuous blood sampling at 04.45 hr the catheter was filled with heparin and connected with the fraction collector. Then for 3 hours blood was delivered at a speed of 10 to 11 cc per fraction of 15 minutes. From the data of table II-1 one can obtain an impression of the accuracy of the sampling rate (cc per 15 min) in 7

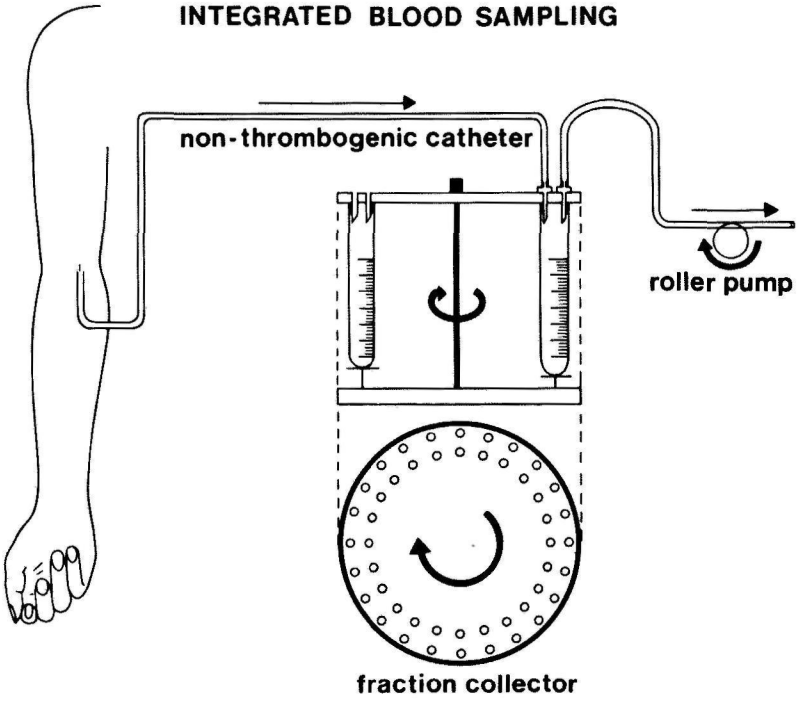

Figure II-2. Schematic representation of the methods used for integrated blood sampling

Table II-1.

Variability of the quantity of blood that was collected every 15 minutes during continuous blood sampling

patient	distribution (ml)	average ± SD (ml)	number of samples
S-R	10.0-12.6	10.8±0.7	n=11
S-Kr	8.0-12.8	11.0±1.2	n=12
H-S	10.0-11.8	11.3±0.5	n=12
K-H	10.4-11.8	11.2±0.6	n=12
H	9.0-11.4	10.9±0.6	n=12
N-M	10.0-11.0	10.7±0.4	n=12
M-G	10.2-12.0	11.2±0.6	n=12

patients in whom the quantity of each sample was accurately measured. After the expiry of a period of 15 minutes the blood was immediately taken out of the fraction collector and centrifuged. The plasma was pipetted off and kept at −20°C. Measures were taken to avoid disturbance of the normal night's rest of the patient. The research was carried out in a peaceful room without the presence of other patients. The room remained in darkness and the blood collection apparatus went on working practically without any noise. The patient was screened off by a curtain. The majority of the patients were not disturbed in their sleep by the test.

II.3.4. *Radioimmunoassays*

Plasma aldosterone was measured by radioimmunoassay with an antiserum raised in sheep against aldosterone-21-monohemisuccinate conjugated to bovine serum albumin (BSA), after chromatography in a Bush B_5 type system, toluene/methanol/water (10:5:5) on Whatman-1 paper (de Man et al. 1980). Plasma 18-OH-DOC was measured by radioimmunoassay raised in sheep against the 21-hemisuccinate of 18-OH-DOC conjugated to BSA, after chromatography in the Bush B_5 system on Whatman-1 paper (Hoefnagels et al. 1978). Plasma cortisol was measured by radioimmunoassay as described by Vecsei (1974). The antiserum was raised in rabbit against cortisol-21-hemisuccinate-BSA. The protocol described in paragraph II.3.2. was, as mentioned above, also carried out in 6 patients after removal of an adrenal adenoma. In addition the protocol was carried out in 2 healthy adults. The distribution of the hormone concentrations measured in these 8 subjects (table II-2) are regarded as control values for this study.

Table II-2.

Concentrations of plasma aldosterone, cortisol and 18-OH-DOC during the night and day in 8 control persons

		plasma aldosterone (ng/100 ml)	plasma cortisol (μmol/l)	plasma 18-OH-DOC (ng/100 ml)
night	(n=96)	1.0-13.4	0.03-0.70	2.8-45.2
day	(n=48)	1.0-29.5	0.06-1.02	2.0-33.9

II.4. Adrenal scintigraphy

Since 1973, in the department of Nuclear Medicine (principal: Prof.

Dr. I. Kazem) scintigraphic examination has been regularly done in patients with primary aldosteronism. The aim of this examination is twofold:
1. Differentiation between an aldosterone-producing adenoma and a bilateral adrenal hyperplasia. The differentiation is of importance, as in the case of a bilateral adrenal hyperplasia no operative exploration of the adrenals should be done (see chapter I).
2. Lateralization of an aldosterone-producing adenoma, to make possible a unilateral operative approach to the adrenal concerned.

II.4.1. *Patients*

The investigation was carried out in 18 patients with primary aldosteronism. Thirteen patients had an aldosterone-producing adenoma (vdV, O-K, vd K-M, W-S, S-R, S-Kr, K-H, H-S, H, M-G, N-M, P-R, S-Kl). In 4 patients (T, v E-v U, C-J and K) the diagnosis of idiopathic aldosteronism was made, and in 1 woman patient (L-v G) an aldosterone-producing carcinoma of the adrenal was found.

II.4.2. *Methods*

Up to 1978 the examination was carried out with the radiocholesterol compound ^{131}I-19-Iodocholesterol (Beierwaltes et al. 1971) and from 1978 onwards with the agent ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol (Basmadjian et al. 1975). The radiocholesterol compounds were given intravenously in doses varying from 1-2 mCi. The uptake of the freely circulating radioactive iodide in the thyroid gland was blocked by oral administration of 1 drop of Sol Lugoli Fortior 3 times a day, beginning 2 to 3 days before giving the radiocholesterol. A more effective blockade of the thyroid gland was found to be feasible by giving 200 mg potassium perchlorate four times a day, beginning one day before giving the radiocholesterol (Barbarino et al. 1975). Adrenal scintigrams were prepared on the third, fifth, seventh and ninth day after giving the radiocholesterol. A Picker II C gamma camera connected with a PDP-8 computer was used for working out the data.
The first days after giving the radiocholesterol the patient took a laxative, in order to eliminate as far as possible the disturbing activity of the liver, bile ducts and gastrointestinal tract. An optimal image was mostly obtained 5 to 7 days after administration of the radiocholesterol. On the seventh day a renal scintigraphy was done with the aid of ^{99m}Tc-ironascorbate complex in order to obtain a correct localization of the adrenal activity. Before and during the examination, dexametha-

sone was given to all of the patients, at a dose varying from 2 to 4 mg per day When using the radiocholesterol compound ^{131}I-19-Iodocholesterol, dexamethasone was given in a dose of mostly 4 mg/day, starting about 3 days before injection of the tracer On the later use of ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol there was a change-over to giving dexamethasone in a dose of 2 mg per day beginning 2-3 weeks before giving the tracer The considerations that led to the long-lasting giving of dexamethasone in the second procedure, will be dealt with in due course (chapter VI)

II 5 Medicamentous treatment

Under this heading the effects of the medicamentous treatment with the aldosterone antagonist spironolactone (Aldacton^R) and the weak potassium-saving diuretic amiloride (Midamor^R) will be discussed In order to obtain more insight into the mechanism of action of both medicaments on the blood pressure, the aldosterone metabolism, and other parameters, in a prospective study – of which a report is given in the article published in chapter VII – the effects of both medicaments in patients with primary aldosteronism are compared with the effects in patients with essential hypertension In chapter III, General clinical data, the results of medicamentous treatment are summarized and compared with the results of surgical operation, according to the protocol which is described in II 5 2

II 5 1 *Treatment with spironolactone versus amiloride*

For the plan of the study protocol we refer the reader to the section "Methods" of the article published in chapter VII The patients with primary aldosteronism who participated in this study were 4 patients with adenomatous primary aldosteronism (S-R, S-Kr, H-S, H) and 2 patients with idiopathic aldosteronism (T, v E-v U) Besides these, 4 patients with primary aldosteronism took part in this study, but are not discussed in this thesis These 4 patients satisfied the criteria for the diagnosis of primary aldosteronism (hypertension, a low PRA after the usual methods of stimulation, a raised aldosterone secretion rate after loading with 18 grams of salt) In them no examination was made as to the diurnal variations of plasma aldosterone, and no adrenal scintigraphy or operation was done So, in view of the fact that in these patients there were no indications of the nature of the primary aldosteronism (adenomatous or idiopathic) they are left out of further discussion in this thesis

II.5.2. *Medicamentous versus operative treatment*

The lowering effect on blood pressure of high doses of spironolactone in 13 patients with an aldosterone-producing adenoma, and in 3 patients with an adrenal hyperplasia, could be compared with the blood pressure lowering effect of operation. In this context the blood pressure after 3 to 4 weeks of policlinical treatment with spironolactone at a dose of 400 mg/day, was compared with the policlinically measured blood pressure 2 to 3 months after the operation. The postoperative period of 2 to 3 months was considered sufficiently long for the appearance of a blood pressure lowering effect, while, if it did not occur, the patients were still not treated with antihypertensives. The level of the untreated blood pressure before operation was determined by reference to the average of the blood pressure values measured during stay in the clinic for measuring of the aldosterone secretion rate.

II.6. Operation

Operations on the adrenals were done in 22 patients. In the case of an adenoma the adrenal concerned was removed in toto, while, in the case of a bilateral adrenal hyperplasia (v N, S-B, J), a subtotal adrenalectomy was done. The adrenals were approached operatively by the abdominal (G-J, Br) or lumbar route. In one woman patient (Ba) in whom the search for the adrenal adenoma by the abdominal route was unsuccessful, the adenoma was removed later on by the lumbar route. In 6 of the 18 patients for whom a lumbar approach to the adrenals was chosen, a bilateral incision had to be made: in 3 patients because of adrenal hyperplasia (v N, S-B, J) in 3 patients (v W, F, S) because of an adenoma localization on the other side than that where the incision was made in the first instance. In 9 patients the lumbotomy took place via a "low" incision, that is to say, below or at the height of the 12th rib, while in the remaining 9 patients a "high" incision was made, in the 10th or 11th intercostal space. With the latter approach the operator obtains a wider operation field of the retroperitoneal area at the level of the adrenals. For this reason in recent years a "high" incision has been preferred.

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SUMMARY OF THE CLINICAL FINDINGS IN PATIENTS WITH PRIMARY ALDOSTERONISM

III.1. Patients

The 28 patients with primary aldosteronism who are discussed in this thesis were referred to the department of Internal Medicine of the Sint Radboud Hospital in the period of 1961-1979.
The sex and age distribution of the patients does not differ much from what is reported in this connection in the literature generally (Conn et al. 1964, Ferriss et al. 1978a, Weinberger et al. 1979): the ratio of men to women in the group of patients with an adenoma (n=18) was 4:14 (22 against 78%), while in the group of patients with a hyperplasia the sex distribution was normal: 5 men to 4 women (table III.-1.). The mean age at which the diagnosis of primary aldosteronism was made was 43.9 ± 10.5 years in patients with an adenoma, and 49.3 ± 8.4 years in patients with a hyperplasia. In table III.-1. a comparison is made of: the age at which the raised blood pressure was found, the age at which the diagnosis of primary aldosteronism was made, and the age at which the patients were submitted to operation. The average time interval between the age at which the raised blood pressure was found and that at which the diagnosis of primary aldosteronism was made amounted to 5.9 years (range 0-18 years) in the group of patients with an adenoma, and 5.0 years (range 0-17 years) in the group of patients with hyperplasia. The mean time interval between the making of the diagnosis and the operation was 1.7 years (range 0-7 years) in patients with an adenoma. The long time interval between establishing the hypertension and the operation proves to have various causes:
1. Some patients have a long-lasting history of hypertension. Although this is not capable of proof, the impression is gained that primary aldosteronism in some patients developed only after these patients had had hypertension for a considerable time (patients O-K, vd K-M, H-S, M-G, N-M)
2. In a few patients in the first instance no exploratory operation was done because of problems in the diagnosis (adenoma or hyperplasia; patients S-R, S-Kr, H-S)
3. Also in a few patients (Ba, W-S) the operative search for the adenoma caused problems.

Table III-1.

Patients with primary aldosteronism and the age at which a raised blood pressure was found, the age at which the diagnosis of primary aldosteronism was made and the age at which the operation was done. The patients are listed according to the date of the operation (or autopsy)

patient		♂/♀	date of birth	age hypertension	age diagnosis	age operation (autopsy)	year operation (autopsy)
ADENOMA							
1	G-J	♀	17 10 1925	39	39	39	1964
2	Br	♂	31 05 1917	39	47	47	1964
3	v W	♂	19 07 1922	45	49	49	1971
4	F	♂	11 04 1926	44	46	47	1973
5	Ba	♀	29 12 1920	46	46	53	1974
6	vd V	♀	18 05 1941	31	32	33	1974
7	O-K	♀	25 02 1919	37	55	55	1974
8	vd K-M	♀	04 11 1926	35	48	49	1975
9	W-S	♀	29 12 1958	15	15	17	1975
10	S-R	♀	21 10 1931	42	43	47	1978
11	S-Kr	♀	10 11 1931	35	41	47	1978
12	H-S	♀	24 08 1919	40	57	59	1978
13	K-H	♀	27 02 1945	29	32	33	1978
14	H	♂	07 01 1941	34	35	37	1978
15	M-G	♀	13 06 1920	40	57	58	1978
16	N-M	♀	02 01 1923	48	54	55	1978
17	P-R	♀	13 05 1931	45	48	48	1979
18	S-Kl	♀	27 11 1933	40	47	47	1980
			$\bar{X}\pm SD$	38 0±7 7	43 9±10 5	45 6±10 4	
HYPERPLASIA							
19	v N	♂	25 05 1916	50	52	52	1968
20	S	♂	30 03 1913	52	55	58 (aut)	1971 (aut)
21	L	♀	03 10 1914	54	55	57 (aut)	1971 (aut)
22	S-B	♀	30 08 1928	42	42	43	1971
23	J	♂	09 07 1927	46	46	46	1973
24	T	♂	19 02 1924	44	51	–	–
25	v E-v U	♀	11 03 1937	34	37	–	–
26	C J	♀	05 04 1923	30	42	–	–
27	K	♂	21 04 1913	47	64	66 (aut)	1979 (aut)
			$\bar{X}\pm SD$	44 3±8 0	49 3±8 4		
CARCINOMA							
28	L-v G	♀	28 12 1930	46	49	49	1979

III 2 Complaints, symptoms and diagnoses with which the patients were referred

The diagnosis of primary aldosteronism was only rarely suspected on the basis of specific and spontaneous complaints by the patient. Only

once was primary aldosteronism thought of on the grounds of the patient's complaints: this was in the case of the woman vd K-M who developed a paralysis of the legs shortly after beginning a diuretic therapy for hypertension. Table III -2. gives a survey of the complaints and symptoms that were the reasons for the referral, or that gave the

Table III-2.

Complaints, symptoms and diagnoses with which the patients were referred to the department of Internal Medicine of the Sint Radboud Hospital

patient		complaints and symptoms	referred by	tentative diagnosis
ADENOMA				
1	G-J	Cerebral hemorrhage Hypertension and hypokalemia	internist	primary aldosteronism
2	Br	Hypertension with deterioration of renal function and transient ischemic attacks	internist	malign hypertension
3	v W	Hypertension and transient ischemic attacks	internist	hypertension
4	F	Hypertension	family doctor	hypertension
5	Ba	Nervosity and weight loss	cardiologist	hyperthyroidism
6	vd V	Attacks of unconsciousness, headache, vomiting Hypertension, hypokalemia	internist	primary aldosteronism
7	O-K	Fatigue Hypertension, hypokalemia	internist	primary aldosteronism
8	vd K-M	Intermittent paralysis during treatment with diuretics Hypertension, hypokalemia	internist	primary aldosteronism
9	W-S	Hypertension	internist	hypertension
10	S-R	Ankle edema Hypertension and hypokalemia	internist	primary aldosteronism
11	S-Kr	Hypertension Unsuccessful treatment	family doctor	hypertension
12	H-S	Hypertension, hypokalemia	internist	primary aldosteronism
13	K-H	Hypertension, hypokalemia	internist	primary aldosteronism
14	H	Hypertension, hypokalemia	internist	primary aldosteronism
15	M-G	Hypertension, intermittent hypokalemia	internist	hypertension
16	N-M	Hypertension Unsuccessful treatment	internist	hypertension, chronic pyelonephritis
17	P-R	Hypertension Unsuccessful treatment	family doctor	hypertension
18	S-Kl	Hypertension Unsuccessful treatment	internist	hypertension
HYPERPLASIA				
19	v N	Hypertension Unsuccessful treatment	cardiologist	hypertension
20	S	Hypertension Unsuccessful treatment	family doctor	hypertension
21	L	Hypertension Unsuccessful treatment	family doctor	hypertension
22	S-B	Hypertension	surgeon	hypertension
23	J	Hypertension Unsuccessful treatment	family doctor	hypertension
24	T	Hypertension Unsuccessful treatment	family doctor	hypertension
25	v E-v U	Hypertension	family doctor	hypertension
26	C-J	Hypertension Unsuccessful treatment	family doctor	hypertension
27	K	Hypertension, hypokalemia	internist	primary aldosteronism
CARCINOMA				
28	L-v G	Hypertension, hypokalemia	internist	recurrence of primary aldosteronism

inducement for the search for primary aldosteronism. It also lists the referring doctor and the diagnosis under which the patient was sent for consultation. A striking fact was that the patients with an adrenal adenoma were often sent for investigation by an internist of some other hospital (14 of the 28 patients). In 6 of these 14 patients the diagnosis of primary aldosteronism was not considered. Patients with an idiopathic aldosteronism were mostly referred by the family doctor (6 out of the 9 patients) and only on one occasion was the diagnosis of primary aldosteronism considered to be a possibility (by the referring internist). Five of the 18 patients with an adenoma came with neurological symptoms. An unsatisfactory result of the treatment of hypertension was the reason for referral in 10 patients. In all of the patients except the woman Ba, the blood pressure was found to be raised on referral. In half of the patients with an adenoma and in 1 patient with idiopathic aldosteronism, the occurrence of hypokalemia was mentioned by the referring doctor.

III.3. Complaints due to primary aldosteronism

The complaints and phenomena with which the clinical picture of primary aldosteronism is accompanied, were summarized by Conn et al. in 1964 with reference to 103 patients with an aldosterone-producing adenoma that had been published in the literature up to that time. The symptomatology was classified by Conn according to the cause under the following headings:

1. Renal (polydipsia, polyuria, nycturia).
2. Muscular (muscular weakness, paralysis, tetany, paresthesias).
3. Hypertensive (headache, visual disorders).

In almost all of the patients who are described in this thesis one or more of these symptoms were found, although asymptomatic patients existed (table III-3). The frequency with which the symptoms were manifested are in good agreement with the percentages mentioned by Conn. In patients with adrenal hyperplasia we found much fewer symptoms than in patients with an adenoma. A peculiar feature is that 33% of our patients had a history of edema formation, although on examination edema was rarely found. According to Conn et al. (1964) in patients with primary aldosteronism edema was almost never ascertained. Nevertheless "edema" was an item in the history that was mentioned by 10% of the 103 patients. After comparison of the percentages of table III-3, it is remarkably that in the survey collected together by Conn, muscular weakness was very frequent (73%), in contrast to the findings in our patients (28%). In our patients "fatigue" was the most frequent complaint: probably "fatigue" is an insufficiently specific

Table III-3

Complaints and symptoms in patients with primary aldosteronism compared with the survey of literature published by Conn (Conn et al 1964)

	adenoma (n=18)	hyperplasia (n=9)	adenoma (n=103) Conn et al 1964
Fatigue	13/18 (72%)	5/9 (55%)	19%
Headache	12/18 (67%)	1/9 (11%)	51%
Nycturia	10/18 (56%)	4/9 (44%)	72%
Polydipsia	8/18 (44%)	2/9 (22%)	46%
Edema	6/18 (33%)	3/9 (33%)	–
Muscle weakness	5/18 (28%)	0/9 (0%)	73%
Visual disturbances	4/18 (22%)	0/9 (0%)	21%
Paresthesias	4/18 (22%)	1/9 (11%)	24%
Tetany	3/18 (17%)	0/9 (0%)	21%
Intermittent paralysis	2/18 (11%)	0/9 (0%)	21%
No symptoms	1/18 (5%)	3/9 (33%)	6%

complaint and is in fact "muscular weakness" Finally, it can be realized from table III-3 that the percentage of symptomless patients is comparably low (5%) with the percentage mentioned by Conn (6%) In patients with a hyperplasia, however, 3 out of the 9 patients were entirely without symptoms A relatively high percentage of symptomless patients in the group with "idiopathic aldosteronism" fits in with the fact that these patients in general have a milder form of primary aldosteronism (Ferriss et al 1978b) Moreover, it is to be expected that in the future the percentage of symptomless patients will rise By an extension of the diagnostic possibilities (routine determination of plasma renin activity and plasma aldosterone) it seems probable that the diagnosis of primary aldosteronism will be performed on a greater scale, before pronounced complaints have developed

III 4 Pregnancy

In 8 of the 14 women (57%) who had undergone pregnancies their clinical histories showed that the blood pressure had risen during those pregnancies Comparison of the years in table III-4 reveals that, with a few exceptions, a considerable time interval lies between the last pregnancy and the detection of hypertension or the diagnosis of primary aldosteronism in both women who had, and others who had not, gone through a pregnancy marked by hypertension Thus,

Table III-4.

The occurrence of hypertension during pregnancy in 14 women in whom later on the diagnosis of primary aldosteronism was made

patient	number of pregnancies	hypertension during pregnancies	last pregnancy in	hypertension detected in	diagnosis primary aldosteronism in
G-J	3	–	1958	1964	1964
O-K	4	–	1950	1956	1974
vd K-M	3	+ (1-3)	1959	1961	1974
S-R	3	+ (2.3)	1963	1972	1974
S-Kr	3	+ (1)	1966	1966	1972
H-S	10	+ (1-10)	1959	1959	1977
K-H	3	–	1973	1974	1977
M-G	7	–	1957	1960	1977
N-M	5	+ (1-5)	1961	1971	1977
P-R	2	–	1961	1976	1979
S-Kl	2	–	1959	1973	1980
v E-v U	3	+ (3)	1971	1971	1974
C-J	3	+ (1-3)	1951	1953	1965
L-v G	3	+ (1-3)	1966	1966	1967

although the percentage of women with hypertension of pregnancy is strikingly high, as measured by these chronological data, there are no clear indications that primary aldosteronism has contributed to the development of hypertension during the pregnancy. From the literature it is evident that primary aldosteronism during pregnancy is only a rare event (Crane et al. 1964, Gordon et al. 1967). On the other hand it must be borne in mind that a beginning overproduction of aldosterone quite early and especially in the pregnancy can have contributed to the development of hypertension. According to Conn et al. (1967) a rise of blood pressure and suppression of the renin activity are the first signs of a developing primary aldosteronism, while hypokalemia appears only at a later stage.

Furthermore, little is known about the influence of the taking of oral contraceptives on the development of a primary aldosteronism or its early manifestation. The patients K-H and S-Kl had taken oral contraceptives a short time before the phenomena of primary aldosteronism revealed themselves. Recently Leichtmann et al. (1980) reported the presence of primary aldosteronism in 2 women patients who at that moment had been taking oral contraceptives for 8 and 5 years, respectively.

Table III-5

Hypertension and its complications

patient		blood pressure (mmHg)	complications
ADENOMA			
1	G-J	172/114 (n=50)	Cerebral hemorrhage Slight enlargement of the heart
2	Br	225/136 (n=33)	Motor aphasias and angina pectoris Hypertensive retinopathy grade III, impaired renal function
3	v W	186/123 (n=10)	Transient ischemic attacks, impaired renal function
4	F	155/103 (n=13)	None
5	Ba	151/86 (n= 8)	Diffuse coronary ischemia
6	vd V	184/125 (n=12)	Attacks of unconsciousness
7	O-K	154/100 (n=10)	Slight enlargement of the heart
8	vd K-M	212/127 (n=15)	None
9	W-S	193/121 (n= 9)	None
10	S-R	198/121 (n=16)	Slight enlargement of the heart
11	S-Kr	174/110 (n= 9)	None
12	H-S	183/106 (n=24)	Epileptic manifestations
13	K-H	177/115 (n=17)	Enlargement of the heart
14	H	199/125 (n=16)	None
15	M-G	207/123 (n=15)	Enlargement of the heart Hypertensive retinopathy Slightly impaired renal function
16	N-M	237/138 (n=19)	Enlargement of the heart Hypertensive retinopathy grade IV
17	P-R	185/121 (n=21)	Enlargement of the heart
18	S-Kl	205/117 (n=12)	None
HYPERPLASIA			
19	v N	243/124 (n=14)	None
20	S	185/98 (n= 8)	Enlargement of the heart
21	L	215/131 (n=22)	Enlargement of the heart and impaired renal function
22	S-B	173/105 (n=12)	None
23	J	169/118 (n=16)	None
24	T	199/127 (n=27)	None
25	v E-v U	150/100 (n= 9)	None
26	C-J	186/106 (n=10)	None
27	K	223/139 (n=14)	Cerebral vascular accident Myocardial infarction
CARCINOMA			
28	L-v G	155/100 (n=20)	None

Table III-5 gives a survey of the blood pressure values and the hypertensive complications in 28 patients with primary aldosteronism. The reported blood pressure values are the mean values that were measured during stay in the clinic for measurement of the secretion rate of aldosterone. Although some patients had only a slightly raised blood pressure, the blood pressure in the majority of the patients was seriously raised, especially when it is remembered that the blood pressure values were measured under clinical circumstances. The seriousness of the blood pressure is also apparent from the number of patients in whom organ damage was found as the sequel of hypertension. A striking feature is the relatively great number of patients with neurological complications (G-J, Br, v W, vd V, H-S, K). Furthermore, in 11 patients cardiovascular complications were demonstrable, varying from myocardial hypertrophy to diffuse coronary ischemia and myocardial infarct, while in 4 patients a diminished kidney function was observed. The existence of an accelerated or malignant hypertension, estimated by the degree of hypertensive retinopathy, was ascertained in 3 patients. In 6 of the 28 patients (=21%) the complications were regarded as serious (G-J, Br, v W, M-G, N-M, K). At first the blood pressure in patients with primary aldosteronism was described as "relatively mild" (Conn et al. 1964). Hypertension progressing into an accelerated or malignant phase was reported only sporadically (Kaplan 1963, del Greco et al. 1966, Aloia and Beutow 1974). From our data and from recent studies (Ferriss et al. 1978a, Clarke et al. 1979) it is apparent that patients with primary aldosteronism are by no means safeguarded against the well-known complications of a raised blood pressure.

III.6. Plasma electrolytes

In table III-6 are given the concentrations (mean ± SD) of plasma sodium, potassium, chloride and bicarbonate, measured during 3 levels of salt intake. The measurements were made on or about the 5th day of each period. The plasma sodium values in patients with adenomatous aldosteronism (APA, n=18) varied from 136 to 146 mmol/l during a salt-free diet; from 137 to 146 mmol/l during intake of 6 grams of salt, and from 139 to 149 mmol/l during intake of 18 grams of salt. The values during intake of salt proved significantly higher than during a salt-free diet. The sodium values were lower than 140 mmol/l in only 5 of the total of 50 determinations that were made during the various salt intakes. Also in the patients with idiopathic aldosteronism (IHA,

Table III-6.

The influence of dietary sodium intake on plasma electrolyte concentrations (mean values ± SD) in 18 patients with adenomatous (APA) and 9 patients with idiopathic (IHA) aldosteronism

		SODIUM INTAKE						
		115 mmol/24 hr			15 mmol/24 hr			315 mmol/24 hr
Plasma Na^+	APA	143 0±2 3	p<0 005	(n=18)	141 8±2 4	p<0 05	(n=14)	143 4±2 7
(mmol/l)	IHA	144 4±3 4	p<0 01	(n= 9)	141 8±1 7	n s	(n= 6)	142 2±3 2
Plasma K^+	APA	2 8±0 4	p<0 01	(n=18)	3 1±0 4	p<0 05	(n=14)	2 8±0 5
(mmol/l)	IHA	3 2±0 3	n s	(n= 9)	3 4±0 4	n s	(n= 6)	3 0±0 5
Plasma Cl^-	APA	101 7±4 0	p<0 025	(n=18)	99 8±4 5	p<0 005	(n=14)	103 4±4 2
(mmol/l)	IHA	104 8±5 4	n s	(n= 9)	103 2±3 0	n s	(n= 6)	104 2±3 2
Plasma HCO_3^-	APA	31 1±2 6	n s	(n=18)	31 4±3 2	n s	(n=14)	31 4±4 0
(mmol/l)	IHA	27 9±1 9	n s	(n= 9)	29 2±4 5	n s	(n= 6)	28 4±2 8

n=9) the plasma sodium values were higher than 140 mmol/l, with the exception of 2 of the total of 24 determinations. It can therefore be put on record that plasma sodium values that on repetition are lower than 140 mmol/l, in general are only rarely found in patients with primary aldosteronism. Moreover, it turned out that 57 of the 74 sodium determinations (of both groups of patients) lie within the normal area of distribution used by our laboratory (138-144 mmol/l).

The mean plasma potassium values were in patients with APA somewhat lower than in patients with IHA, but the differences were not statistically significant. In patients with APA hypokalemia was a constant finding: during a salt-free diet the values varied from 2.2 to 3.8 mmol/l; during the intake of 6 grams of salt from 1.9 to 3.5 mmol/l; and during the intake of 18 grams of salt from 1.9 to 3.5 mmol/l. On only one occasion was a plasma potassium value found that was within the normal distribution area (3.8 to 4.6 mmol/l). In patients with IHA, 4 out of the total of 24 determinations were found to lie within the normal distribution area. In both groups, salt intake was found to lower the plasma potassium values. This lowering was statistically significant only in the APA group.

The mean plasma chloride values were lower in patients with APA than in those with IHA, but the values did not differ significantly. Chloride values lower than normal (101 to 107 mmol/l) were frequently found in patients with APA: 21 of the total of 50 determinations were lower than 101 mmol/l, while only on 4 occasions was a value higher than 107 mmol/l found. Taking salt with the diet turned out to cause a significant rise of plasma chloride concentrations in patients with APA.

The mean plasma bicarbonate values, were higher in patients with APA than in patients with IHA. Only during intake of 6 grams of salt this difference was also statistically significant ($p<0.005$). Taking salt

gave no significant change in the bicarbonate values in either of the groups. In patients with APA the plasma bicarbonate concentrations were raised: 44 of the total of 50 determinations, while 6 determinations lay within the normal distribution area (26 to 28 mmol/l). In patients with IHA plasma bicarbonate was raised in 15 of 24 determinations.

III.7. The sodium and potassium excretion in the 24 hours urine

In table III-7 can be seen the mean values of the sodium and potassium excretion, measured on the 5th day of each of the 3 periods of salt intake, at an estimated potassium intake of 50 to 70 mmol/day. The values of the sodium and potassium excretion did not vary significantly in the patients of either of these groups. After salt loading there was in both groups of patients a significant increase of the potassium excretion to be seen. With one exception, the excretion of potassium in all patients during uptake of 18 grams of salt, was greater than 80 mmol/24 hr. A significant increase of the potassium excretion after acute or chronic loading with salt in patients with primary aldosteronism, is in good agreement with the findings reported in the literature (Rovner et al. 1965, Espiner et al. 1967, Christlieb et al. 1971) and is explained by an increased rejection of potassium in the distal tubules of the kidney.

Table III-7.

The influence of dietary sodium intake on the 24 hours urinary excretions of sodium and potassium (mean values ± SD) in 18 patients with adenomatous (APA) and 9 patients with idiopathic (IHA) aldosteronism

		SODIUM INTAKE							
		115 mmol 24 hr			15 mmol/24 hr			315 mmol/24 hr	
Urinary Na^+	APA	121 3±57 0	p<0 001	(n=18)	24 9±13 7	p<0 001	(n=14)	304 9±75 2	
(mmol/24 hr)	IHA	169 4±66 6	p<0 001	(n= 7)	23 1±20 2	p<0 001	(n= 6)	377 5±66 1	
Urinary K^+	APA	78 5±31 4	p<0 05	(n=17)	68 0±29 2	p<0 001	(n=13)	112.1±33 9	
(mmol/24 hr)	IHA	67 5±26 1	n s	(n= 7)	48 4±23 0	p<0 02	(n= 6)	93 3± 8 1	

III.8. The plasma renin activity

In 16 patients with APA during a salt-free diet the plasma renin activity (PRA) was assayed at 11.30 hr a.m. after 3 hours ambulation. The PRA values varied from 15 to 66 ng/10 ml/3 hr (mean value ± SD:

38.2 ± 17.1 ng/10ml/3hr, n=16). The PRA of healthy adults, measured under comparable conditions, varies from 115 to 595 ng/10 ml/3 hr. So, in all of the patients with APA markedly suppressed renin values were found. The PRA in patients with IHA varied from 21 to 147 ng/10 ml/3 hr (mean value ± SD: 67.0 ± 41.5 ng/10ml/3hr, n=9). The plasma renin activity in the group of patients with APA was significantly lower than in the IHA group ($p<0.025$). The results of the plasma renin determinations are, like those of the plasma electrolytes, a confirmation of the current notion, that idiopathic aldosteronism is a relatively mild form of primary aldosteronism (Distler et al. 1969, Baer et al. 1970, Luetscher er al. 1974, Ferriss et al. 1978b), which is expressed in less serious biochemical deviations.

III.9. Medicamentous treatment versus operation

In figure III-1 the results of treatment with high doses of spironolactone are compared with the results of operative treatment in 13 patients with an adenoma and 3 patients with a hyperplasia. Treatment with spironolactone 400 mg/day for 3-4 weeks resulted in a significant lowering of blood pressure from 193.4 ± 23.7/119.2 ± 9.5 mmHg to 155.9 ± 28.3/102.5 ± 16.5 mmHg (n=16, $p<0.001$). The blood

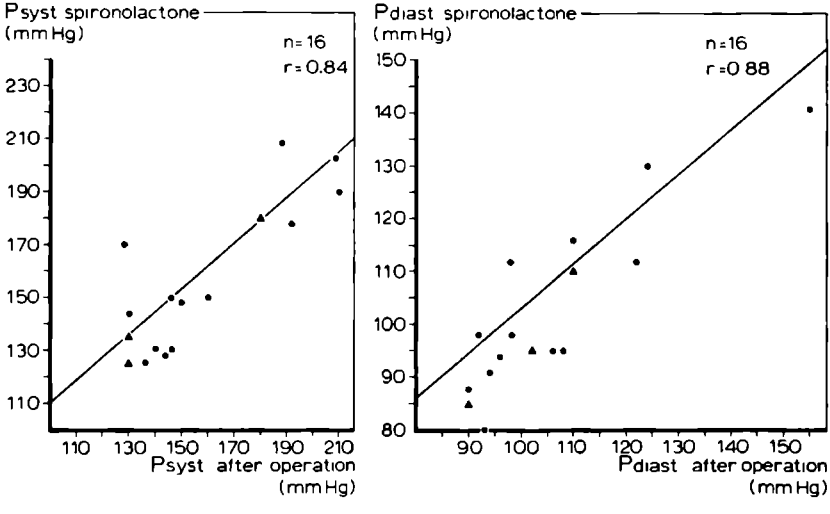

Figure III.-1. Comparison of the results of medicamentous treatment with spironolactone and the results of operation in 13 patients with adenomatous and 3 with idiopathic aldosteronism

Table III-8.

Follow-up after operation (or diagnosis), blood pressure and antihypertensive treatment at the last policlinical control and complications or causes of death in 28 patients with primary aldosteronism

patients		follow up (months)	blood pressure (mmHg)	antihypertensives		complications/causes of death
ADENOMA						
1	G-J	60	130/95	None		–
2	Br	66	245/145	Methyldopa	†14 6 71	encephalopathy, renal insufficiency
3	v W	69	112/95	Propranolol, chlorthalidone, hydralazine	†14 1 77	cause unknown
4	F	72	132/89	None		–
5	Ba	83	146/88	None		myocardial infarction
6	vd V	84	180/116	Chlorthalidone		–
7	O-K	80	160/100	None		–
8	vd K-M	69	120/88	Metoprolol		–
9	W-S	75	138/98	Chlorthalidone		–
10	S-R	35	125/85	Metoprolol, chlorthalidone		–
11	S-Kr	34	135/100	None		–
12	H-S	28	170/100	None		angina pectoris
13	K-H	28	125/90	None		–
14	H	30	148/90	Propranolol		–
15	M-G	27	185/110	Prazosine	†18 9 80	bronchus carcinoma
16	N-M	30	170/106	Spironolactone		–
17	P-R	20	120/80	None		–
18	S-Kl	5	135/85	None		–
HYPERPLASIA						
19	v N	138	160/85	Chlorthalidone		–
20	S	28*	180/95	Rauwolfia	†13 1 74	acute pancreatitis
21	L	31*	180/110	Hydralazine	† 2 3 71	dissecting aneurysm aortae
22	S-B	54	124/88	None	† 5 1 76	respiratory insufficiency
23	J	84	150/98	None		–
24	T	45*	176/118	Amiloride		–
25	v E-v U	81*	130/88	Spironolactone		–
26	C-J	192*	150/94	Spironolactone		–
27	K	17*	150/100	Metoprolol	†16 3 79	myocardial infarction cerebrovascular accident
CARCINOMA						
28	L-v G	18	110/80	None		local recurrence of tumor

*No operation Follow up after diagnosis of primary aldosteronism

pressure values during treatment with spironolactone did not differ significantly from the values recorded 2 to 3 months after operation: 155 9 ± 28.3/102.5 ± 16.5 mmHg versus 157.4 ± 28 8/105 2 ± 15.9 (n=16, n.s.). As appears from the correlation coefficients between the blood pressure values after treatment with spironolactone and those after operation (figure III-1) it is possible on the grounds of

the blood pressure after 3 to 4 weeks treatment with spironolactone to obtain a reliable impression about the blood pressure that may be expected after operation. These results are in agreement with what was reported in the literature by Spark and Melby (1968), Brown et al. (1969 and 1972), Crane and Harris (1970) and Ferriss et al. (1975 and 1978c). The spironolactone test is less accurate in predicting the postoperative fall in blood pressure in patients without adenoma (Ferriss et al. 1978c), although in our 3 patients with a hyperplasia the medicamentous and postoperative blood pressure values were in good agreement with each other.

Table III-9.

Literature review of the results of operation in patients with primary aldosteronism, expressed in percentages of patients in whom the blood pressure normalized after operation

	ADENOMA unilateral adrenalectomy	HYPERPLASIA unilateral or (sub)total adrenalectomy
Conn et al. 1968	63%	–
Distler et al. 1969	80%	20%
George et al. 1970	56%	0%
Biglieri et al. 1970	60%	0%
Baer et al. 1970	83%	0%
Cain et al. 1972	75%	–
Ferriss et al. 1975	50%	20%
Ferriss et al. 1978c	56%	15%
Philipp et al. 1978	50%	17%
Weinberger et al. 1979	68%	20%
Auda et al. 1980	64%	21%
Vaughan et al. 1981	71%	–

III.10. Follow-up

After the operation (or after the making of the diagnosis of primary aldosteronism, see table III-8) the patients were followed up for 5 to 192 months (average 56.5 ± 39.8 months). Seven patients died during the follow-up: 3 patients (Br, L, K) as the sequel of vascular complications of a persisting hypertension, and 3 patients (M-G, S, S-B) as the consequence of other causes. Patient v W died suddenly and no

autopsy could be performed. Also in the table are set forth the blood pressure values that were measured in the last policlinical control and the antihypertensives with which the patient was being treated at that moment. The blood pressure values show that in the majority of the patients who had undergone operation (18 patients with an adenoma, 3 with a hyperplasia and one with a carcinoma) the effect on the blood pressure, even after a longlasting follow-up, was favourable: only in 2 of the 22 patients (9%) no important fall in the blood pressure was achieved, not even after antihypertensive treatment was started again (Br, M-G). In 11 patients (50%; v W, vd V, O-K, vd K-M, W-S, S-R, S-Kr, H-S, H, N-M, v N) a definite fall of the blood pressure occurred after the operation. In these patients there remained a slightly raised blood pressure that mostly was found to be effectively treated by simple antihypertensive therapy. In 9 patients (41%; G-J, F, Ba, K-H, P-R, S-Kl, S-B, J, L-v G) the blood pressure after operation fell off to normal values without the use of antihypertensive medication. In the case of patient Br the failure of a lowering of blood pressure to occur after operation is ascribable to a progressive worsening of kidney function. In the woman M-G, the operation remained without result as the consequence of a recurrent primary aldosteronism. On the other hand this woman also had a diminished kidney function because of a serious nephrosclerosis, which was discovered at autopsy. The operation data are less favorable than one might expect from the data in the literature. Table III.-9. shows that, according to the literature, removal of an adenoma causes the blood pressure to fall to normal values in 50 to 80% of the patients. On the contrary, in patients with idiopathic aldosteronism, operation induces a normal blood pressure in only 0 to 21% of the patients. A normalization of the blood pressure was achieved in the group examined by us in 6 of the 18 patients (33%) with an adenoma and in 2 of the 3 patients with a hyperplasia. To sum up: it seems to us likely that the less favorable results are ascribable to the following factors: a long-lasting hypertension before the diagnosis of primary aldosteronism was made (patients O-K, vd K-M, H-S, N-M); recurrence of primary aldosteronism (M-G); kidney disorders (Br and v W). The results of operation in our patients with idiopathic aldosteronism are remarkable but do not allow any conclusions to be drawn because of the limited size of the group. But, in any case they give no grounds for rejection of the notion that we also maintain, namely, that patients with idiopathic aldosteronism must be treated preferably by medicaments.

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CHAPTER IV

THE VALUE OF ESTIMATIONS OF ALDOSTERONE FOR THE DIAGNOSIS OF PRIMARY ALDOSTERONISM AND FOR THE DISTINCTION OF THE ADENOMATOUS AND IDIOPATHIC FORMS

In this chapter evaluations are given successively of the results of estimations of the rate of secretion of aldosterone, the rate of excretion of a metabolite in the urine, the 18-glucuronide of aldosterone, and of the levels of aldosterone in peripheral venous blood under varying conditions. In chapter V a prospective study is made on variations in the blood level during 24 hours, and, especially, during the early morning, in a group of patients with the adenomatous form of primary aldosteronism and in 4 patients with idiopathic aldosteronism. In this chapter additional observations in a group of patients "after removal of an aldosterone-producing adenoma" are compared with the results in the abovementioned study.

IV.1. The aldosterone secretion rate

As set forth in chapter II.2. the measurements of the aldosterone secretion rate (ASR) were made under standardized conditions during continued use of a strictly salt-free diet with about 15 mmol sodium per day and a potassium content that in the individual diets varied from 50 to 70 mmol/day. Secretion measurements of aldosterone were done after 6 grams of salt had been given in divided doses for 5 days (ASR 115), then after no extra salt had been added for 5 days (ASR 15), and, finally after giving 18 grams of salt per day for 5 days (ASR 315). In table IV.1. the results are displayed. For the sake of comparison the values obtained among normal test persons under identical conditions are given. Figure IV-1 shows that after loading with 18 grams of salt (ASR 315) all of the values in patients with adenomatous primary aldosteronism (group I) and those from others with the idiopathic form (group II) were, without exception, higher than in the control group. For ASR 115 it is also true that all the secretion values in group I were higher than in normal persons. However, 3 out of the 9 measurements in group II lie within the normal distribution area. With regard to ASR 15 there is a very obvious "overlap" of values between the group of normals and the I and II patient groups. There is even no statistically

significant difference between the values of both patient groups and normal persons. These data illustrate the fact that in none of the levels of salt intake do measurements of the aldosterone secretion rate make

Table IV-1.

The secretion rates of aldosterone in 18 patients with adenomatous, and in 9 patients with idiopathic aldosteronism, measured during the ingestion of 15 mmol Na^+/24 hr (ASR15), 115 mmol Na^+/24 hr (ASR115) and 315 mmol Na^+/24 hr (ASR315)

	ASR15	ASR115	ASR315
ADENOMA			
1. G-J	396	370	–
2. Br	1255	1257	–
3. v W	1750	429	–
4. F	516	408	–
5. Ba	732	551	–
6. vd V	–	248	–
7. O-K	–	1944	1721
8. vd K-M	–	851	981
9. W-S	–	440	455
10. S-R	920	544	266
11. S-Kr	–	862	793
12. H-S	–	642	1079
13. K-H	400	331	459
14. H	908	702	666
15. M-G	230	270	215
16. N-M	470	353	253
17. P-R	–	385	387
18. S-Kl	240	259	244
HYPERPLASIA			
19. v N	481	476	–
20. S	281	401	–
21. L	418	222	–
22. S-B	–	242	219
23. J	426	340	388
24. T	–	474	432
25. v E-v U	460	250	199
26. C-J	468	143	163
27. K	160	108	108

feasible any difference between the groups I and II. The ASR 15 values in patients from group I varied from 230-1750 μg/24 hr (mean ± SD, 711 ± 469 μg/24 hr, n=11) and in patients from group II from 160-481 μg/24 hr (mean ± SD, 385 ± 120 μg/24 hr, n=7, n.s.). The secretion values during uptake of 6 grams of salt varied in group I from 248 to 1944 μg/24 hr (mean ± SD, 603 ± 424 μg/24 hr, n=18) and were statistically significantly higher ($p<0.025$) than the values in group II that varied from 108 to 474 μg/24 hr (mean ± SD, 295 ± 135 μg/24 hr, n=9). The ASR 315 values manifest no statistical difference

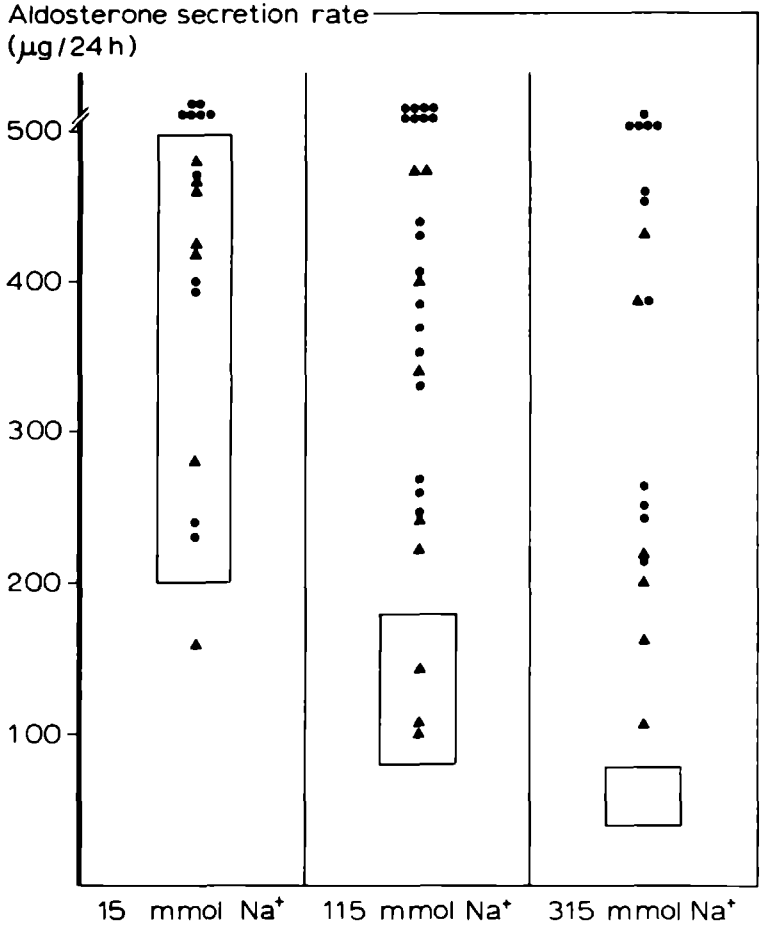

Figure IV-1. Aldosterone secretion rates in patients with adenomatous (●) and idiopathic (▲) aldosteronism, measured during an intake of 15 mmol Na^+/day, 115 mmol Na^+/day and 315 mmol Na^+/day

between the two groups: in group I the values varied from 215 to 721 μg/24 hr (mean ± SD, 627 ± 453 μg/24 hr, n=12) and in group II from 108 to 432 μg/24 hr (mean ± SD, 251 ± 129 μg/24 hr, n=6) The ASR values in group I as in group II prove to be not significantly influenced by salt loading Nevertheless in group I, in 7 out of 11 patients, and in group II in 5 out of 7 patients, the ASR 115 values were lower than the ASR 15 values On comparison between the ASR 115 and the ASR 315 values there was found in group I in 6 out of 12 patients, and in group II in 3 out of 6 patients that the values were lower after increasing the salt intake

IV.2. The urinary excretion of aldosterone-18-glucuronide

During each of the 5 days of the study, the protocol of which was set forth in chapter II 3 2., measurements were made of the excretions of the metabolite aldosterone-18-glucuronide in:

1. 8 patients with adenomatous primary aldosteronism (group I)
2. 4 patients with idiopathic aldosteronism (group II)
3. 6 patients in whom in the past an aldosterone-producing adenoma had been removed (group III)

According to the arrangement of the study, the effect of the body posture on the rate of excretion of the metabolite can be studied by comparing the values of day 1 (ambulation) with day 2 (rest in bed), and of day 4 with day 5 (ambulation and rest in bed, respectively, during the use of dexamethasone) Besides, one can ascertain the influence of giving dexamethasone for 3 days on the excretion of aldosterone. Table IV-2 and figure IV-2 give the individual data and the mean values In the same way that was valid for the secretion values of aldosterone with the use of 6 grams of salt per day, it can be seen that the excretion values of the aldosterone metabolite can provide no strict borderline between the groups I and II, on either day 1 (during ambulation) or on day 2 (during rest in bed) The excretion values in group III (after removal of an aldosterone-producing adenoma) are, with a single exception, lower than those in the groups I and II. The influence of body posture on the excretion of aldosterone-18-glucuronide under basal conditions is seen by comparing the values of day 1 with those of day 2. The influence of the body posture during dexamethasone can be obtained by comparing the values of day 4 with those of day 5. In the group of patients with an adenoma no effect of body posture is seen, either under basal conditions, or during dexamethasone treatment In the groups II and III one sees, with one single exception, somewhat lower values on the days of complete bedrest than on the days in which the patients are out of bed, in both basal

Table IV-2

The 24-hours excretions of aldosterone-18-glucuronide and the influence on it of body posture before and during the use of dexamethasone in patients with adenomatous aldosteronism, idiopathic aldosteronism, and "after removal of an aldosterone-producing adenoma"

			dexamethasone 2 mg/day		
	day 1	day 2	day 3	day 4	day 5
I ADENOMA	♀	⊶	♀	♀	⊶
S-R	40 0	36 0	36 0	50 0	17 0
S-Kr	34 0	36 0	11 0	12 0	30 0
H-S	36 1	33 8	22 7	33 0	64 3
K-H	19 3	12 6	6 9	7 7	10 7
H	65 4	71 0	28 2	44 9	35 8
N-M	14 3	9 0	11 0	15 0	6 0
P-R	20 0	56 0	16 0	29 0	36 0
M-G	25 0	28 0	15 0	17 4	22 5
II HYPERPLASIA					
I	23 8	23 8	22 9	28 6	23 7
v E-v U	24 6	23 6	20 6	17 2	11 8
C-J	34 3	11 6	22 0	21 2	15 2
K	10 3	8 7	6 4	9 7	8 3
III ADENOMA AFTER OPERATION					
N-M	6 0	6 0	4 0	4 0	4 0
K-H	4 0	3 0	3 0	4 0	3 0
K-M	7 8	5 6	7 5	6 4	5 0
vd V	15 0	8 2	12 0	15 0	13 0
O-K	9 0	8 0	6 0	10 0	9 0
F	7 0	1 5	3 0	6 0	4 0

conditions and during dexamethasone From table IV-2 and figure IV-2 it will be seen also that the excretion of the aldosterone-18-glucuronide on the first day of dexamethasone (day 3) was lower in every patient from every group than on day 1 (on both days the patients were out of bed) On the second and third days of dexamethasone administration (days 4 and 5) the excretion values in the groups I and III did not differ significantly from those on the corresponding days 1 and 2 The data from group II do not lend themselves to any statistical compilation Evidently, there is a short-lasting effect of suppression of ACTH by

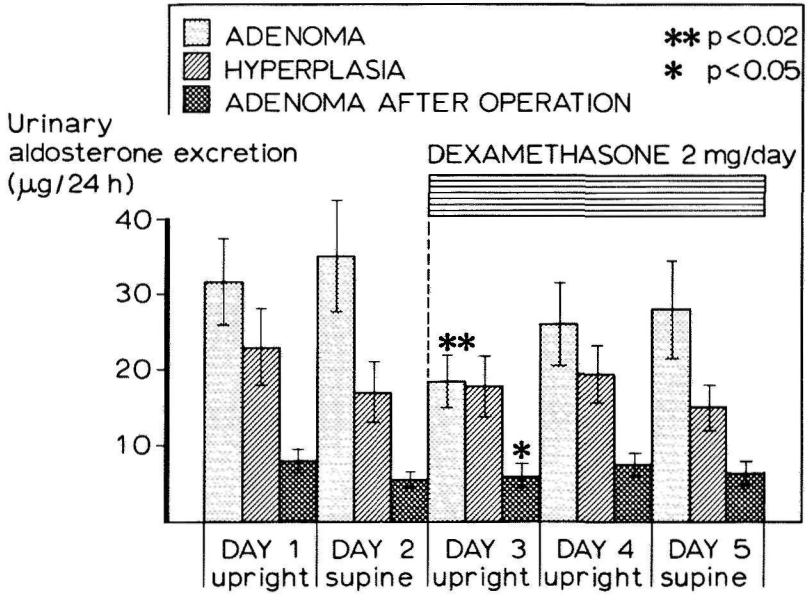

Figure IV-2. The influence of body posture and dexamethasone treatment on urinary aldosterone excretion in patients with adenomatous- and idiopathic aldosteronism and in patients "after removal of an aldosterone-producing adenoma"

dexamethasone on the excretion of the aldosterone-18-glucuronide: on the first day when it is given, the excretion falls off in both groups with primary aldosteronism as in the group "after removal of an adenoma".

IV.3. Measuring aldosterone in peripheral venous blood

In every patient of the three groups examined (adenomatous aldosteronism, idiopathic aldosteronism and "after removal of an adenoma") a number of samples of blood were collected in accordance with the protocol described in chapter II.3.2. With this protocol design an impression can be obtained about the aldosterone concentrations at various moments of the day and night. In the study published in chapter V the results in patients with primary aldosteronism are discussed. In this paragraph the results are compared with those in a group of 6 patients in whom the research was carried out after removal of an aldosterone-producing adenoma on some previous occasion (group III).

IV.3.1. *Levels of aldosterone in blood during the night*

In table IV-3 and figure IV-3 the individual and mean values per patient and per group are placed alongside each other. From this it will be seen that:

1. The mean nocturnal hormone values in group I, varying from 19.6 ± 3.5 (SD) to 65.0 ± 5.6 ng/100 ml, are much higher than those in group II (7.7 ± 1.6 to 14.4 ± 5.2 ng/100 ml) and in group III (5.7 ± 3.0 to 13.5 ± 3.2 ng/100 ml). Also on comparison of the nocturnal values per individual from group I with those of the patients from the

Table IV-3.

The variability of the plasma aldosterone concentrations in patients with adenomatous aldosteronism, idiopathic aldosteronism and "after removal of an aldosterone-producing adenoma"

			day 1				day 2		
	04 45 hr-07 45 hr		07 45 hr	12 00 hr	16 00 hr	20 00 hr	12 00 hr	16 00 hr	20 00 hr
	mean	range							
I ADENOMA									
S-R	36.9	31.8-45.7	32.7	34.7	22.3	14.6	30.3	14.7	10.7
S-Kr	46.7	32.2-57.9	32.2	54.6	33.9	32.9	42.3	24.8	28.2
H-S	65.0	54.9-73.4	71.2	52.6	45.5	7.1	30.3	16.2	11.6
K-H	51.3	27.6-66.0	47.5	18.3	15.6	26.7	22.9	10.2	15.5
H	61.5	39.4-80.7	60.7	72.1	78.7	17.8	42.4	41.0	76.4
N-M	19.6	15.5-26.8	20.8	24.9	15.8	8.8	20.1	16.6	9.3
P-R	36.4	25.7-47.7	35.9	13.0	20.3	8.9	49.8	37.8	26.3
M-G	32.3	25.5-37.9	28.4	23.7	6.8	9.0	36.0	18.5	10.0
II HYPERPLASIA									
T	7.7	5.3- 9.8	8.9	12.1	16.9	11.1	14.0	13.2	14.9
v E-v U	10.0	4.1-14.8	13.7	28.1	40.7	11.2	12.3	21.2	12.4
C-J	13.4	9.4-17.5	13.3	49.6	40.2	21.7	18.3	18.4	8.9
K	14.4	5.5-19.8	5.5	21.8	9.4	16.0	11.5	7.7	7.4
III ADENOMA AFTER OPERATION									
K-H	11.4	7.4-14.3	7.4	13.1	16.6	11.5	9.1	9.6	6.5
N-M	10.5	4.9-21.9	4.9	25.3	22.9	9.0	10.4	13.6	2.0
vd K-M	13.5	9.1-18.5	11.0	29.5	22.2	20.7	10.5	11.6	4.2
vd V	6.5	4.0-12.4	4.0	16.6	15.9	7.8	5.7	2.8	8.6
O-K	13.1	11.7-14.7	13.4	16.9	11.6	11.7	11.5	6.4	3.6
F	5.7	2.2-10.9	8.5	9.3	9.7	9.7	6.2	7.7	5.4

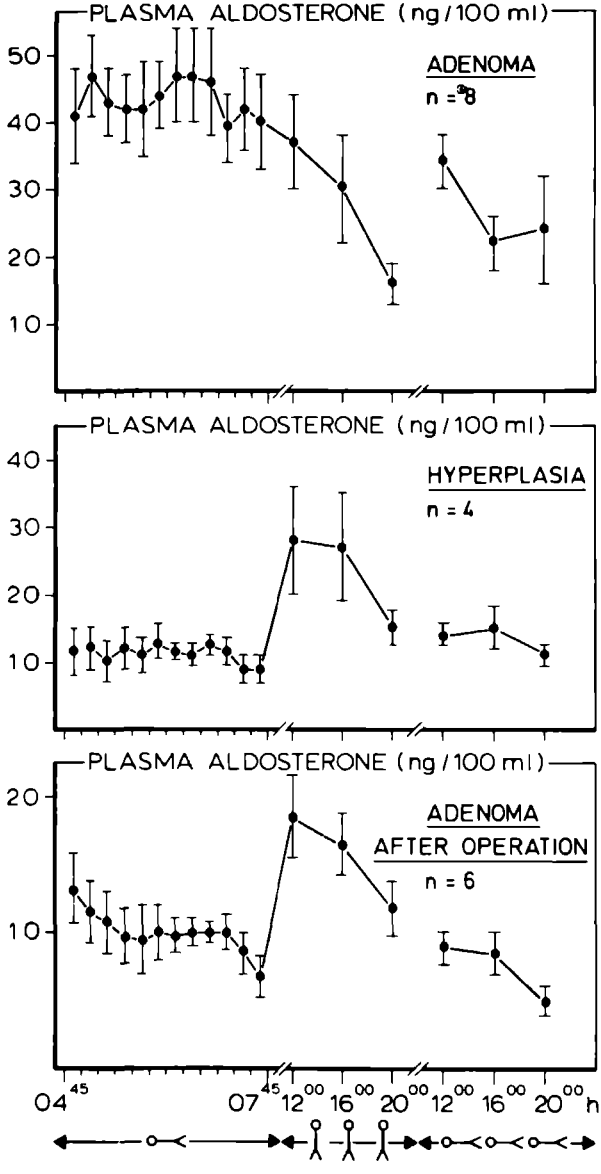

Figure IV-3. Nocturnal and daytime aldosterone concentrations in patients with adenomatous and idiopathic aldosteronism and in patients "after removal of an aldosterone-producing adenoma"

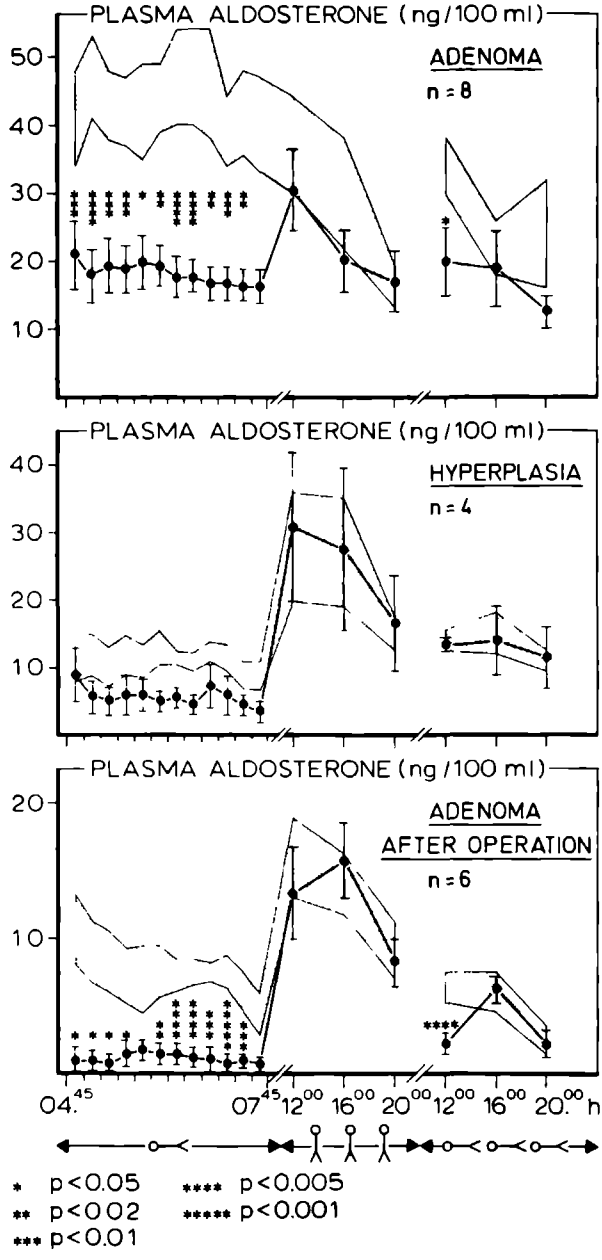

Figure IV-4. Effects of treatment with dexamethasone 2 mg/day on nocturnal and daytime aldosterone concentrations in patients with adenomatous and idiopathic aldosteronism and in patients "after removal of an aldosterone-producing adenoma"

groups II and III it will be seen that practically all aldosterone values of the patients with an aldosterone-producing adenoma, between 04 45 and 07.45 hr, are considerably higher than those of the patients from both of the other groups In the woman patient N-M from group I, at some points of time in the night, values were found that were lower than those of the patient K, who had highest values in group II, the woman patient N-M also had the lowest excretion values of aldosterone-18-glucuronide in group I, according to table IV-2

2. The mean aldosterone values in the late night in patients with idiopathic aldosteronism are strikingly low and do not differ significantly from the values that were measured in patients from whom an adenoma had been removed in the past

3 The plasma aldosterone concentrations during the late night in all patients manifested considerable variations, as may be seen in the distribution of the values in the individual patients (table IV-3) and from the figures presented in the case histories of the individual patients (see appendix) To what extent episodic variations of aldosterone (caused by short-lasting spurts of secretion) play a rôle in this, cannot be said for certain, because the method for collection of the blood samples (a continuous blood sampling) is unsuitable for showing very rapid changes in the hormone concentrations.

In figure IV-4 the aldosterone concentrations (mean ± standard error of mean) during treatment with dexamethasone 2 mg/day are compared with the corresponding aldosterone values under basal conditions in all of the three groups of patients The aldosterone values during the last part of the night (that is to say, 21 to 24 hours after giving the first dose of dexamethasone) in groups I and III were found to be significantly lower than the comparable basal values. But it appeared on careful comparison of all individual values (tables IV-3 and IV-4) that in 1 patient from group I (N-M) there could be no question of suppression by dexamethasone, as 9 of the 12 nocturnal values were higher during dexamethasone administration than on the basal day. This woman was also remarkable quite otherwise the excretion of the aldosterone-18-glucuronide was the lowest of group I, and so, too, was the plasma level in the first night of sampling Further, in one patient of group II (T) and in one of group III (F), a number of nocturnal plasma values during dexamethasone were higher than on the control day. In general it is obvious that the degree of suppression of the nocturnal aldosterone level on the first day of the administration of dexamethasone is rather variable (for this compare with the data per patient reported in the figures of the appendix)

Table IV-4.

The variability of the plasma aldosterone concentrations in patients with adenomatous aldosteronism, idiopathic aldosteronism and "after removal of an aldosterone-producing adenoma" during administration of dexamethasone 2 mg/day

	day 4						day5		
	04 45 hr-07 45 hr		07 45 hr	12 00 hr	16 00 hr	20 00 hr	12 00 hr	16 00 hr	20 00 hr
	mean	range							
I ADENOMA	⟜		⟜	🧍	🧍	🧍	⟜	⟜	⟜
S-R	23.6	21.6-25.0	23.6	45.6	36.3	38.2	17.7	15.6	11.2
S-Kr	8.6	6.1-10.6	9.6	8.3	7.2	3.8	20.9	12.5	14.6
H-S	24.7	20.7-26.4	26.4	36.1	33.5	17.3	52.9	42.0	29.2
K-H	7.9	5.7-11.3	11.3	10.4	7.3	8.3	10.1	10.1	8.3
H	29.4	17.4-45.2	17.4	52.8	19.5	32.8	11.0	43.9	9.3
N-M	25.7	20.8-29.2	25.7	33.4	32.0	10.0	8.9	6.4	3.8
P-R	20.7	16.0-27.0	22.0	40.0	15.0	17.0	25.0	14.0	16.0
M-G	9.4	6.5-15.6	12.7	18.0	10.3	7.9	15.1	9.3	8.9
II HYPERPLASIA									
T	8.9	5.0-12.8	5.0	23.4	16.5	12.1	14.4	15.3	10.1
v E-v U	1.4	0.9- 2.5	1.0	24.7	16.1	7.7	12.1	6.7	3.7
C-J	10.2	6.5-18.2	6.5	63.0	63.5	37.7	16.9	27.4	21.0
K	2.4	1.4- 4.3	2.5	13.5	13.0	8.0	11.4	6.7	–
III ADENOMA AFTER OPERATION									
K-H	2.2	2.0- 3.9	3.9	13.7	10.4	7.8	3.0	4.4	6.1
N-M	3.6	2.0- 7.5	2.8	–	22.6	7.0	4.6	9.9	3.9
vd K-M	3.2	1.0- 6.2	2.6	27.6	24.8	15.7	5.5	11.0	3.4
vd V	2.4	1.4- 4.7	1.4	13.7	20.4	17.3	2.9	9.9	1.2
O-K	6.1	4.4- 7.5	5.8	17.3	21.9	9.3	7.9	9.0	9.2
F	4.3	2.3- 6.2	3.4	6.6	9.5	7.5	3.9	8.7	5.3

IV.3.2. *Levels of aldosterone in blood during the day*

From table IV-3 and figure IV-3 it is evident that the aldosterone values in plasma determined at the points of time 12.00, 16.00 and 20.00 hr have a tendency to decrease in the course of the day, on both day 1 (during ambulation) and on day 2 (during rest in bed). Statistically suchlike appears significant only in group I (Friedman test: for day 1 $p<0.05$ and for day 2 $p<0.02$). Moreover, a strict differentiation between the 3 groups is not to be found: only at the point of time

12.00 hr of day 2 do the aldosterone values in group 1 appear without exception to be higher than in the other 2 groups. With reference to the last values of the nocturnal sampling period (between 07.30 and 07.45 hr and the value at 12.00 hr on the first day, the effect of change of body posture on the aldosterone levels can be compared in the 3 groups. Table IV-3 shows that ambulation during the morning causes a rise of the aldosterone level in all of the patients in the groups II and III, while in the group of patients with adenomatous primary aldosteronism a falling-off occurred in 4 of the 8 patients. The absence of a clear rise after the stimulus of "ambulation during the morning" is considered by some authors as a criterion for the differentiation of patients with adenomatous aldosteronism from patients with idiopathic aldosteronism. Our data illustrate that this assumption is only to a very small degree correct. Table IV-4 and figure IV-4 show the effect of dexamethasone on the aldosterone levels in blood on the days 4 and 5, that is to say, on the second and third days of administration of dexamethasone. In the paragraph, in which the excretion values of the aldosterone-18-glucuronide are commented on, the conclusion was that on the second and third days of dexamethasone, no suppressive effect was recognizable any longer. This applies also to the aldosterone levels in blood: in comparisons of the values during days 1 and 5 (during ambulation) and those of days 2 and 5 (during rest in bed) there is no evidence of systematic lower values in any of the groups on the days on which dexamethasone is used. In the published study that is reproduced in chapter V it is stated that during administration of dexamethasone the aldosterone level rises significantly in patients with adenomatous aldosteronism during ambulation in the morning (from 18.3 ± 6.6 to 30.6 ± 16.5 ng/100 ml), while under basal conditions, there was no significant change. Figure IV-4 and table IV-4 show that also in the group of patients "after removal of an adenoma" the aldosterone levels rise as well as under basal conditions as during dexamethasone. A possible explanation of this phenomenon in patients with adenomatous primary aldosteronism, will be seen in the discussion in chapter V. Furthermore, an impression can be gained about the effect of body posture on blood levels of aldosterone, if the aldosterone values measured at the points of time 12.00, 16.00 and 20.00 hr of day 1 (ambulation) are compared with those at the same points of time on day 2 (rest in bed). In the same way the effect of body posture can be followed up by comparing the values of aldosterone at the same points of time on day 4 with those on day 5 (ambulation and rest in bed, respectively, during the administration of dexamethasone). If the results of the comparisons under basal conditions and during dexamethasone are added together (figure IV-5) it turns out that during bed rest (day 2 and 5) the plasma aldosterone values in the groups II and III

almost without exception are lower than during ambulation (days 1 and 3). On the contrary, in group I such an effect of body posture on the aldosterone concentrations is not recognizable Finally, the measurements of plasma renin activity at the points of time 12 00, 16 00 and 20.00 hr of day 1 (during ambulation) are compared with the values of day 2 (during bed rest). In the same way comparison is made of the values obtained under identical conditions during administration of dexamethasone (days 4 and 5) In figure IV-6 the values of plasma renin activity under basal conditions and under dexamethasone are added together and grouped among the body postures. It becomes apparent that during an intake of 6 grams of salt, the PRA values do not differ significantly from each other in the three groups In groups II and III the values in the recumbent posture are mostly lower than those obtained during upricht posture In group I, however, no clear effect of body posture on the plasma renin activity was detectable

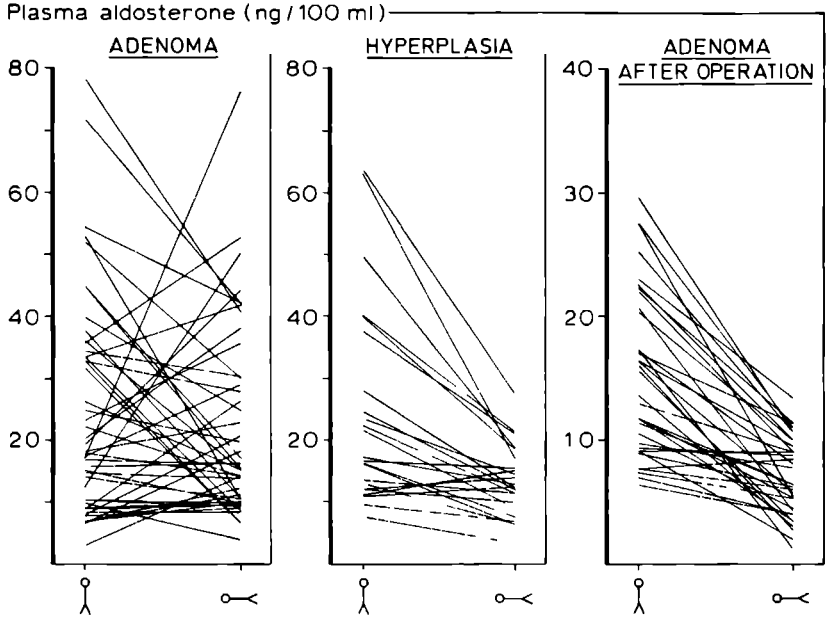

Figure IV-5. The influence of body posture on plasma aldosterone concentrations in patients with adenomatous and idiopathic aldosteronism and in patients "after removal of an aldosterone-producing adenoma"

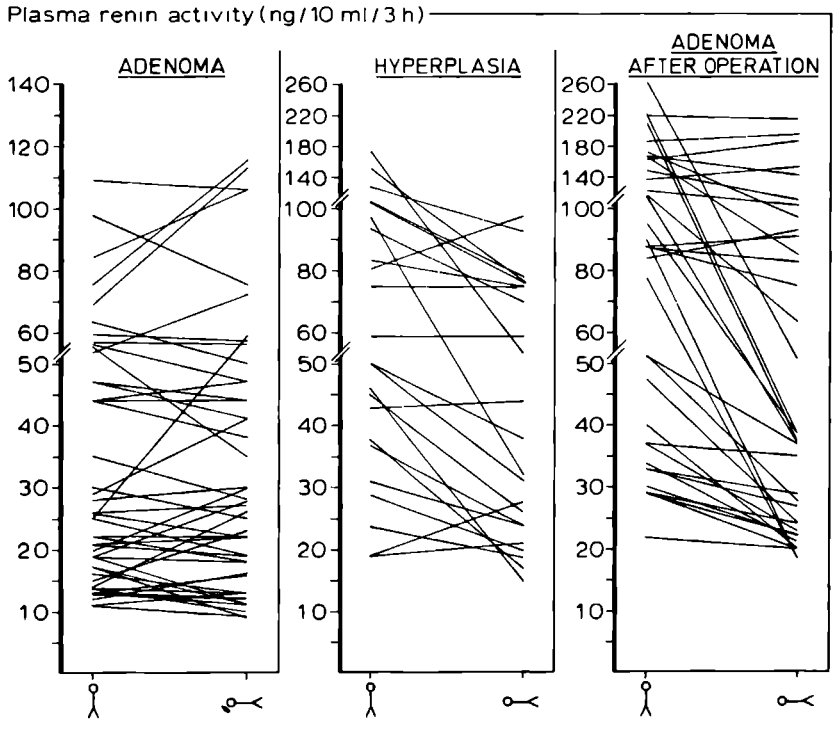

Figure IV-6. The influence of body posture on plasma renin activity in patients with adenomatous and idiopathic aldosteronism and in patients "after removal of an aldosterone-producing adenoma"

IV.4. The influence of ACTH on aldosterone

In a number of case records (see appendix) reference is made to the relation between the levels of aldosterone and those of cortisol and 18-OH-DOC as representives of the zona fasciculata activity in patients with primary aldosteronism. In the three groups of patients who were studied according to the protocol described earlier, these 3 corticosteroids were measured in all of the samples of blood. From the results of the measurements, the correlation coefficients were calculated between the values of the three hormones (table IV-5) It will be noticed that the correlation coefficients of the values of cortisol and 18-OH-DOC are significant for each patient in the three groups. Therefore, it can be argued that the finding of a significant correlation coefficient between these hormones, is an indirect measure for ACTH-dependent hormone secretion If with this a comparison is made with the correlation

Table IV-5.

The correlation coefficients between the plasma concentrations of aldosterone, cortisol and 18-OH-DOC in patients with adenomatous aldosteronism, idiopathic aldosteronism and "after removal of an aldosterone-producing adenoma"

	aldosterone vs cortisol night, days 1 and 2	aldosterone vs 18-OH-DOC night, days 1 and 2	cortisol vs 18-OH-DOC night, days 1 and 2
I ADENOMA			
S-R	0.82***	0.85***	0.95***
S-Kr	0.57**	0.45*	0.76***
H-S	0.44	0.72***	0.63**
K-H	0.90***	0.96***	0.89***
H	0.53*	0.72***	0.85***
N-M	0.44	0.65**	0.92***
P-R	0.21	0.70***	0.56*
M-G	0.34	0.28	0.82***
II HYPERPLASIA			
T	0.55*	−0.06	0.56*
v E-v U	0.34	0.03	0.62**
C-J	−0.14	−0.12	0.98***
K	0.11	0.46*	0.77***
III ADENOMA AFTER OPERATION			
K-H	0.02	0.40	0.70***
N-M	0.10	−0.03	0.85***
vd K-M	0.16	0.31	0.91***
vd V	0.27	0.35	0.95***
O-K	0.31	0.24	0.53*
F	0.81***	0.76***	0.95***

* $p<0.05$
** $p<0.01$
*** $p<0.001$

coefficients between the values of aldosterone and cortisol and between those of aldosterone and 18-OH-DOC, it becomes obvious that the correlation coefficients between the values of aldosterone and those of both of the zona fasciculata steroids, less frequently reach the level of statistical significance, especially in groups II and III. From this it can be deduced that the secretion of aldosterone in patients with adenomatous aldosteronism is more under control of ACTH than in

patients from either of the other groups. However, the influence of ACTH on aldosterone in patients with adenomatous aldosteronism may show a rather wide interindividual variation.

IV 5. Summary

For a discussion of the results we refer the reader also to the "discussion" in chapter V

From determinations of the secretion of aldosterone, at 3 levels of salt intake with the diet, emerges the value of salt loading for establishing the diagnosis of primary aldosteronism; exclusively at a sodium intake of 315 mmol/day it turns out that the values of secretion of patients with primary aldosteronism, without exception, are found to be higher than in normal test persons. At a sodium intake of 15 mmol/day a clear "overlap" was found between the values of patients and normal test persons. These results are in good agreement with the studies in which likewise determinations of secretion were done after oral salt loading for several days (Collins et al. 1970, Demanet and Vrijens 1971, Cain et al. 1972). On the other hand we conclude that a "normal" rate of secretion of aldosterone during a moderate salt loading with 115 mmol/day, by no means excludes the diagnosis of primary aldosteronism. Also, it was recently shown by Weinberger et al (1979), that during a diet with a normal salt content the values of aldosterone excretion in 31% of their patients with primary aldosteronism were "normal". Measuring the secretion rate of aldosterone before and after salt loading proved to have no value for the differentiation between adenomatous and idiopathic aldosteronism. Also in the literature we did not find any indications that measuring aldosterone before and after giving salt and/or mineralocorticoids would contribute to a differentiation between the two affections. This conclusion holds equally true for measurings of the rate of excretion of the aldosterone-18-glucuronide, although these were measured in our study only during a moderate dietary salt intake But such a difference can be brought out with the aid of measurement of aldosterone in blood, as will be shown in chapter V.

The measurements of the excretion of the aldosterone-18-glucuronide in relation to the body posture showed that the excretion values, both basally and during dexamethasone, in practically all patients in the groups II (IHA) and III ("after removal of an adenoma") were higher during ambulation than during recumbency, while no influence of the body posture was found in group I (APA). The influence of the body posture on the aldosterone values in plasma was in agreement with the influence on the aldosterone values in urine: a rise of aldosterone

during "ambulation" in the groups II and III and no appreciable influence in group I (figure IV-5).
A similar but less consistent influence of the body posture, was found for the plasma renin values which during "ambulation" were in general higher in the groups II and III, but not in group I (figure IV-6). In still another respect the findings in patients "after removal of an adenoma" are comparable with that which is found in patients with IHA: relatively low aldosterone values during the night with a marked rise of the values during the following day during "ambulation" (figure IV-3). In patients with APA, on the contrary, remarkably higher nocturnal values were found and a decrease of aldosterone during the following day when performing "ambulation". Finally, the findings in group III were comparable with those in group II as regards the slight influence of ACTH on the aldosterone values during the day and the night. The influence of ACTH as derived from the correlation coefficients between aldosterone and cortisol and between aldosterone and 18-OH-DOC was, on the contrary, more clearly recognizable in patients with APA (table IV-5)
The conclusions run as follows: the regulation of aldosterone before and after removal of an aldosterone-producing adenoma, is essentially different. We have shown that before operation the influence of ACTH on the day and night regulation of aldosterone is clearly recognizable (albeit with interindividual variations), whereas after operation the renin angiotensin system displays a far clearer relation to the plasma aldosterone values In the second place we found that the influence of the various manoevres on the plasma aldosterone concentrations in patients with idiopathic aldosteronism was comparable qualitatively with that which was found in patients in whom an aldosterone-producing adenoma had been removed The regulation of aldosterone in the groups II and III is in essence not otherwise than what was found in the literature with regard to normal test persons (Vagnucci et al 1974, Armbruster et al 1975, Katz et al. 1975, Lightman et al. 1981)

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CHAPTER V

NOCTURNAL, DAYTIME, AND POSTURAL CHANGES OF PLASMA ALDOSTERONE BEFORE AND DURING DEXAMETHASONE IN ADENOMATOUS AND IDIOPATHIC ALDOSTERONISM

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V.1. Abstract

The relative importance of ACTH and the renin angiotensin system for control of aldosterone was studied in eight patients with adenomatous primary (APA) and four with idiopathic aldosteronism (IHA). Plasma aldosterone (PA) and cortisol (PC) were measured in blood collected during the night at 15-min intervals between 05.00-08.00 hr by integrated sampling on day 1 and in casual samples during the daytime while patients were in the upright and in the supine position (days 1 and 2, at 12.00, 16.00 and 20.00 hr).
PRA was measured in all daytime samples. On days 3, 4 and 5, 2 mg dexamethasone were given, and the same protocol for blood sampling was repeated on days 4 and 5.
During the night, mean PA in IHA patients was markedly lower than that in APA patients. PA significantly correlated with PC in both groups. Dexamethasone reduced the mean nocturnal PA in both groups to equal proportions.
In the daytime, the mean recumbent PA in IHA patients was also significantly lower than that in APA patients but was equal in both groups while subjects were in the upright posture. Daytime PA significantly correlated with PC in APA patients and with PRA in IHA patients. During upright posture, dexamethasone did not reduce daytime PA in either group. In the supine position, dexamethasone reduced daytime PA values in APA but not in IHA patients.
Thus, short time fluctuations of PA during the night are equally influenced by ACTH in APA and IHA patients, though at markedly different levels of aldosterone production. During the daytime, the influence of ACTH on PA remains apparent in the group with APA. However, the renin-angiotensin system seems to play a predominant role in the control of PA during the daytime in patients with IHA. During dexamethasone and ACTH suppression, PA in APA patients rises in response to upright posture as it does in IHA patients.

V.2. Introduction

ACTH plays a significant role in the control of plasma aldosterone (PA) in patients with aldosterone-producing adenomas (APA). The quantitative correlation between circadian hormone levels of PA and plasma cortisol (PC) (Cain et al. 1972, Ganguly et al. 1973, Kem et al. 1973, Schambelan et al. 1976, Biglieri et al. 1974); the synchronicity of episodic secretions of PA and PC, as assessed by frequent blood sampling techniques (Vetter et al. 1974, Katz et al. 1975, Kem et al. 1976, Vetter et al. 1978); and the exaggerated response of PA to the

infusion of physiological amounts of synthetic ACTH (Kem et al 1978) support this thesis In patients with idiopathic hyperaldosteronism (IHA), there is some evidence that PA is under the control of both ACTH (Ganguly et al. 1973, Schambelan et al. 1976, Kem et al 1976, Vetter et al 1978) and the renin-angiotensin system (Ganguly et al. 1973, Schambelan et al. 1976, Vetter et al 1978).
Conflicting results have been reported with respect to the effectiveness of dexamethasone treatment in reducing PA in patients with primary aldosteronism (Newton and Laragh 1968, Slaton et al 1969, Vetter and Vetter 1975) A variable ACTH dependency of aldosterone production might explain these discrepancies (Wenting et al 1978) In addition, however, differences in doses and duration of dexamethasone treatment may account for some of the reported differences Ganguly et al. (1977) found a transient fall and a subsequent return of PA within 3 days of dexamethasone treatment
This study was designed to further evaluate the role of ACTH and the renin-angiotensin system in the control of aldosterone production in patients with primary aldosteronism Special attention has been paid to the effectiveness of dexamethasone treatment in reducing PA in patients with APA and IHA and to postural changes of PA in these disorders

V 3 Materials and methods

V 3 1 *Patients*

Eight patients with APA and 4 with IHA were studied In all patients, the diagnosis of primary aldosteronism was based on the concurrence of hypertension, mild or frank hypokalemia, suppressed PRA during upright posture after 5 days of sodium restriction (Drayer et al 1975), and a high secretory rate of aldosterone which failed to suppress to normal values after a daily sodium intake of 315 mmol during 5 days (Kloppenborg et al 1972) The clinical and biochemical characteristics are presented in table V-1 The diagnosis of APA was based on biochemical data and an adrenal scintigram using ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol (Sarkar et al 1977). Scintigrams were performed after treatment with dexamethasone (2 mg/day) during the 2 weeks before the administration of the isotope In seven of eight patients with APA, the adrenal scintigram correctly identified an adrenal adenoma, which was confirmed by operation In one patient with histologically proven APA, the adrenal scintigram failed to show an accumulation of radioactivity in either adrenal In the four patients with IHA, the diagnosis was based on biochemical data, which showed the characte-

Table V-1.

Clinical and biochemical data in 12 patients with primary aldosteronism

patient no	age	sex	blood pressure (mmHg)	potassium (mEq/l)	PRA* (ng/10 ml/3hr)	ASR** (µg/24hr)
ADENOMA						
1.	45	F	180/140	2.9	20	266
2.	45	F	155/100	3.2	29	793
3.	57	F	180/100	1.9	63	1079
4.	33	F	165/110	3.0	38	459
5.	36	M	194/120	2.9	44	666
6.	54	F	240/140	2.0	66	253
7.	38	F	200/120	2.9	26	387
8.	57	F	204/126	3.0	53	215
HYPERPLASIA						
9.	53	M	198/120	2.5	34	432
10.	40	F	160/108	3.9	112	199
11.	55	F	186/106	3.4	147	163
12.	64	M	238/146	2.8	69	108

* measured after 5 days sodium restriction (N: 115-595)
** measured after 5 days sodium loading (N: 55±17)

ristics of a relatively mild hyperaldosteronism. The presence of an adrenal adenoma was excluded by the absence of an asymmetrical adrenal uptake of the isotope on the scintigrams performed after 2 weeks of treatment with dexamethasone. In patient 12, who died after a cerebrovascular accident complicated by a myocardial infarction, the diagnosis of IHA was histologically confirmed by postmortem examination.

V.3.2. *Protocol*

Antihypertensive treatment was discontinued for at least 2 weeks before the start of the study. Studies were carried out in a metabolic ward after an equilibration period of 3 days. The patients used a salt-restricted diet containing 10 meq sodium and 50-70 meq potassium per day. Sodium chloride (6 g/day) was added to the diet in weighed capsules. None of the patients used supplementary potassium. The

study period lasted for 5 days. At 23.00 hr on the day before the first day of the study, a nonthrombogenic catheter was inserted into an antecubital vein, through which a 5% glucose infusion was started. At 04.45 hr on the first day of the study, the catheter was connected to a withdrawal pump and a fraction collector. Twelve integrated blood samples of 11 cc/15 min were automatically collected from 04.45 hr – 07.45 hr. Special attention was paid so as not to disturb the patients' sleep. Blood samples were centrifuged immediately after completion of a 15-min collection period and were kept frozen at −20°C until determination of PA and PC. Subsequently, casual blood samples were drawn on day 1 at 12.00, 16.00 and 20.00 hr while patients were ambulatory from 08.00 to 22.00 hr, and on day 2 at 12.00, 16.00 and 20.00 hr, on which day the patients remained supine for 24 hr. Dexamethasone (0.5 mg four times a day) was administered on days 3, 4 and 5. The protocol for blood sampling, as described above, was repeated on days 4 and 5, starting with the integrated nocturnal blood sampling on day 4 at 04.45 hr.

PA was measured by RIA using a chromatographical purification step and antiserum generated in sheep against aldosterone-21-monohemisuccinate-bovine serum albumin (Man de et al. 1980). In eight normal individuals, mean PA values during the night, as assessed by integrated blood sampling, ranged from 1.0-13.4 ng/100 ml. PC was measured by RIA, according to the method described by Vecsei (1974). PRA was measured by RIA, as described earlier (Drayer et al. 1975).

Results are presented as the mean ± SEM. Student's t tests for paired and nonpaired data were employed for comparison of data within or between groups of patients. Calculation of the correlation coefficient according to Pearson was used for regression analysis. For calculation of the correlation coefficients between hormones, normalized values were used to eliminate the disparity of ranges in hormone concentrations among the individual patients.

V.4. Results

V.4.1. *Effects of dexamethasone on nocturnal PA in APA and IHA patients (figure V-1)*

The mean of the 12 PA values obtained in each patient by integrated blood sampling during the night ranged from 19.6 ± 1.0 to 65.0 ± 1.6 ng/100 ml in APA patients and from 7.6 ± 0.5 to 13.5 ± 1.5 ng/100 ml in IHA patients. The mean nocturnal PA level of all patients with APA was significantly higher than that of all patients with IHA. During dexamethasone treatment, the mean of the 12 nocturnal PA

values in patients with APA ranged from 7 9 ± 0 5 to 30 5 ± 2 5 ng/100 ml, and in patients with IHA, it ranged from 1 4 ± 0 1 to 10 4 ± 1 2 ng/100 ml Dexamethasone induced a fall in nocturnal PA values in 7 of 8 patients with APA and in 3 of 4 patients with IHA The mean nocturnal PA levels were significantly lower during dexamethasone than before treatment, both in patients with APA as well as in those with IHA Mean nocturnal PA values after dexamethasone treatment were still significantly higher in APA than in IHA patients

V 4 2 *Effects of dexamethasone on daytime PA in APA and IHA patients (figure V-1)*

No differences in PA values were found during upright posture (day 1) between patients with APA and IHA However, during the supine posture, PA values were significantly higher in patients with APA than in those with IHA Treatment with dexamethasone did not significantly reduce the uprigth daytime PA values in patients with APA or IHA However, during the supine posture, dexamethasone treatment reduced the daytime PA values in patients with APA but not in those with IHA

V 4 3 *Effect of upright posture on PA before and during dexamethasone in APA and IHA patients (figure V-1)*

No significant difference was found between upright and supine daytime PA values before (27 4 ± 4 1 vs 25 7 ± 3 3 ng/100 ml, p=n s) and during dexamethasone treatment (22 5 ± 3 0 vs 17 4 ± 2 6 ng/100 ml, p=ns) in patients with APA However, in patients with IHA, upright and supine daytime PA values differed significantly both before (23 2 ± 3 9 vs 13 3 ± 1 3 ng/100 ml, $p<0.01$) and during dexamethasone treatment (24 9 ± 5 7 vs 13 2 ± 1 9 ng/100 ml, $p<0.02$)
In patients with APA, 12 00 hr upright PA values, after 4 hr of ambulation, were not significantly different from mean nocturnal PA values (36 7 ± 7 4 vs 43 4 ± 1 7 ng/100 ml, p=n s) However, after dexamethasone treatment PA rose significantly after 4 hr of ambulation, from 18 5 ± 1 0 to 30 6 ± 5 8 ng/100 ml ($p<0.05$) In all four patients with IHA, 12 00 hr upright PA values were markedly higher than the mean nocturnal PA values before (27 9 ± 7 9 vs 10 9 ± 0 6 ng/100 ml) and during dexamethasone treatment (31 1 ± 11 0 vs 5 9 ± 0 6 ng/100 ml)

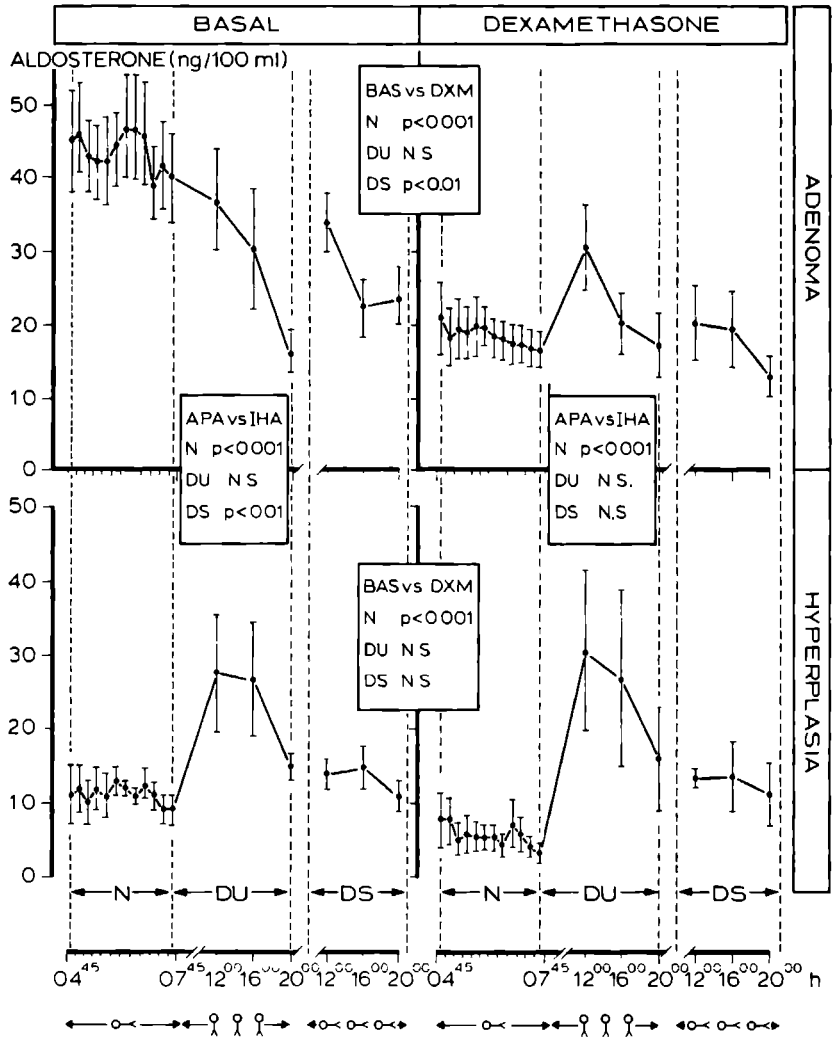

Figure V-1. Comparisons of PA values during the night (N), in the daytime during upright posture (DU), and in the daytime during supine position (DS) in eight patients with APA and four patients with IHA before and during dexamethasone treatment

V.4.4. *PRA in APA and IHA patients*

Ambulatory PRA values obtained by casual blood sampling at 12.00 hr, 16.00 hr and 20.00 hr did not differ significantly from supine PRA

values in APA patients (33 ± 5 vs 35 ± 5 ng/10 ml/3 hr; p=n.s.). However, in patients with IHA, ambulatory PRA values were significantly higher than supine values (64 ± 10 vs 45 ± 7 ng/10 ml·3 hr; $p<0.01$).
Dexamethasone treatment did not result in a significant change in ambulatory or supine PRA values in patients with APA (38 ± 5 vs 39 ± 6 ng/10 ml/3 hr; p=n.s.) or IHA (76 ± 15 vs 50 ± 9 ng/10 ml/3 hr; p=n.s.)
A significant correlation between the normalized daytime values of PA and PRA (days 1 and 2) was found both in patients with APA ($r=0.31$; $n=48$; $p<0.05$) and in patients with IHA ($r=0.43$; $n=24$; $p<0.05$). However, during treatment with dexamethasone, the normalized values of daytime PA and PRA (days 4 and 5) no longer showed a significant correlation in patients with APA ($r=0.01$; $n=48$; p=n.s.), whereas in patients with IHA, the correlation between PA and PRA reached a higher level of statistical significance than under basal circumstances ($r=0.78$; $n=24$; $p<0.001$).

V.4.5. *PC in APA and IHA patients*

PC levels during the night, obtained by integrated blood sampling, were similar in patients with APA and IHA (12.7 ± 0.5 vs 11.3 ± 0.5 μg/100 ml; p=n.s.). In addition, plasma daytime cortisol values (days 1 and 2) did not differ significantly in the two groups (7.3 ± 0.5 vs 7.8 ± 0.8 μg/100 ml; p=n.s.).
During the night, the normalized values of PC and PA were significantly correlated both in patients with APA ($r=0.35$; $n=93$; $p<0.001$) and in those with IHA ($r=0.52$; $n=45$; $p<0.001$). However, in the individual patients, the correlation of normalized PA and PC values showed a wide variation, ranging from $r=0.12$ ($n=12$) to $r=0.77$ ($n=11$) in APA patients and from $r=-0.22$ ($n=11$) to $r=0.78$ ($n=12$) in IHA patients. In fact, four of eight patients with APA and one of four patients with IHA showed no significant correlation between the two nocturnal hormone levels.
During the daytime (days 1 and 2), the normalized PA and PC values were significantly correlated in patients with APA ($r=0.32$; $n=48$; $p<0.05$), but not in patients with IHA ($r=0.31$; $n=24$; p=n.s.).
In all patients studied, dexamethasone treatment resulted in PC levels lower than 3.6 μg/100 ml, indicating normal suppressibility of this hormone.

In this study it was found that PA levels during the late hours of the night, as assessed by integrated blood sampling, were markedly lower in the group of patients with IHA than in those with APA.
ACTH activity during the late hours of the night, as derived from the levels of PC, did not differ significantly between the two groups of patients and, therefore, cannot account for the observed differences in the levels of nocturnal PA. On the other hand, the short time fluctuations of PA during the late hours of the night seemed to be influenced by ACTH equally in both groups of patients, as is apparent from the significant correlations between the normalized values of PA and PC. In addition, in both groups of patients, the mean nocturnal PA levels showed a similar percent decrease after treatment with dexamethasone, whereas PC decreased adequately in all patients to values found in subjects with normal ACTH suppressibility. Therefore, we conclude that PA production during the night is under the control of ACTH in both groups of patients, and that the ACTH control occurs at different levels of adrenal aldosterone production. These data are in accordance with the data of Kem et al. (1978), who found that patients with APA and IHA are uniformly hyperresponsive to the administration of physiological doses of ACTH. It has to be emphasized that in our study, nocturnal PA and PC did not correlate significantly in four of eight patients with APA and in one of four patients with IHA. Therefore, within the groups of patients with primary aldosteronism, the individual degree of ACTH-dependent aldosterone production may show a rather wide variation, as was reported earlier by Wenting et al. (1978).
The nocturnal PA level measured in patients with APA was invariably higher than that in patients with IHA in our study. In the study of Kem et al. (1976) nocturnal PA levels in two of three patients with IHA were in the same range as those found in four patients with APA, and only one patient with IHA showed markedly lower PA values averaging 10 ng/100 ml. In the study of Vetter et al. (1978) three of eight patients with IHA had low nocturnal PA values, not exceeding 20 ng/100 ml during the period of study. In three of the five patients with IHA reported by Schambelan et al. (1976), PA values at 04.00 hr were consistently lower than the 04.00 hr values found in six patients with APA. Therefore, it seems reasonable to conclude that patients with IHA are not a homogenous group with respect to the levels of nocturnal PA. A subgroup of patients with IHA is apparent in which nocturnal PA values are markedly lower than those in patients with APA.
In contrast to the marked differences in PA levels during the night, the

daytime PA values during ambulation were similar in both groups During supine posture (day 2), PA values in APA patients were slightly higher than those in IHA patients It is well known that patients with IHA, compared to patients with APA, usually demonstrate a relatively mild form of hyperaldosteronism (Ferriss et al 1978) Yet, the two groups cannot be separated on the basis of their 24 hr aldosterone secretion rates because of a considerable overlap, as was also found in this study The finding of low nocturnal PA values may be helpful, at least in some patients, to differentiate between patients with APA and IHA

In accordance with earlier studies (Cain et al 1972, Ganguly et al 1973, Kem et al 1973, Schambelan et al 1976, Biglieri et al 1974), the daytime PA values (days 1 and 2) in patients with APA were, regardless of the stimulus of upright posture, primarily under the control of ACTH, demonstrating a diurnal pattern significantly correlated to the diurnal pattern of PC Although PRA in these patients was markedly suppressed, a significant correlation was also calculated between the normalized PA and PRA daytime values (days 1 and 2) However, it is unlikely that PRA contributed to the fall of PA, since PA was not significantly correlated to PRA during dexamethasone treatment (days 4 and 5) In contrast, the daytime PA values in patients with IHA were primarily under the control of the renin-angiotensin system, PA values rose significantly in response to upright posture, PA and PC were not significantly correlated, and, finally, the positive and significant correlation between PA and PRA values before dexamethasone treatment (days 1 and 2) reached an even higher level of siginificance during dexamethasone treatment (days 4 and 5)

In patients with IHA, treatment with dexamethasone did not reduce the daytime PA values during ambulation or while in the supine position The rise of PA in response to upright posture remained unaltered during dexamethasone treatment In patients with APA, upright and supine basal PA values did not differ significantly However, during dexamethasone treatment, supine PA values were significantly reduced, while upright PA values remained essentially unchanged In addition, a significant rise of PA during dexamethasone treatment was observed after 4 hr of ambulation on the morning of day 4, contrary to the well known absence of such a postural rise before dexamethasone administration In previous reports, the postural changes in PA during dexamethasone in patients with primary aldosteronism have not been studied in detail According to Ganguly et al (1977), the postural decrease of PA after ambulation in the morning remained unchanged on the first 2 days of dexamethasone treatment in six patients with APA In the study of Schambelan et al (1976), two patients with APA did not show a postural rise, while one patient with

APA had marked postural increase of PA during dexamethasone treatment. This rise of PA in response to upright posture apparently was not mediated by the renin-angiotensin system, since PRA values throughout the day were low and unresponsive to change of posture, both before and during dexamethasone treatment. Although the metabolic clearance rate (MCR) of aldosterone was not measured, we believe that a decrease of MCR, as has been described during dexamethasone treatment (Zager et al. 1976), might be responsible for the observed postural increase of PA in patients with APA.

In recent years, numerous investigators have tried to unravel the complex interplay of factors known to regulate aldosterone in normal man and patients with aldosteronism. The present study indicates that attention to circadian factors and posture as well as to subtle differences in sensitivity of the zona glomerulosa to ACTH and angiotensin might lead to a more complete knowledge of aldosterone physiology and pathophysiology, such as in classical APA and IHA.

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CHAPTER VI

ADRENAL SCINTIGRAPHY IN PRIMARY ALDOSTERONISM
Improved visualization after long-term pre-treatment with dexamethasone

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Dexamethasone-modified adrenal scintigrams were performed on 13 patients with an aldosterone-producing adenoma and on one patient with an aldosterone-producing carcinoma Adrenal scintigrams using ^{131}I-19-Iodocholesterol were obtained after short pre-treatment with dexamethasone, while ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol scintigrams were performed after long-term pre-treatment with dexamethasone during 9-21 days Using the former procedure the adrenal scintigrams correctly identified the adenoma in 3 of 8 patients, while with the latter procedure the adrenal scintigrams localized the adenomas in 8 out of 9 patients, including 3 patients in whom the former procedure had failed The adrenal carcinoma was not visualized with ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol Thus, the sensitivity of ^{131}I-19-Iodocholesterol scintigrams to detect aldosterone-producing adenomas was only 37 5% Uptake of radioactivity in the normal contralateral adrenal gland accounted for the low detection rate On the other hand, the ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol scintigrams, performed after long-term pre-treatment with dexamethasone, had a sensitivity of 89% It is suggested that long-term pre-treatment with dexamethasone contributed to the improved sensitivity by a more effective suppression of radioactivity uptake in the normal adrenal gland

Nebennierenszintigraphie bei primaren Aldosteronismus

Nebennierenszintigraphien wurden bei 13 Patienten mit primarem Aldosteronismus und chirurgisch nachgewiesenen Adenomen und bei einer Patientin mit einem Aldosteronproduzierenden Karzinom durchgefuhrt Bei Verwendung von ^{131}I-19-Iodocholesterol nach kurzfristiger Vorbehandlung mit Dexamethason wurden nur bei 3 der 8 Patienten die Adenome korrekt diagnostiziert Bei Verwendung des neueren Praparats 6β-^{131}I-Iodomethyl-19-Nor-Cholesterol und langfristiger (9 bis 21 Tage) Vorbehandlung mit Dexamethason wurden 8 von 9 Adenomen richtig lokalisiert, darunter 3, die mit der alteren Technik nicht gefunden wurden Bei der Patientin mit einem primaren Aldosteronismus infolge eines Karzinoms, konnte der Nebennierenrindentumor nicht abgebildet werden Kurzfristige Vorbehandlung mit Dexamethason und die Applikation von ^{131}I-19-Iodocholesterol genugen nicht fur die Lokalisation von Aldosteronproduzierenden Adenomen Mit dem neueren 6β-Derivat des Cholesterols konnen nach einer ein- bis dreiwochigen Vorbehandlung mit Dexamethason die Adenome in einem hohen Prozentsatz der Falle richtig lokalisiert werden, da die langzeitige Vorbehandlung mit Dexamethason anscheinend die Radio-

activitatsaufnahme durch die normale Nebenniere stärker unterdrückt.

VI.2. Introduction

Since the introduction of ^{131}I-19-Iodocholesterol in 1971 as a radiopharmaceutical suitable for imaging the human adrenal glands (Beierwaltes et al. 1971), its usefulness in the diagnosis of a variety of functional and structural disorders of the adrenals has now been well established in the literature (Barliev 1979, Chatal et al. 1976, Forman et al. 1974, Hoefnagels et al. 1976, Hogan et al. 1976, Lieberman et al. 1971, Moses et al. 1974, Seabold et al. 1976). The development of the radiopharmaceutical ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol in 1975 (Basmadjian et al. 1975, Kojima et al. 1975) has further contributed to the improvement of the quality of adrenal visualization. The higher adrenal uptake of this radiopharmaceutical and the more favourable target-to-background ratio account for more optimal adrenal imaging. In primary aldosteronism, adrenal imaging is a reliable method to localize aldosterone-producing adenomas (Conn et al. 1971, Conn et al. 1972, Freitas et al. 1979, Hogan et al. 1976). In addition, pretreatment with dexamethasone not only enhances the asymmetrical adrenal uptake by suppression of the normal adrenal gland, but also facilitates the differential diagnosis between adenomatous hyperaldosteronism and idiopathic aldosteronism due to bilateral (micro- and macronodular) hyperplasia (Conn et al. 1976, Sarkar et al. 1977, Seabold et al. 1976). In the period from 1972 to 1979, radiocholesterol scintigrams were performed in our Institute, on 13 patients with aldosterone-producing adenomas and on one patient with an aldosterone-producing carcinoma. Preliminary results in four patients were reported earlier (Hoefnagels et al. 1976). The present study reports on additional experiences with ^{131}I-19-Iodocholesterol in primary aldosteronism and presents the results of adrenal imaging with the newer radiopharmaceutical ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol in patients with adenomatous hyperaldosteronism. Special attention was paid to the value of long-term pre-treatment with dexamethasone for the better recognition of aldosterone-producing adenomas.

VI.3. Patients

Table VI-1 presents the clinical and biochemical characteristics of the patients included in this study. All patients had hypertension, hypokalemia, suppressed plasma renin activity after 5 days of salt restriction and an elevated aldosterone secretory rate after 5 days sodium loading.

Table VI-1.

Clinical and biochemical data in 14 patients with primary aldosteronism

patient no	sex	age	blood pressure (mmHg)	plasma K^+ (mmol/l)	PRA** (ng/10 ml/3hr)	ASR*** (μg/24hr)
1.	F	35	185/120	2.7	21	555
2.a	F	17	195/125	2.0	44	455
b*			195/120	2.8	25	315
3.	F	55	165/105	1.9	25	1721
4.	F	49	210/125	2.7	53	981
5.	F	46	200/120	2.9	20	266
6.	F	46	175/110	3.2	29	793
7.	F	58	185/105	1.9	63	1079
8.	M	37	200/125	2.9	53	666
9.	F	33	175/115	3.0	38	459
10.	F	55	240/140	2.0	66	253
11.	F	48	185/120	3.2	26	387
12.	F	58	210/125	3.0	44	215
13.	F	45	205/117	3.0	43	244
14.	F	49	155/100	1.9	6	683

* After removal of the right adrenal gland

** Plasma renin activity on the 5th day of a 15 mmol sodium diet (Normal values: 115-595)

*** Aldosterone secretion rate on the 5th day of a 315 mmol sodium diet (Normal values: 55±17)

In patients 1-13 the diagnosis aldosterone-producing adenoma was confirmed by histologic examination of the surgically removed adrenal gland and by the decrease of urinary aldosterone excretion to subnormal values immediately after operation. Patient 14 had a recurrence of the syndrome of primary aldosteronism, 12 years after removal of a benign aldosterone-producing adenoma of the right adrenal gland. At operation a carcinoma, subcapsularly located at the upper pole of the right kidney, was removed. Postoperatively aldosterone excretion and blood pressure normalized. In patient 2, the initially removed right adrenal gland was found normal at histologic examination. Post-operatively blood pressure and aldosterone secretion remained elevated. One year later, after removal of a classical adenoma from the left adrenal gland, blood pressure and aldosterone excretion returned to normal.

Patients did not receive the aldosterone antagonist spironolactone during the study because of the known interference of this drug with

the biosynthesis of aldosterone (Hoefnagels et al. 1980). Spironolactone was withdrawn at least 4 weeks before the administration of the radiopharmaceutical. If necessary, spironolactone medication was replaced by amiloride 20 mg/day combined with chlorthalidone 100 mg/day.

VI.4. Materials and methods

The radiopharmaceutical ^{131}I-19-Iodocholesterol* and ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol** were obtained commercially. Each new batch was controlled for radiochemical purity by paper chromatography. ^{131}I-19-Iodocholesterol was administered intravenously in a dose of 1-2 mCi and ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol in doses varying from 0.6-2.0 mCi. Thyroid uptake was blocked by either Lugol's iodide 3 drops a day, starting 3 days before administration of the tracer or by potassium perchlorate 200 mg q.i.d., starting the day before radiocholesterol was administered. Thyroid blocking was continued till completion of the study. Adrenal scintigrams were obtained by a Picker II^{c} gamma camera, with an on line PDP-8 computer for data processing. Scintiphotos were made daily between the 2nd and the 9th day after injection of the tracer. With both radiopharmaceuticals, optimal imaging was obtained from the 5th to the 9th day p.i. All scintigraphic investigations were performed during dexamethasone suppression. Dexamethasone was given in a dose of 2-4 mg/day, starting 1 to 8 days before administration of the tracer and continued during the examination period. However, when ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol was used, dexamethasone 2 mg/day was given 9-21 days before the tracer injection. Because of the higher adrenal uptake of this radiopharmaceutical compared to ^{131}I-19-Iodocholesterol, we deliberately opted for a longer dexamethasone suppression to prevent adrenal uptake in the normal adrenal glands.

VI.5. Results

Patients 1-4 were examined using ^{131}I-19-Iodocholesterol, whereas patients 9-13 received the newer agent ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol. In patients 5-8 both radiopharmaceuticals were used with an interval of at least one year. The results are presented in tables VI-2 and VI-3 and in figures VI-1 and VI-2 In patients 1, 3 and 4, the

* (Sorin, Saluggia, Italy)
** (Byk Malinckrodt, Dietzenbach-Steinburg, Germany)

Table VI-2.

Results of adrenal scintigraphy with ^{131}I-19-Iodocholesterol in 8 patients with primary aldosteronism, performed after a short pretreatment with dexamethasone

patient no	dexamethasone		thyroid blockade	^{131}I-19-Iodocholesterol	scintigram*		pathology
	dose	days of therapy before tracer injection		dose (i.v.)	left	right	
1.	4 mg	3 days	lugol 3 dd 1 gtt	2.1 mCi	–	++	adenoma 2 cm R
2.a	4 mg	2 days	lugol 3 dd 1 gtt	1.9 mCi	–	++	normal adrenal R
b**	4 mg	2 days	$KClO_4$ 4 dd 200 mg	2.0 mCi	–		adenoma 1.5 cm L
3.	4 mg	8 days	lugol 3 dd 1 gtt	2.0 mCi	++	±	adenoma 2 cm L
4 a	4 mg	2 days	lugol 3 dd 1 gtt	2.0 mCi	++	+	
b	4 mg	3 days	lugol 3 dd 1 gtt	1.5 mCi	++	–	adenoma 1 cm L
5.	4 mg	1 day	lugol 3 dd 1 gtt	1.0 mCi	++	++	see table VI-3
6.	2 mg	1 day	$KClO_4$ 4 dd 200 mg	2.0 mCi	+	++	see table VI-3
7.	2 mg	6 days	$KClO_4$ 4 dd 200 mg	2.0 mCi	++	++	see table VI-3
8.	4 mg	3 days	$KClO_4$ 4 dd 200 mg	2.0 mCi	–	–	see table VI-3

* – = no visualization + = discernible visualization ++ = unequivocal visualization
** scintigraphy performed after right adrenalectomy

Table VI-3.

Results of adrenal scintigraphy with ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol, performed after long-term pretreatment with dexamethasone in 10 patients with primary aldosteronism

patient no	dexamethasone		thyroid blockade	^{131}I-6β-Iodomethyl-19-Nor-Cholesterol	scintigram*		pathology
	dose	days of therapy before tracer injection		dose	left	right	
5	2 mg	14 days	$KClO_4$ 4 dd 200 mg	1.9 mCi	++	±	adenoma 1.5 cm L
6.	2 mg	9 days	$KClO_4$ 4 dd 200 mg	1.7 mCi	–	++	adenoma 1.3 cm R
7.	2 mg	13 days	$KClO_4$ 4 dd 200 mg	1.8 mCi	++	±	adenoma 2.0 cm L
8.	2 mg	15 days	$KClO_4$ 4 dd 200 mg	1.6 mCi	–	–	adenoma 1.5 cm L
9.	2 mg	21 days	$KClO_4$ 4 dd 200 mg	1.7 mCi	++	–	adenoma 1.4 cm L
10	2 mg	14 days	$KClO_4$ 4 dd 200 mg	0.6 mCi	–	++	adenoma 1.0 cm R
11.	2 mg	21 days	$KClO_4$ 4 dd 200 mg	1.9 mCi	++	–	adenoma 1.8 cm L
12	2 mg	14 days	$KClO_4$ 4 dd 200 mg	2.0 mCi	–	++	adenoma 2.5 cm R
13	2 mg	14 days	$KClO_4$ 4 dd 200 mg	2.1 mCi	–	++	adenoma 1.9 cm R
14	2 mg	21 days	$KClO_4$ 4 dd 200 mg	1.9 mCi	±	±	carcinoma 3 cm R

* For legends see table VI-2

^{131}I-19-Iodocholesterol scans correctly identified the adrenal adenoma. In patient 2, the right adrenal gland was surgically removed because of an increase of radioactivity in the right adrenal gland, with complete suppression of the left adrenal gland. The radioactivity uptake of the

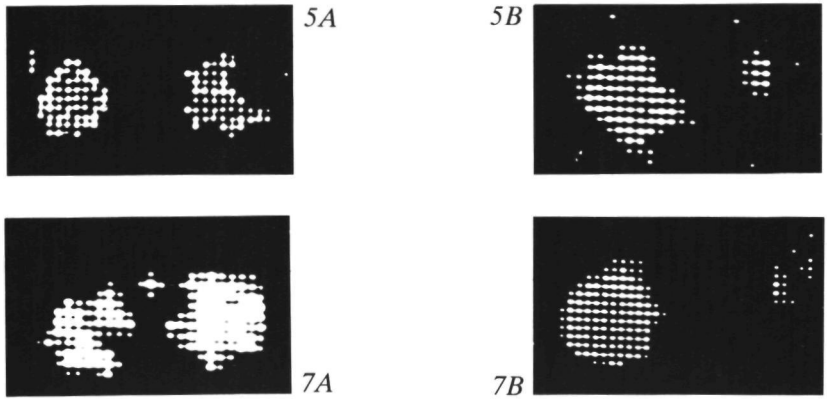

Figure VI-1. Adrenal scintigrams in patients 5 and 7, performed with ^{131}I-19-Iodocholesterol after short pretreatment with dexamethasone show an equal uptake of activity in both adrenal glands (5A and 7A). The scintigrams of the same patients using ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol and long-term pretreatment with dexamethasone show a marked asymmetrical uptake with a clear visualization of the adenoma-harboring gland and an almost complete suppression of the normal gland (5B and 7B)

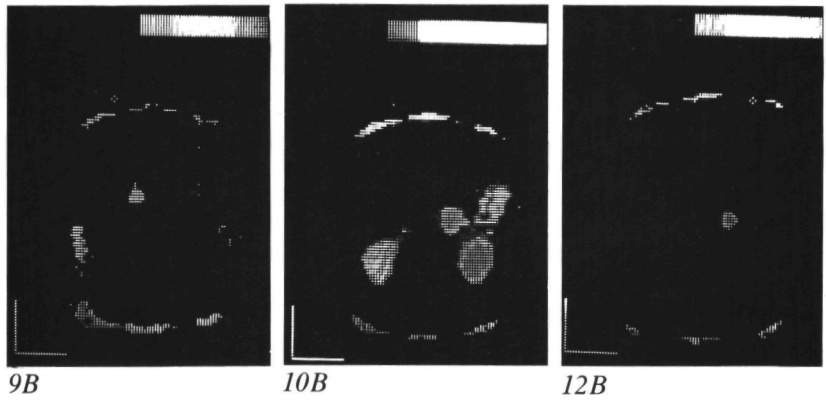

Figure VI-2. Adrenal scintigrams in patients 9, 10 and 12 performed with ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol after long-term pretreatment with dexamethasone (9B, 10B, 12B). In patient 10 the adrenal scintiscan is superimposed on a renal scintigram performed with ^{99m}Tc-ironascorbate. Accumulation of activity, corresponding to the site of the tumor, is found in the left (9B), the right (10B) and the right (12B) adrenal gland. The normal contralateral glands are completely suppressed

removed gland measured on the 16th day after administration of the radiopharmaceutical, was about 1 μCi, after correction for decay. Histologic examination of the adrenal tissue did not reveal an adrenocortical adenoma, nor adrenocortical hyperplasia. After operation, signs and symptoms of hyperaldosteronism persisted (table VI-1). After one year the adrenal suppression scan with ^{131}I-19-Iodocholesterol was repeated and did not show any uptake of radioactivity in the remaining left adrenal gland. However, at operation, a 1.5 cm adenoma was removed, with subsequent post-operative normalization of blood pressure and aldosterone excretion. In patient 4, the scintigrams showed asymmetrical uptake during the first investigation. Because the result was considered inconclusive, adrenal scintigraphy with ^{131}I-19-Iodocholesterol was repeated after one year. At this time the adrenal scintiscans identified unequivocally an adenoma of 1 cm in the left adrenal gland while the right adrenal gland was completely suppressed. In patients 5, 6 and 7 the ^{131}I-19-Iodocholesterol scans showed a bilateral adrenal uptake without definite asymmetrical distribution of the tracer. These patients were suspected to have a bilateral adrenal hyperplasia. For this reason surgical exploration was not performed. However, adrenal scintiscans in these patients were repeated after the radiopharmaceutical ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol became available. The scintigrams with the newer radiocholesterol showed a clear lateralization of the radioactivity and the presence of an adrenal adenoma at the suspected side was confirmed by operation. In patient 8, no accumulation of radioactivity over the adrenal regions was found both after ^{131}I-19-Iodocholesterol scintigraphy and after ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol scintigraphy.
In the patients 9-12, the ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol scans showed accumulation of radioactivity at the site of the adenoma with almost complete suppression of the normal gland. In patient 14, the adrenal scintigrams showed poor concentration of the radioactivity over both adrenal regions. At operation, a 3 cm adrenocortical carcinoma, located subcapsularly at the upper pole of the right kidney, was removed.

VI.6. Discussion

Adrenal scintigraphy with ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol during long-term dexamethasone suppression correctly identified an aldosterone-producing adenoma in 8 out of 9 patients (89%). In contrast ^{131}I-19-Iodocholesterol scintigraphy during short-term dexamethasone suppression, demonstrated the adenoma correctly in only 3 out of 8 patients (37.5%). We suggest that the short-term dexametha-

sone suppression and not the radiopharmaceutical ^{131}I-19-Iodocholesterol itself accounts for the rather poor results with this scanning agent. In patients 5, 6 and 7, ^{131}I-19-Iodocholesterol scintiscans during short-term dexamethasone treatment, showed a bilateral, almost symmetrical uptake. Based on these findings these patients were suspected to have a bilateral adrenal hyperplasia. Spurious interpretation of these adrenal scans was merely caused by substantial uptake of radioactivity in the normal adrenal gland, which was thought to be suppressed by dexamethasone treatment. Indeed, in patient 2 the right adrenal gland, visualized on a dexamethasone suppression scan with ^{131}I-19-Iodocholesterol, contained 1 μCi radioactivity (= 0.05% of the administered dose), although no adrenal pathology was found. Conn et al. reported that the normal adrenal gland, contralateral to the tumor, may escape from the suppressive action of dexamethasone, when scanning is delayed beyond 6-7 days after administration of ^{131}I-19-Iodocholesterol. However, a marked asymmetric distribution of radioactivity usually persists to ± 19 days p.i. In contrast, we found on the 6th and 8th day p.i. symmetric distribution of radioactivity in patients 5 and 7 (figure VI-1). The availability of the newer radiopharmaceutical ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol, which has been reported to have a 5-fold higher adrenal uptake than ^{131}I-19-Iodocholesterol (Basmadjian et al. 1975, Kojima et al. 1975), prompted us to prepare patients with primary aldosteronism by a longer pre-treatment with dexamethasone, starting about 14 days before injection of the tracer. Long-term dexamethasone administration caused an almost complete suppression of the normal adrenal gland in all patients and did not prevent clear visualization of the adenomatous gland in 8 out of 9 patients. In patient 8 both radiopharmaceuticals failed to concentrate in the adrenal adenoma. On a previous adrenal scintigram, performed elsewhere without dexamethasone suppression, both adrenals were imaged with symmetrical distribution of the radioactivitity. Therefore, it is unlikely that the failure to visualize the adrenal adenoma in this patient was caused by dexamethasone treatment. Indeed, Seabold et al. (1976) found that treatment with dexamethasone did not influence the uptake of radioactivity in the adenoma: the percentages of administered radioactivity per gramme of tissue in the adenomas, assayed post-operatively, were comparable in patients with and without dexamethasone treatment.
In patient 14 the concentration of the radiopharmaceutical apparently was insufficient to visualize the aldosterone-producing carcinoma. Failure to detect hormonal active adrenal carcinomas with radiocholesterol has been ascribed to the insufficient tracer uptake per gramme in tumor tissue (Moses et al. 1974). In contrast, metastatic adrenocortical tumors detected by radiocholesterol have been reported by several authors (Chatal et al. 1976, Forman et al. 1974, Sarkar et al. 1975). The results

of our experience reported in this paper lead us to the conclusion that ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol adrenal scintigraphy is a reliable non-invasive method for the correct localization of aldosterone-producing adenomas. In the group of patients in whom ^{131}I-19-Iodocholesterol was used as scanning agent, the failure to detect an aldosterone-producing adenoma in at least 3 patients was caused by accumulation of radioactivity in the normal contralateral gland. A longer pretreatment period with dexamethasone (during 14-21 days) may result in a more effective suppression of the normal adrenal gland. Long-term dexamethasone treatment does not prevent an adequate visualization of the adenoma-harboring adrenal gland.

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CHAPTER VII

SPIRONOLACTONE AND AMILORIDE IN HYPERTENSIVE PATIENTS WITH AND WITHOUT ALDOSTERONE EXCESS

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VII.1. Abstract

The antihypertensive action of spironolactone has been ascribed to both a nonspecific diuretic and a specific antimineralocorticoid effect. To better evaluate the relative importance of these effects, we compared its effects with the mineralcorticoid-independent drug amiloride. Spironolactone (400 mg/day) and amiloride (40 mg/day) were given to 10 patients with essential hypertension (EH) and to 10 patients with hypertension and supranormal aldosterone secretion (SNA). After 6 wk, blood pressure responded better to spironolactone (−20.5%) than to amiloride (−10.4%) in patients with SNA, but the response was similar in patients with EH (−7.4% and −6.5%). The decrease in body weight – as a measure of volume depletion – was greater after spironolactone than after amiloride both in patients with SNA (−4.6% and −0.8%) and in patients with EH (−3.7% and −0.6%). After both drugs, plasma sodium decreased (−3.4% and −2.6%) and plasma potassium increased (+37.2% and +32.6%) to the same extent in patients with SNA, reflecting a similar degree of antimineralocorticoid – like activity. After spironolactone patients with SNA showed a greater rise in PRA than after amiloride (412% and 82%). Despite the greater rise in PRA, the rise in aldosterone excretion was in the same range after both drugs (113% and 195%), pointing to inappropriately low aldosterone excretion after treatment with spironolactone. We conclude that differences in volume depletion or antimineralocorticoid-like activity cannot explain the better response in blood pressure of patients with SNA after spironolactone than after amiloride. Our data provide evidence for a specific antialdosterone effect of spironolactone in lowering the blood pressure, especially in patients with aldosterone excess.

VII.2. Introduction

Amiloride increases natriuresis and potassium resorption in the distal tubules of the kidney (Baer et al. 1967, Bull and Laragh 1968, Lant et al. 1969). Although its mode of action is independent of aldosterone, a marked fall in blood pressure was observed in a patient with hyperaldosteronism (Kremer et al. 1973a). This report was later confirmed, describing significant falls in blood pressure after treatment with amiloride in 19 patients with hyperaldosteronism, as well as in 5 patients with suspected mineralocorticoid excess. The weak diuretic amiloride induced only a modest fall in blood pressure in patients with essential hypertension (Kremer et al. 1973b, Kremer et al. 1977).
Spironolactone competes with aldosterone for the cytosol receptors in

the kidney and antagonizes the aldosterone-mediated sodium-potassium exchange in the distal renal tubules (Kagawa et al. 1964). Spironolactone has a well-known blood pressure-lowering effect in patients with hyperaldosteronism, as well as in some patients with essential hypertension. Its action has been ascribed to a nonspecific diuretic effect (Bravo et al. 1973, Hoffbrand et al. 1976, Jose et al. 1970, Liebau and Jarosch-v. Schweder 1974) and to a specific antimineralocorticoid effect (Spark and Melby 1971). Spironolactone, or some of its metabolites, has been shown to interfere with the biosynthesis of aldosterone by competition for the adrenal 11- and 18-hydroxylases (Cheng et al. 1976). It is unclear whether the inhibition of aldosterone synthesis is related to the spironolactone induced fall in blood pressure (Laidlaw 1977). An intrapatient comparison of the effects of the aldosterone-independent diuretic amiloride and the aldosterone-dependent diuretic spironolactone might shed light on its specific antialdosterone action in relation to its blood pressure-lowering effect. In our study, amiloride and spironolactone were given in high doses to 10 patients with and 10 patients without aldosterone excess. Special attention was paid to the disparate effects of both drugs on blood pressure and the renin-angiotensin-aldosterone system.

VII.3. Patients and methods

Patients. For this study, 20 patients were selected from our outpatient clinic, including 10 patients with hypertension and supranormal aldosterone secretion after salt loading (Kloppenborg et al. 1972) and 10 patients with essential hypertension and normal aldosterone values. The data of the patients are presented in table VII-1 All patients had a casual off-treatment, diastolic blood pressure of at least 95 mmHg. The blood pressure values given in the table were measured at the end of the placebo period by Arteriosonde. The measurements are known to be lower than casual blood pressure measurements (Drayer et al. 1976). The diagnosis "supranormal aldosterone" was based on clinical and biochemical criteria: hypertension, spontaneous mild or frank hypokalemia (plasma potassium <3.8 mmole/1), low plasma renin activity (PRA) after stimulation with chlorthalidone 100 mg/day during 5 days, (Drayer et al. 1975) and high aldosterone secretory rate (ASR) measured after dietary sodium loading with 315 mmole sodium per day during 5 days (Kloppenborg et al. 1972). Four of these patients had surgically proved adrenal adenomas (Nos. 1, 5, 6 and 8). The second group of 10 patients were considered to have essential hypertension, with no evidence of pheochromocytoma, renovascular disease, or renal impairment. They had low (n=4) or normal (n=6) stimulated PRA.

Table VII-1.

Clinical and biochemical data in 10 patients with supranormal aldosterone secretion and in 10 with essential hypertension

patient no	age (yr)	sex	MAP* (mmHg)	PRA** (pmole.hr $^{-1}$.ml $^{-1}$)	ASR*** (nmole/24 hr)	plasma K^+ (mmole/l)	plasma creatinine (μmole/l)
HYPERTENSION AND SUPRANORMAL ALDOSTERONE							
1.	46	F	108	1.23****	2.196	2.6	68
2.	44	F	131	3.93	415	3.4	65
3.	40	F	105	2.25	551	3.5	60
4.	48	F	117	2.82	366	3.5	75
5.	46	F	136	0.60****	737	2.2	61
6.	58	F	124	1.89****	2.989	3.3	86
7.	45	M	127	2.73	548	3.3	93
8.	36	M	131	1.59	1.845	2.8	72
9.	48	M	111	0.90	460	3.8	70
10.	53	M	121	2.52	1.197	3.7	119
ESSENTIAL HYPERTENSION							
1.	35	F	108	3.00****	89	3.7	65
2.	51	F	110	1.68	166	4.4	68
3.	40	M	100	5.16	205	3.9	74
4.	44	M	117	1.65	249	3.9	82
5.	40	F	117	17.73	–	4.2	69
6.	43	F	107	23.25	–	3.9	80
7.	23	F	100	18.93	–	4.0	50
8.	47	M	112	8.28	–	3.7	102
9.	41	M	97	12.48	–	4.1	82
10.	35	M	104	9.09	–	4.3	88

* Measured with the arteriosonde after 6 wks placebo, normal value 64-102
** Measured after chlorthalidone, normal value 8.25-30.0
*** Measured after sodium loading, normal value 152±47
**** Measured after a sodium restricted diet, normal value 3.45-17.85

In the patients wiht low PRA, aldosterone excess was excluded by the presence of a normal ASR after 5 days sodium loading with 315 mmole sodium per day. In the other patients ASR was considered to be normal in view of normal PRA and normal potassium values. The aldosterone excretion measured at the end of the placebo period was normal in these patients. All patients were off antihypertensive treatment for at least 4 wk before the experiment. During the first 6 wk they

were given spironolactone, 200 mg/day during the first 2 wk, and 400 mg/day during the remaining 4 wk. A placebo period followed, lasting 6 wk. Finally, amiloride was given for 6 wk, 20 mg/day in the first 2 wk, and 40 mg/day during the remaining 4 wk. The patients received tablets and capsules of identical appearance during the study in a dose of 4 tablets and 4 capsules a day. The patients were seen on an outpatient basis at 2-wk intervals. Blood pressure was measured by Arteriosonde. The representative blood pressure was chosen to be the average of the mean arterial pressures calculated from the measurements obtained during 30 min recumbency at 5-min intervals. The patients were weighed and blood was taken for measurements of plasma electrolytes and plasma urea. At the end of each treatment period after 2-hr ambulation an additional blood sample was drawn at noon for measurements of PRA and plasma electrolytes. The aldosterone excretion and sodium excretion were measured in urine collected during the last 24 hr before the visit at the end of each treatment period. Excluding major changes in dietary sodium intake throughout the study, the 24-hr sodium excretions at the end of each study period were not significantly different (180 ± 20 mmole after spironolactone, 186 ± 17 mmole after placebo, and 210 ± 12 mmole after amiloride).

Methods. Plasma electrolytes were measured by flame photometry with internal standard. The average of the 2 measurements obtained at the end of each treatment period was used for calculation. Plasma urea was measured by a standard laboratory procedure. PRA and aldosterone excretion and secretion were measured by radioimmunoassay (Drayer and Benraad 1975, de Man and Benraad 1977). The measurements at the end of each treatment period with an active drug were expressed as a percentage of the measurements at the end of the placebo period. For intrapatient comparison of the effects of the 2 drugs, the percentage changes after amiloride were subtracted from those after spironolactone. Student's t test and Wilcoxon test for pair differences were employed for statistical analysis within groups of patients, and Student's t test for nonpaired data was used for comparisons between groups. The data are presented as mean ± SEM. Regression analysis was performed by means of the Spearman rank test.

VII.4. Results

Patients with supranormal aldosterone (n=10; Figure VII-1). Spironolactone and amiloride treatment resulted in a decrease in blood pressure (−20.5% and −10.4%), rise in aldosterone excretion (+113% and +195%), fall in plasma sodium (−3.4% ± 0.8%and

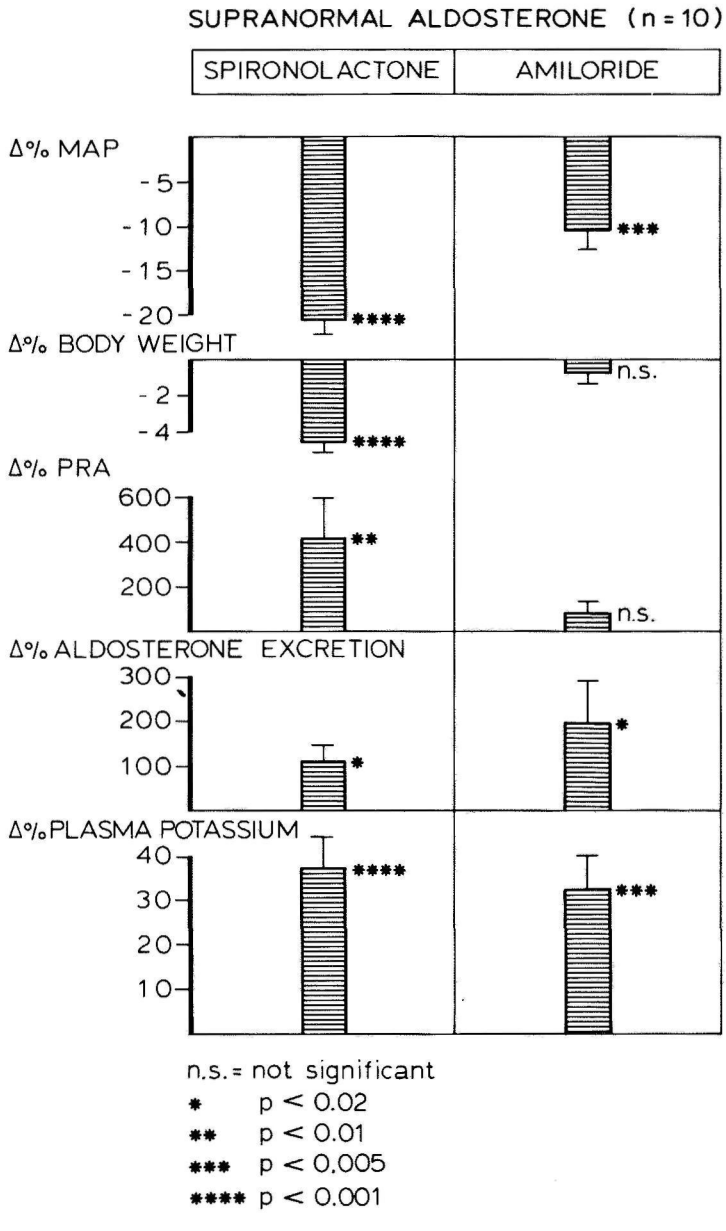

Figure VII-1. Mean changes ± SEM in some clinical and biochemical variables after treatment with spironolactone and amiloride in patients with supranormal aldosterone secretion (n=10)

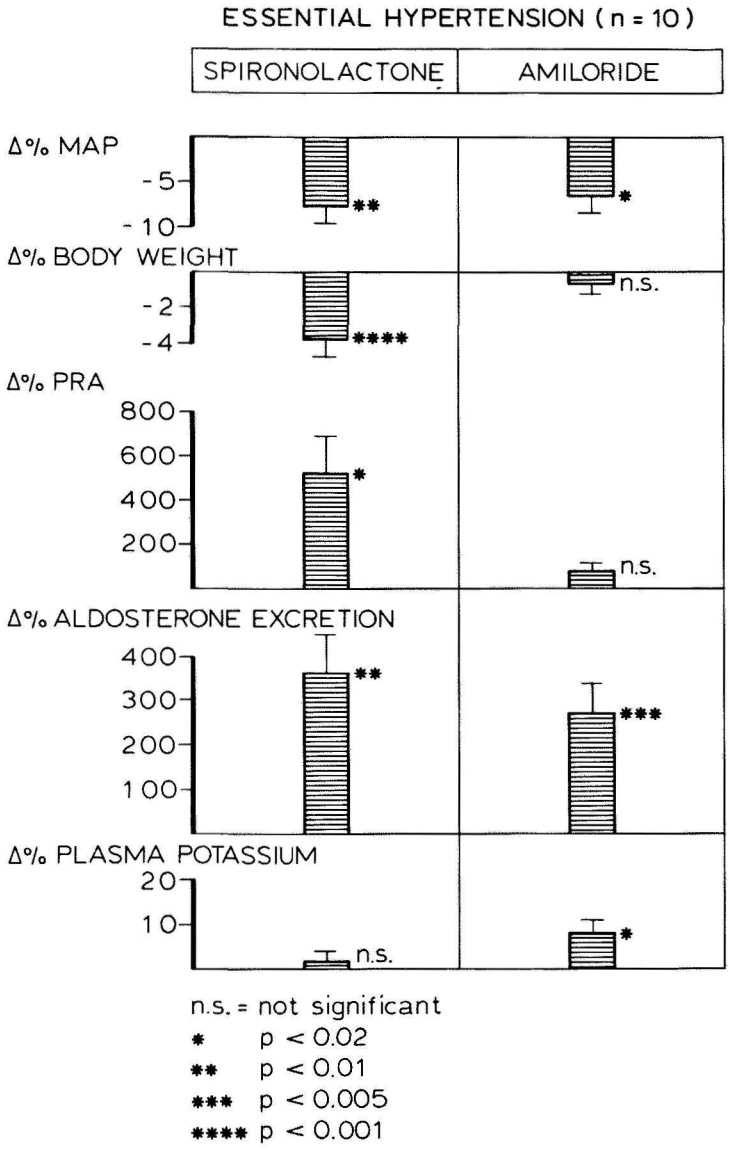

Figure VII-2. Mean changes ± SEM in some clinical and biochemical variables after treatment with spironolactone and amiloride in patients with essential hypertension (n=10)

−2.6% ± 0.7%), rise in plasma potassium (+37.2% and +32.6%), and plasma urea (+78.9% ± 7.6% and +22.8% ± 7.4%). There were significant changes in body weight (−4.6%) and PRA (+412%) only after spironolactone.

Patients with essential hypertension (n=10; Figure VII-2). The mean decreases in blood pressure after spironolactone and amiloride were small but significant (−7.4% and −6.5%). Both drugs induced changes in aldosterone excretion (+363% and +273%) and plasma sodium (−2.9% ± 0.5% and −1.0% ± 0.6%). Significant changes in body weight (−3.7%), PRA (+523%), and plasma urea (+32.7% ± 9.0%) were found only after spironolactone. Plasma potassium was not changed by spironolactone but was followed by a small and significant rise after amiloride (+8.0%).

Intrapatient comparison of the effects of spironlactone and amiloride (table VII-2).

Patients with supranormal aldosterone. Spironolactone induced a greater fall in blood pressure and body weight and a greater rise in PRA and plasma urea. The increase in aldosterone excretion was much the same for both drugs, so also for plasma sodium and potassium.

Patients with essential hypertension. The decreases in blood pressure induced by each drug were small and did not differ significantly.

Table VII-2.

Differences between the effects of spironolactone and amiloride in patients with supranormal aldosterone (n=10) and in patients with essential hypertension (n=10)

parameter	supranormal aldosterone (spironolactone-amiloride)		essential hypertension (spironolactone-amiloride)	
Δ% MAP	−10.1±1.6	p<0.001	− 0.9±1.9	n.s.
Δ% Body weight	− 3.7±0.5	p<0.001	− 3.1±0.8	p<0.005
Δ% Aldosterone excretion	−81±82	n.s.	+152±116	n.s.
Δ% PRA	+329±165	p<0.01	+446±170	p<0.01
Δ% Sodium	− 0.8±0.5	n.s.	− 1.9±0.6	p<0.02
Δ% Potassium	+ 4.6±4.5	n.s.	− 7.1±2.1	p<0.01
Δ% Urea	+56.1±6.3	p<0.01	+25.9±7.3	p<0.01

Spironolactone induced a greater decrease in body weight, a greater rise in PRA, and a greater rise in plasma urea, but, aldosterone excretion rose to the same extent after both treatments. Spironolactone induced a significant greater fall in plasma sodium, amiloride a greater increase in plasma potassium.

All patients (n=20). The fall in blood pressure after treatment with spironolactone correlated with the PRA after stimulation with chlorthalidone ($r=-0.61$, $n=16$; $p<0.05$) and with the ASR after sodium loading ($r=+0.53$, $n=14$; $p<0.05$). The increase in aldosterone excretion after spironolactone correlated inversely with the aldosterone excretion measured at the end of the placebo period ($r=-0.84$, $p<0.001$). The fall in blood pressure after amiloride did not correlate with stimulated PRA ($r=0.18$) or with the ASR after sodium loading ($r=0.20$). The changes in aldosterone excretion after amiloride were not related to placebo values ($r=-0.40$).

VII.5. Discussion

In patients with supranormal aldosterone (SNA), both spironolactone and amiloride induced a fall in blood pressure. They induced only a moderate fall in blood pressure in patients with essential hypertension (EH). Spironolactone induced more than 10% fall in MAP in all patients with SNA and in only 2 patients with EH. Amiloride induced a greater than 10% fall in blood pressure more frequently in patients with SNA (6 patients) than in patients with EH (2 patients). The mean fall in blood pressure was in the same range for both drugs in the patients with EH. The mean fall in blood pressure in the patients with SNA was greater after spironolactone than after amiloride. Possible reasons for the greater response of blood pressure after spironolactone in patients with SNA, include (1) differences in degree of volume depletion; (2) differences in antimineralocorticoid effects; (3) inhibition of aldosterone biosynthesis by spironolactone. In patients with SNA, spironolactone induced more volume depletion than amiloride. Similar differences in volume depletion were, however, found in patients with EH in the presence of comparable falls in blood pressure after both drugs. It therefore seems unlikely that spironolactone caused a more pronounced fall in blood pressure than amiloride in patients with SNA, only because of the greater volume depletion it induced.
The drugs differ in sodium and potassium handling in the kidney. Spironolactone exerts an antimineralocorticoid effect by blocking the mineralocorticoid receptors in the tubular cells of the distal nephron. Amiloride does not have a specific antimineralocorticoid effect but

causes comparable changes in plasma electrolytes by blocking the sodium-potassium exchanges at the luminal side of the tubular cells of the distal nephron.

Assuming a relationship between the antimineralocorticoid effect of spironolactone, as defined here, and the fall in blood pressure, one could argue that a better response of the blood pressure to this drug will be accompanied by greater changes in plasma electrolytes. We found that the plasma sodium and potassium change in patients with SNA were of the same order for both drugs. Marked differences were found in the response of the blood pressure, and therefore, the antimineralocorticoid effect of spironolactone, indicated by changes in sodium and potassium, cannot explain the greater fall in blood pressure after spironolactone in patients with SNA. The difference in blood pressure response could imply that spironolactone, apart from its antimineralocorticoid effect on plasma electrolytes, induces an additional effect on blood pressure.

Another factor in the greater blood pressure response after spironolactone in patients with SNA might be the inhibitory effect of spironolactone on the biosynthesis of aldosterone. This inhibitory effect was first demonstrated in vitro by Erbler (1972). It was also reported that spironolactone may interfere with biosynthesis of aldosterone in normal man (Abshagen et al. 1976 Erbler 1974, Erbler et al. 1976) and patients with hyperaldosternism (Bravo et al. 1975, Mantero et al. 1973, Sundsfjord et al. 1974). Conn and Hinerman (1977) discerned two phases of the effects of spironolactone treatment on aldosterone excretion in patients with hyperaldosternism: phase I which lasted for 4 to 6 wk, in which aldosterone excretion diminished (this was ascribed to the inhibitory effect of spironolactone on the biosynthesis of aldosterone), and phase II, in which an increase in aldosterone excretion was observed. According to Conn and Hinerman the increase in aldosterone excretion of 50% to 100% in phase II was most likely the result of prolonged stimulation by angiotensin II and the chronic state of sodium deficiency.

We found a marked rise in PRA and aldosterone after 6 wk treatment with spironolactone. Patients with SNA had a large rise in PRA and more marked signs of volume depletion after spironolactone than after amiloride. Despite the presence of stronger stimuli for aldosterone secretion after spironolactone, the increase in aldosterone excretion was of the same order after both drugs. These findings point to an inappropriately low aldosterone secretion after spironolactone. From the comparison of the effects of both drugs on aldosterone secretion, we tend to conclude that inhibition of aldosterone biosynthesis was present in patients with SNA after 6 wk on spironolactone and therefore resulted in greater blood pressure response. We also found

indirect evidence for inhibition of aldosterone biosynthesis by spironolactone in patients with EH, bu. the signs of inhibition of aldosterone secretion by spironolactone in this group of patients were less striking. Moreover, the difference in blood pressure response between spironolactone and amiloride in patients with EH was not significant. In fact, the greatest inhibition of aldosterone biosynthesis and the greatest hypotensive effect of spironolactone was found in patients with supranormal aldosterone.

The negative correlation between the aldosterone excretion at the end of the placebo period and the increase in aldosterone excretion after treatment with spironolactone in the whole group of patients, emphasizes the greater aldosterone inhibition in patients with SNA. Such a correlation was not found after amiloride. The greater inhibition of aldosterone secretion in patients with SNA after treatment with spironolactone may account for the greater fall in blood pressure in these patients. It has been demonstrated (Weber et al. 1977) that in patients treated with chlorthalidone, blood pressure fell most in patients with the least increase in aldosterone during treatment. This relationship was independent of volume depletion. The authors postulated a direct pressor action of aldosterone to explain this phenomenon. Our data support this hypothesis.

A significant positive correlation confirming earlier data (Benraad et al. 1978) was found in the whole group of patients between supranormal aldosterone – ASR after sodium loading – and the blood pressure fall after spironolactone. Such a correlation was not found with amiloride.

We therefore conclude that our data provide indirect evidence for specific antialdosterone effects of spironolactone, enhancing the fall in blood pressure after treatment with spironolactone, especially in patients with supranormal aldosterone secretion.

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CHAPTER VIII

THE PATHOLOGICAL ANATOMY OF THE ADRENALS IN PATIENTS WITH PRIMARY ALDOSTERONISM

VIII.1. Introduction

In 25 of the 28 patients with primary aldosteronism who are discussed in this thesis, the pathology of the adrenal tissue obtained by operation or autopsy could be studied. The findings of the anatomicopathologist in the individual patients are reported in the clinical histories that are discussed later on (see appendix). In this paragraph the macroscopic and microscopic findings are summarized, the following points being dealt with in particular:

1. The macroscopic pathology of the adrenal tissue removed in relation to the functional pathology. In this connection we shall go into the question of whether there is a correlation between the size of the tumor and the rate of secretion of aldosterone.
2. The microscopic pathology of the aldosterone-producing adrenal adenomas. Although adrenal adenomas are mostly built up of cells resembling those of the zona fasciculata, the histological architecture can be of a varied pattern. The cell types are classified and the findings are compared with the classical histopathological classification of Neville and Symington (1966).
3. The microscopic pathology of the adrenal cortex lying outside the adrenal adenoma. As appears from the descriptions in individual clinical histories (see appendix), anomalies are frequently found in the adrenal cortex lying outside the adenoma. The anomalies in this part of the adrenal cortex may vary from a slight or an obvious widening of the zona glomerulosa to a micronodular or macronodular hyperplasia of the adrenal cortex.
4. "Spironolactone bodies". Treatment with the aldosterone antagonist spironolactone causes in some patients the formation of cytoplasmatic inclusions in aldosterone-producing cells, the so-called "spironolactone bodies". The literature mentions as possible factors in the formation of "spironolactone bodies": the total quantity of spironolactone used, the duration of the medication and the time interval between the medication and the operation. These factors will be examined.

5 Adrenal carcinoma and primary aldosteronism The presence of an adrenal carcinoma with a selective overproduction of aldosterone is a very rare finding A description of the pathological findings in the woman patient L-G is given in chapter IX of this present thesis by Boers et al (1981) After that article had gone to press a local recurrence of an aldosterone-producing carcinoma was removed from her in 1980 We therefore made an addendum to chapter IX with regard to the clinical and pathological findings in this recurrent tumor In paragraph VIII-6 we give a synoptic survey of the literature on 11 patients with an aldosterone-producing carcinoma The problems that arise in the histopathological differentiation between benign and malignant aldosterone-producing tumors will be discussed

VIII 2. The macroscopic pathology of the adrenals

In the 18 patients with an aldosterone-producing adrenal adenoma the adrenal tissue to be examined was obtained by operation In the woman M-G an adenoma in the contralateral adrenal was found as well at autopsy In 15 patients a unilateral adrenalectomy was done, in 2 patients (F and W-S) a subtotal adrenalectomy (in the woman patient W-S by means of 2 operations) and in 1 woman patient (Ba) a total adrenalectomy The weights of the adenoma-containing adrenals varied from 3.8 to 30 grams (12 patients, see table VIII-1).
Taking the normal weight of adrenals to be from 5 to 5 7 grams (established by Kreiner and Dohm (1979) in sudden death patients) the weight of the adrenal had increased in 10 of the 12 patients, while in 2 patients the weight was lower than normal. The adenomas were not weighed after removal of the adjacent adrenal tissue According to Conn et al. (1964) the weight of an aldosterone-producing adenoma is mostly less than 6 grams and only exceptionally more than 10 grams The maximal diameter of the adrenal adenomas varied from 0 8 to 3 cm (see table VIII-1) It is well known that the diameter of aldosterone-producing adenomas is only rarely more than 3 cm (Conn et al 1964) In 2 patients (Br and S-R), on making serial sections of the adrenal, a smaller adenoma was found in an otherwise atrophic adrenal cortex, while in 3 patients (v W, M-G, N-M) macronoduli were encountered in the adjacent adrenal cortex The presence of a bilaterally localized tumor (patient M-G) is mentioned only sporadically in the literature (Kawasaki et al 1971) In the majority of patients with primary aldosteronism the tumor is solitary (91%), whereas multiple tumors are mostly unilaterally localized (Neville and Symington 1966) The adenomas were more frequently localized in the left adrenal, in approximate agreement with the percentage of 73% that was reported

Table VIII-1.

The adrenal pathology in relation to the functional pathology in patients with an aldosterone-producing adenoma

patient	♂/♀	adrenal weight (g)	maximum diameter of the adenoma (cm)	adenoma localization L(eft) R(ight)	aldosterone secretion (μg/24 hr)
G-J	♀	–	2.0	L	370
Br	♂	30	2.5 and 0.2	L	1257
v W	♂	9	1.9 (+ macro-noduli)	L	429
F	♂	–	0.8	L	408
Ba	♀	–	1.0	R	551
vd V	♀	11.5	2.0	R	248
O-K	♀	–	2.0	L	1941
vd K-M	♀	6.2	3.0	L	851
W-S	♀	–	1.5	R	440
S-R	♀	3.8	1.5 and 0.3	L	544
S-Kr	♀	4.1	1.3	R	862
H-S	♀	8.4	2.0	L	642
K-H	♀	7.3	1.4	L	331
H	♂	–	1.5	L	702
M-G	♀	9.5	2.5 (+ macro-noduli)	R	270
		–	1.8 (+ macro-noduli)	L	
N-M	♀	12.5	1.0 (+ macro-noduli)	R	353
P-R	♀	11.3	1.8	L	385
S-Kl	♀	8.2	1.9	R	259

by Conn et al. (1964). On section all adrenal adenomas showed the yellow colour that is characteristic for this type of tumor, and were localized intraglandularly or projected above the surface of the gland. The size of the tumor, measured by the maximal diameter, proved to be not significantly correlated with the secretion of aldosterone measured during a diet with 6 grams of salt ($r=0.28$, $n=18$; n.s., table VIII-1). But it did turn out that a significant correlation existed as between the weight of the adrenal containing the adenoma and the secretion of aldosterone during such a diet ($r=0.48$, $n=12$; $p<0.05$, table VIII-1). In assessing these correlations it is necessary to take into account

Table VIII-2.

The adrenal pathology in relation to the functional pathology in patients with idiopathic aldosteronism

patient	♂/♀	adrenal weight (g)	microscopic pathology	aldosterone secretion (μg/24 hr)
v N	♂	–	hyperplasia of the zona glomerulosa	476
S	♂	50 (L+R)	hyperplasia	401
L	♀	20 (L+R)	micronodular hyperplasia	222
S-B	♀	7 (2/3L+R)	hyperplasia of the zona glomerulosa	242
J	♂	–	hyperplasia of the zona glomerulosa	340
K	♂	70 (L+R)	micronodular hyperplasia	108

the fact that the interval of time between the measuring of aldosterone and the operation varied from a few weeks to even several years. We have not found any mention in the literature of a correlation between the rate of secretion of aldosterone and the size of the tumor (or the weight of the adrenal). In the 6 patients in whom no adrenal adenoma was found, the adrenal tissue was obtained at autopsy (S, L and K) or by operation (v N, S-B and J). It is a striking fact that the weight of these adrenals varied considerably, and so, too, did the values of the aldosterone secretion (table VIII-2). The very obvious increase in size of the adrenals of the patiens S, L and K, in whom the tissue was obtained at autopsy, can probably be explained by the severe illnesses that preceded their death. In the patient K the greatest weight of the adrenal and lowest secretion of aldosterone were found. In none of the 6 patients macroscopic anomalies of the adrenal cortex were found, except for a widening of the adrenal cortex in patient K. According to Neville and O'Hare (1979) no macroscopic anomalies are found in the adrenals of most patients with idiopathic aldosteronism, whereas in a minority (20%) of these patients macronoduli are found.

VIII.3. The microscopic pathology of the adrenals

Although no close relationship exists between the morphology and the function of the three histologically distinguishable layers of the adrenal cortex (zona glomerulosa, zona fasciculata and zona reticularis), the

biosynthesis of aldosterone, in contradistinction to most other adrenal steroids, is restricted to one zone, namely, the zona glomerulosa. The extraordinary fact that precisely the aldosterone-producing adenomas have turned out to be built up by cells that are not distinguishable by light microscopy from the cells of the normal zona fasciculata is a paradoxical discovery that so far has not been elucidated. However, the preponderant fasciculata-like cell type already suggests (as we show elsewhere in this thesis) that the steroid production of the tumor takes place to a considerable degree under the influence of ACTH. According to the classic description of Neville and Symington (1966), cells of the zona glomerulosa – and zona reticularis (or "compact") – type are also to be found in adenomas. Furthermore, cells are encountered that have cytological properties of the zona glomerulosa and of the zona fasciculata and are therefore called "hybrid cells". Hybrid cells are like fasciculata-like cells, but are smaller. The nucleus-cytoplasm ratio is more in agreement with that of the zona glomerulosa cells. Although all 4 cell types may be present, the histological picture is mostly dominated by the great, clear, lipid-laden cells of the fasciculata type. It is still not sufficiently known whether, and, if so, to what extent, each of the 4 cell types mentioned contributes to the production of aldosterone. But it has been ascertained from in vitro studies that adenomas produce not only aldosterone but also corticosterone and cortisol, although in vivo the secretion values of both of the latter hormones are not raised (Biglieri et al. 1963, Kaplan 1967). This shows that not only morphologically, but also biochemically, the adenoma cells display a hybrid character. Thus Brode et al. (1962) demonstrated that the steroid production of the adenomas in vitro, expressed in the ratio 17-hydroxy-/17 deoxysteroids yielded a ratio that lays between that of a normal zona glomerulosa and a normal zona fasciculata. It is also probable that zona glomerulosa and zona fasciculata type cells both morphologically and functionally, can reciprocally change over to one another, as was shown by Hornsby et al. (1974) by means of "monolayer cultures" of the zona glomerulosa of the rat. Furthermore, it is known from electron microscopic studies of adenoma cells, that the morphology of mitochondria and agranular endoplasmatic reticulum in many cases agrees with that of zona glomerulosa cells (Kovacs et al. 1974, Kano et al. 1979, Eto et al. 1979). In table VIII-3 a survey is given of the various cell types that were encountered in 19 adenomas.

In all tumors, except in the 4 last mentioned in table VIII-3, the zona fasciculata cell type was predominant. In the tumors of varied composition all 4 cell types were represented. In one adenoma (from patient F) exclusively zona glomerulosa cells were found, which is a well known, but rare histological variant of an aldosterone-producing adrenal adenoma (Neville and O'Hare 1979). The photographs give an illustration

Table VIII-3.

Classification of cell types in 19 adenomas

cell types	number of adenomas	see figure
Fasciculata type	7	VIII-1
Fasciculata and reticularis type	6	
Fasciculata and "hybrid" type	1	VIII-2
Fasciculata and glomerulosa type	1	VIII-3
Glomerulosa type	1	VIII-4
Varied composition	3	VIII-5, VIII-6
Total	19	

of the various histological pictures. The light microscopic findings in patients with an idiopathic aldosteronism have already been reported in table VIII-2. When the zona glomerulosa was clearly recognizable and focally or diffusely showed an increase, the term hyperplasia of the zona glomerulosa was used. When an increase of the width of the cortex was found, without clearly recognizable increase of the zona glomerulosa, "hyperplasia" was reported in the table. When, as well, light microscopic cortical noduli were met, micronodular hyperplasia was the term used.

In patients with idiopathic aldosteronism probably the overproduction of aldosterone takes place in the hyperplastic zona glomerulosa, while the micro- or macronoduli make no contribution to the production of aldosterone (Neville and O'Hare 1979). Various authors regard the presence of cortex noduli as the sequel rather than the cause of the hypertension (Shamma et al. 1958, Dobbie et al. 1969, Neville 1978). The precence of cortex noduli in the adrenal (both micro- and macronoduli) is a frequent finding at autopsy of patients without functional anomalies of the adrenals (Shamma et al. 1958). In contradistinction to what was assumed earlier, no functional significance is assigned to cortex noduli in adrenals of patients with primary aldosteronism. In vitro it was proven that these noduli, in contrast to the classic solitary adenomas, produce no aldosterone, while the cells from which the noduli are built up, are devoid of the ultrastructural features of cells that produce aldosterone (Neville 1978). "Spironolactone bodies" (see also the following paragraph) were never found in such noduli. Dobbie (1969) has suggested that the occurrence of cortex noduli, independently of the presence or absence of functional adrenal pathology, is the sequel of hyaline thickenings of the vascular walls, and proliferation

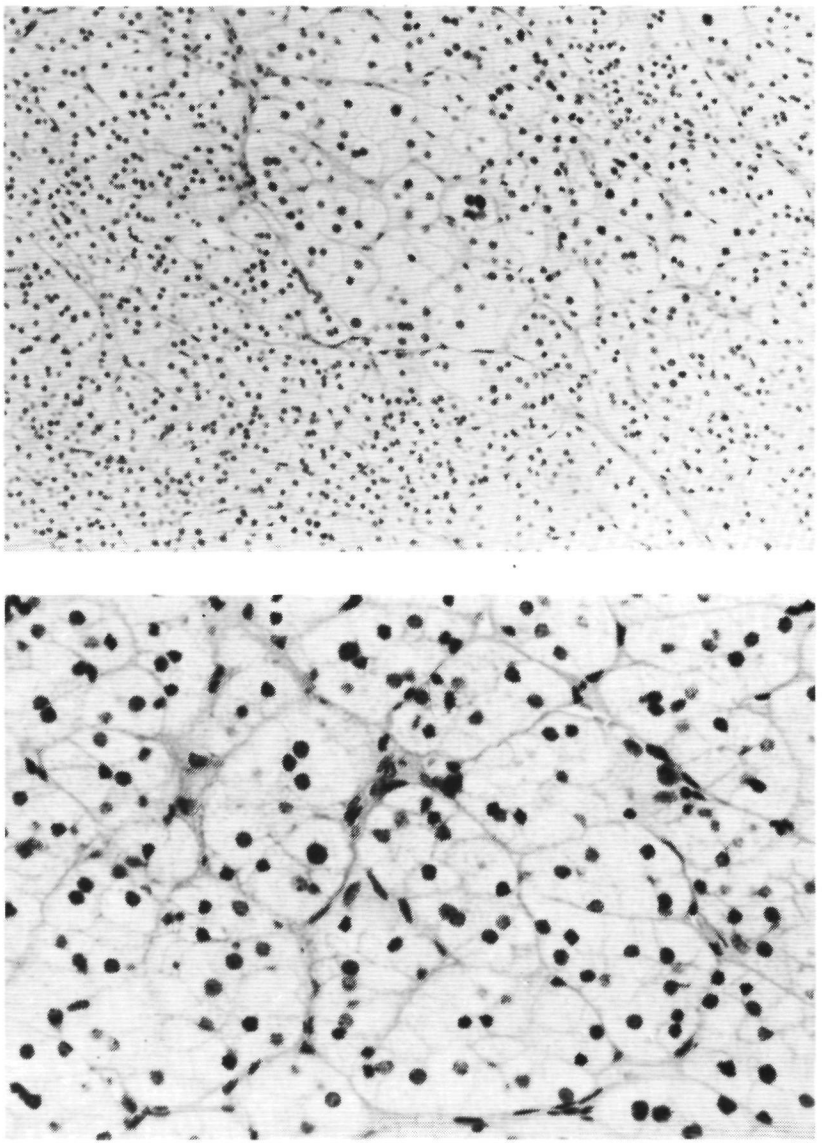

Figure VIII-1. Patients S-Kl. Part of the adenoma composed of lipid-laden clear cells similar to those of the normal zona fasciculata. HE; x140 (upper figure). Detail of upper figure. The cells are arranged in small alveoli separated by fine fibrovascular connective tissue. HE; x350 (lower figure)

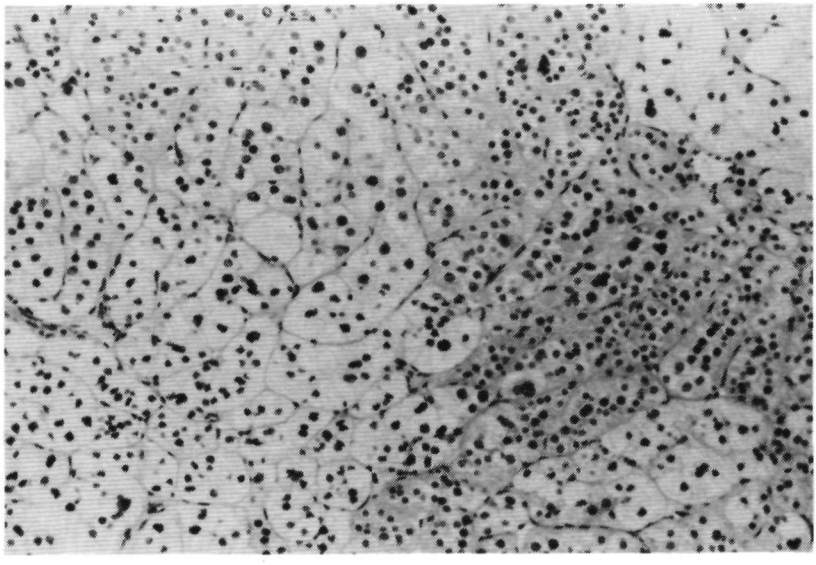

Figure VIII-2. Patient N-M. Zona fasciculata type cells are seen on the left and cells of the "hybrid" or "intermediate" type on the right. The latter exhibit a slight degree of nuclear pleomorphism and their cytoplasm is smaller. HE; x140

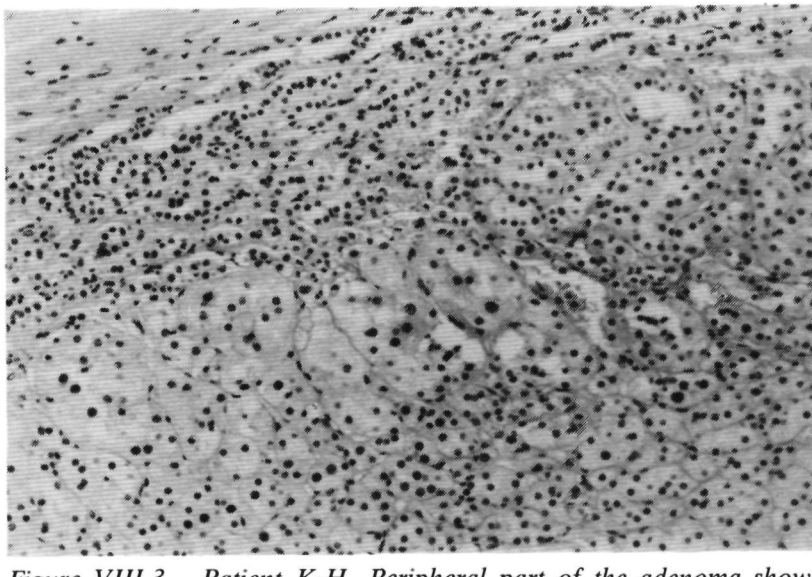

Figure VIII-3. Patient K-H. Peripheral part of the adenoma shows nests or cords of zona glomerulosa-type cells between the capsule (upper left) and zona fasciculata-type cells (center). HE; x140

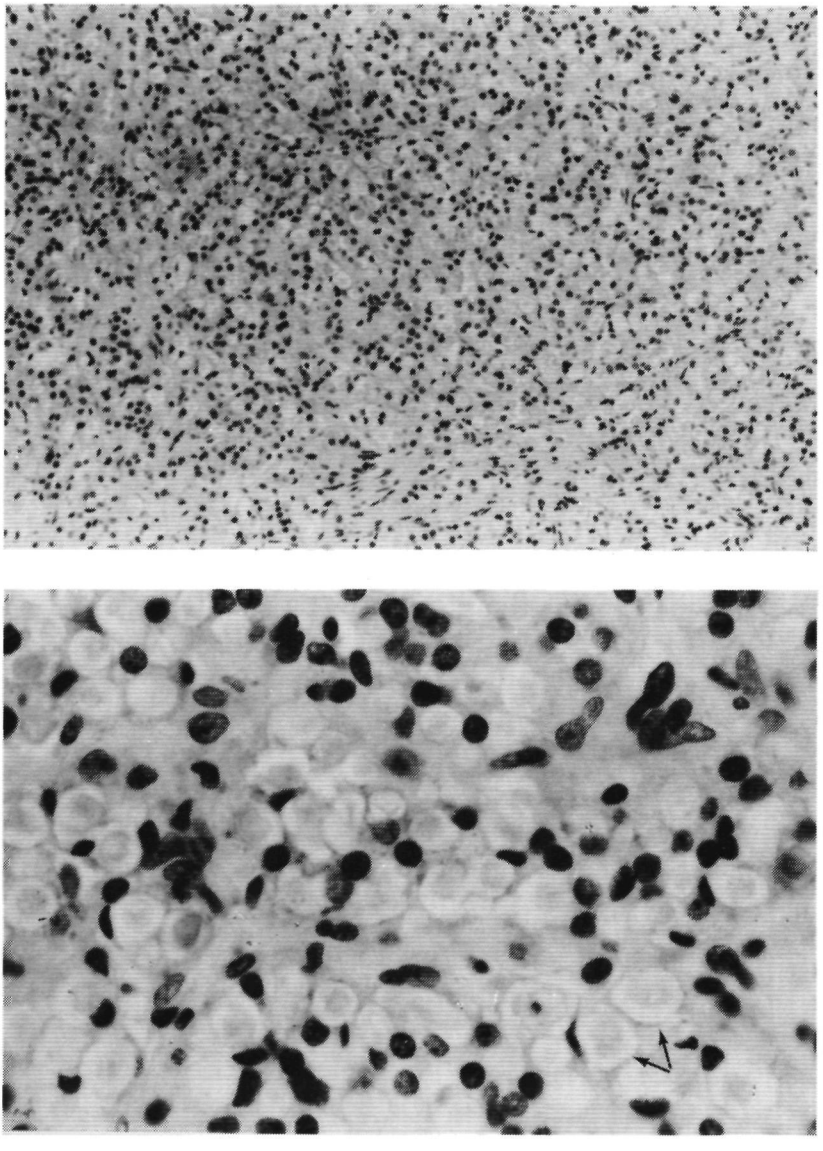

Figure VIII-4. Patient F. Zona glomerulosa-type cells are almost the sole component of this adenoma. Rounded intracytoplasmatic inclusions (spironolactone bodies) can be observed in practically each cell. HE; x140 (upper figure) Detail of upper figure. Numerous laminated spironolactone bodies (↑) are easily identified in the cytoplasm of the zona glomerulosa-type cells. HE; x550 (lower figure)

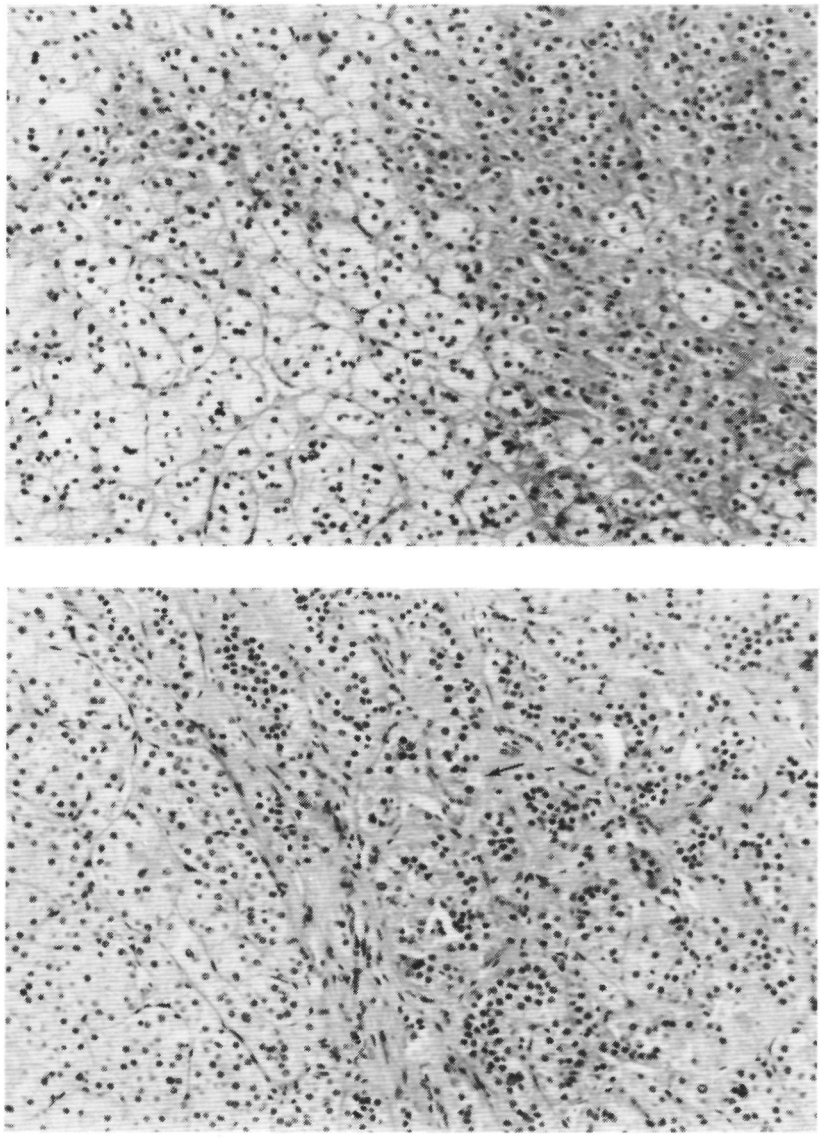

Figure VIII-5. Patient v-W. Two examples of the various cellular components in an adenoma are illustrated: zona fasciculata-type (left) and dark zona reticularis-type (or compact) cells in the right part of the picture. HE; x140 (upper figure). Elsewhere in the adenoma zona fasciculata-type cells containing spironolactone bodies (↑) seem to be present. HE; x140 (lower figure)

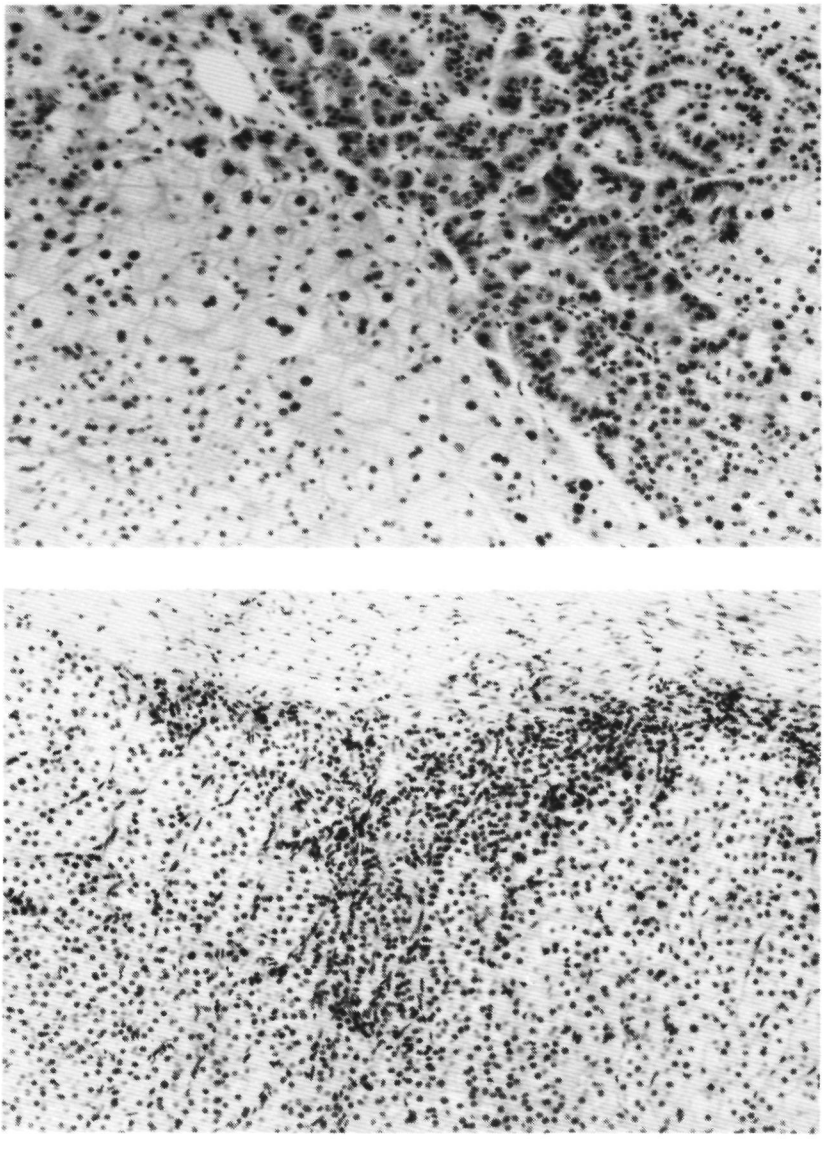

Figure VIII-6. Patient Ba. A focus of zona fasciculata-type cells is seen on the left with small dark, eosinophilic compact (or zona reticularis-type) cells on the right. HE; x140 (upper figure). Outside the adenoma a broadened layer of zona glomerulosa cells extends inward in a tongue-like manner between the cords of zona fasciculata cells. HE; x140 (lower figure)

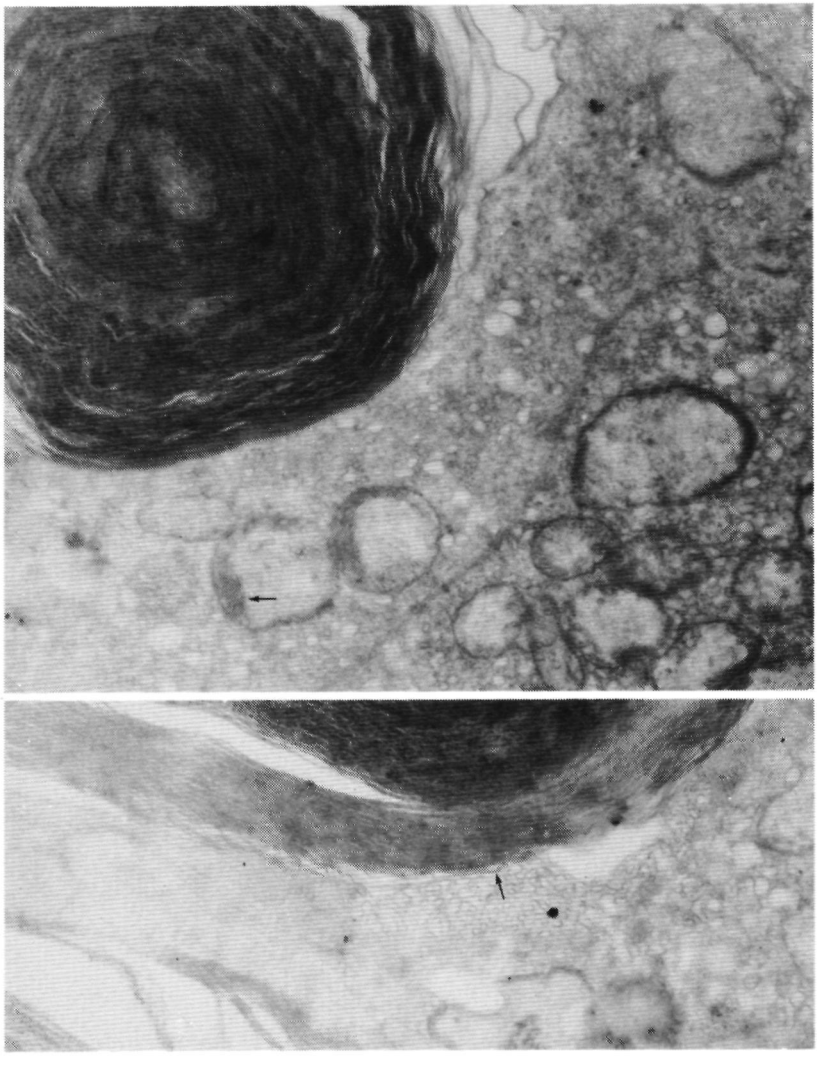

Figure VIII-7. Patient F. Part of a zona glomerulosa cell containing an osmiophilic spironolactone body in an advanced phase of development. In the surrounding cytoplasm several rounded or elongated mitochondria with lamellar cristae (↑) can be seen. The endoplasmic reticulum appears vesicular. x21.700 (upper figure). Outer portion of a spironolactone body exhibiting the regular concentric orientation of numerous smooth membranes. There is continuity (↑) of these membranes with vesicular smooth endoplasmic reticulum suggesting derivation from this organelle. x21.700 (lower figure)

of the intima of the capsular arteries. Apparently by local ischemia and atrophy of the adrenal cortex, compensatory hyperplasia occurs in the cortical parts that are supplied with blood by the arteriae comitantes, that in general are less liable to arteriopathic changes (Dobbie and Symington 1966). In point of fact, cortex noduli are found more frequently in advancing age and in patients with hypertension (Shamma et al. 1958, Dobbie et al. 1967).

VIII.4. Microscopic pathology of the adrenal cortex lying outside the adenoma

In the earliest publications on adrenal pathology in primary aldosteronism, in general, little attention was devoted to the adrenal cortex lying outside the adenoma. In the original publication by Conn (1956), it was reported that the contralateral adrenal cortex was "somewhat thinner than normal". Microscopical examination showed this to be due to a diminution of the zona fasciculata*. Brode et al. (1962) were the first to report a hyperplasia of the adjacent zona glomerulosa, in which sometimes the zona glomerulosa extended deeply into the cortex. Neville and O'Hare (1979) reported in their review, based on the pathological findings in 80 patients with primary aldosteronism, that the adjacent zona glomerulosa in all of the adrenals with adenoma examined by them, presented a hyperplasia accompanied or not by micronoduli. Also, in the adrenals examined by us there was regularly a focal or diffuse increase of the adjacent zona glomerulosa to be observed. In assessing the width of the zona glomerulosa it is necessary to take into account the fact that this layer in the normal adult adrenal – and certainly during advancing age (Symington 1969) – is often only focally present and sometimes can not be identified histologically. For these reasons a zona glomerulosa that is present as a continuous layer in the periphery of the adrenal cortex, must be considered as hyperplastic. In 17 patients with 18 adenomas the adjacent adrenal cortex could be assessed and a hyperplastic zona glomerulosa was found in ten adrenals (figure VIII-6). In 3 patients the adrenal cortex of the contralateral adrenal could be examined and two of them turned out to have a hyperplastic zona glomerulosa. Moreover, as well as a hyperplasia of the adjacent adrenal cortex, micronoduli of the cortex were found in 7 patients; these were built up by cells of the zona fasciculata type.

* Based on these grounds and on the presence of the fasciculata cell type in the adenoma that was removed – it was concluded by Conn that aldosterone is produced in the zona fasciculata. But shortly afterwards Ayres et al. (1956) showed that the production of aldosterone takes place exclusively in the zona glomerulosa.

The finding that in a considerable part of the patients with an aldosterone-producing adenoma the zona glomerulosa is not atrophic, as might have been expected, strongly supports the suggestion that a hyperplasia of the zona glomerulosa precedes the development of an adenoma that produces aldosterone.

VIII.5. "Spironolactone bodies"

In 1963, 6 years after the aldosterone antagonist spironolactone was introduced for clinical use (Liddle 1957), Janigan reported the occurrence of cytoplasmatic inclusions in zona glomerulosa cells of 18 patients with liver cirrhosis who had been treated with spironolactone in a total dose varying from 0.6 – 16 grams. The eosinophile inclusions, in which 2 to 4 concentric rings were recognizable, measured 2 – 25 μ, and were surrounded by a clear halo. The chemical composition proved to be a phospholipide-protein complex. On electron microscopic examination, spironolactone bodies proved to be built up of concentric membranes closely packed together, with a central lipoid nucleus. There was a continuous connection between the outer membrane of a spironolactone body and the agranular endoplasmatic reticulum. On these grounds it was supposed that the spironolactone body was built up of windings of the smooth endoplasmatic reticulum (Jenis and Hertzog 1969). The first publications on the presence of "spironolactone bodies" dealt with autopsy material of patients who had been treated with spironolactone because of liver cirrhosis or cardiac decompensation. An autopsy artefact could not, therefore, be entirely excluded. In 1973 Kovacs et al., however, reported the presence of "spironolactone bodies" in an adrenal removed operatively from a woman with primary aldosteronism and adrenal hyperplasia. In the widened zona glomerulosa and, especially, in its outer layer, many "spironolactone bodies" were met. "Spironolactone bodies" were later on also found in an adenoma, that produced aldosterone, in a patient who had been treated preoperatively with spironolactone (Cain et al. 1974). In the zona glomerulosa adjacent to the adenoma no "spironolactone bodies" were met. The functional significance of these "spironolactone bodies" was at first unclear. The construction, consisting of membranes from the endoplasmatic reticulum (in which many of the enzymes concerned with the synthesis of aldosterone are localized) pointed to "spironolactone bodies" being the morphological expression of an increased aldosterone production during treatment with spironolactone (Kovacs 1974). However, it remained unexplained why "spironolactone bodies" were never found in adrenal adenomas of patients who had not been treated with spironolactone, not even in tumors that produced conside-

rable quantities of aldosterone In 1977, Conn and Hinerman wrote a clarifying study on the functional significance of "spironolactone bodies" in aldosterone-producing adenomas. The number of inclusions in the adenomas of all 23 patients in whom the adenoma-harboring adrenal was removed during spironolactone medication, was found to depend on the length of time of the treatment with spironolactone, and not on the dose used After a rapid increase of the number of inclusions during the first 40 to 60 days, a gradual decrease was seen from the 50th to the 170th day of spironolactone medication. In addition it was shown, that the excretion of aldosterone during the first weeks of spironolactone treatment, diminished and subsequently – about one month later – increased to above the level of the basal excretion. In view of the period of rapid increase of the number of spironolactone bodies coinciding with a diminution of the excretion of aldosterone, it was probable that the appearing of the spironolactone bodies formed the morphological expression of inhibition of the production of aldosterone The absence of spironolactone bodies in the zona glomerulosa outside the adenoma was in agreement with the concept that the zona glomerulosa there contributes nothing to the production of aldosterone. Further, from the absence of spironolactone bodies in the zona fasciculata, it was concluded that the inhibition of aldosterone induced by spironolactone probably takes place after the biosynthesis of corticosterone. The gradual increase of the excretion of aldosterone after 4 to 6 weeks of treatment with spironolactone was explained as the result of the natriuresis and rise of the plasma renin activity induced by spironolactone. In the group examined by us there were 18 patients who had been treated with spironolactone (table VIII-4) for 1 to 53 months. Spironolactone bodies were found in only 4 patients. This low incidence may be founded on both a relative long average duration of medication and on the time interval between stopping the medication and the operation In 2 patients with an adenoma (F and v W, figures VIII-4, VIII-5 and VIII-7) the spironolactone bodies were localized in the adenoma, and in patient F, also in the zona glomerulosa lying outside the adenoma as well as in the contralateral adrenal. If it is agreed with Conn that spironolactone bodies are the pharmacological hallmarks of cells with raised aldosterone production, it must be accepted that the overproduction of aldosterone in patient F has not been limited to the adrenal adenoma In 2 patients with an adrenal hyperplasia (v N and S) "spironolactone bodies" were spread over the zona glomerulosa of both adrenals It is a remarkable fact that 3 out of 4 patients with "spironolactone bodies" had taken the medication up to the day of the operation. In one patient (F) the aldosterone values were measured in the immediate preoperative phase. On the day before the operation low plasma aldosterone values were obtained: in the mor-

Table VIII-4.

Dose and duration of spirolactone medication in relation to the origination of "spirolactone bodies"

patient	adrenal pathology	duration of medication (months)	total dose spironolactone (g)	time lag between medication and operation	"spironolactone bodies"
v W	adenoma	1	14	0 days	+
F	adenoma	4	48	9 days	+
Ba	adenoma	2.5	10	5.7 years	–
vd V	adenoma	7	61	5.5 months	–
O-K	adenoma	9	52	3 months	–
vd K-M	adenoma	4.5	54	3 months	–
W-S	adenoma	4	30	7 months	–
S-R	adenoma	28	169	12 days	–
S-Kr	adenoma	53	218	11 days	–
H-S	adenoma	8	47	3 days	–
K-H	adenoma	1.5	19	8 days	–
H	adenoma	27	111	27 days	–
M-G	adenoma	2	20	2 months	–
N-M	adenoma	7	85	1 day	–
S-Kl	adenoma	4	22	3 months	–
v N	hyperplasia	3.5	22	0 days	+
S-B	hyperplasia	2.5	24	0 days	+
J	hyperplasia	3	9	3 months	–

ning at 9.00 hr 4.9 ng/100 ml, and at 12.00 hr, after 3 hours of ambulation, 12.6 ng/100 ml. Also, at that moment the plasma potassium concentration was normal (4.5 mmol/l) and, so too, was the blood pressure (130/80 mmHg). The number of "spironolactone bodies" in this patient was very high and the relation between the inhibition of the aldosterone production and "spironolactone bodies" is suggestive. In connection to the discussion of this paragraph it is relevant to recall that an indirect indication of an interference of spironolactone with the biosynthesis of aldosterone was obtained from the comparison of the aldosterone excretions after 6 weeks of treatment with spironolactone, 400 mg per day, and those after 6 weeks treatment with a placebo and after 6 weeks treatment with amiloride, in patients with a raised aldosterone production (chapter VII). The arguments for a relative inhibition of the biosynthesis of aldosterone under the influence of spironolactone were derived from the fact that in patients with a raised basal aldosterone excretion the output of aldosterone after 6 weeks of

treatment with spironolactone 400 mg per day, did, it is true, show a significant rise, but dit not vary essentially from the excretion of aldosterone after 6 weeks treatment with amiloride 40 mg per day, in spite of the fact that the plasma renin activity and the degree of volume depletion after treatment with spironolactone showed a greater rise than after treatment with amiloride (Hoefnagels et al. 1980, see also the discussion in chapter VII).

VIII.6. The aldosterone-producing carcinoma of the adrenals

Among the causes of death from malignant tumors, the carcinoma of the adrenals, with its 0.2%, occupies a modest place (Richie and Gittes 1980). The hormonally active adrenal carcinomas – and they constitue approximately the half of such tumors (Greenberg and Marks 1978) – can be the source of clinical symptoms that in a number of cases make early recognition possible. The endocrine manifestations of an adrenal carcinoma may be: Cushing's syndrome, virilization, feminization, pubertas praecox, primary aldosteronism, or a combination of these affections. Adrenal carcinomas that manifest themselves mainly by an overproduction of mineralocorticoids are described only by reference to examples, and the total of cases so far reported is probably less than 20 (Foye and Feichtmeir 1955, Brooks et al. 1957, Zimmerman et al. 1959, Crane et al. 1965, Santander et al. 1965, Neville and Symington 1966, Alterman et al. 1969, Brooks et al. 1972, Filipecki et al. 1972, Revach et al. 1977). A few cases of DOC-producing adrenal carcinomas have been published (Crane et al 1965, Powell-Jackson et al. 1974) and a few aldosterone-producing carcinomas arising from ectopic adrenal tissue in ovaries (Ehrlich et al. 1963, Todesco et al. 1975) or kidney (Boers et al. 1981).

The first publication of an aldosterone-producing adrenal carcinoma (Foye and Feichtmeir 1955) is also remarkable because the authors give a good clinical description of the syndrome of primary aldosteronism (muscular weakness, thirst, polyuria, hypertension, hypokalemic alkalosis) without knowing about Conn's earlier publication (1955), as appears from their references to the literature. However, the patient apparently did not satisfy one of the criteria for the making of the diagnosis of primary aldosteronism (Conn 1955): the urinary excretion of the 17-ketosteroids was markedly raised. From the case reports of patients with carcinomas of the adrenals that produce aldosterone (see table VIII-5) that were subsequently published, it turned out that the clinical picture was often indistinguishable from that of primary aldosteronism due to a benign aldosterone-producing adenoma: namely, muscular weakness, tetany, thirst, polyuria, hypertension and hypoka-

Table VIII-5.

Literature review of some clinical and pathological findings in 11 patients with an aldosterone-producing adrenal carcinoma

author	patient	pathology of the tumor removed by operation	postoperative survival period	autopsy
Foye 1955	♂ 60 years	tumor of 4 cm (right) consisting of hybrid and glomerulosa type cells	6 months	metastases in lungs, liver and bone marrow
Brooks 1957	♂ 35 years	tumor of 1400 g (left), necroses, vascular thrombi, giant cells, hybrid and compact type cells	5 weeks	none
Zimmerman 1959	♀ 38 years	tumor of 583 g (right), necroses, bleedings and compact type cells	not known	lung and vertebral metastases
Crane 1965	♀ 64 years	tumor of 1010 g (left), necroses, bleedings, large cells with eosinophile cytoplasm	12 weeks	metastases in lungs, liver and abdominal lymph nodes
Santander 1965	♀ 50 years	tumor of 90 g (right) with cells of fasciculata and compact type (autopsy)	6 weeks	metastases of lung and liver
Neville 1966	♀ 26 years	tumor of 2032 g (right), bleedings, necroses, thick-walled vessels with thrombi, glomerulosa and hybrid type cells	not known	not known
Alterman 1969	♂ 68 years	tumor of 30 g (left), necroses and bleedings on the cut surface, polynuclear cells, invasion of blood and lymph vessels	4 months	metastases in pituitary gland, lung, pleura, bones
Brooks 1972	♂ 35 years	tumor of 1000 g (left), necroses, pleomorphic cells cysts	not known	metastases in lungs
Filipecki 1972	♀ 34 years	tumor of 320 g (right), encapsulated, necroses, calcifications, invasion of vessels and capsule, polynuclear cells	living, no indications of recurrence or metastases (follow-up 6 months)	
Revach 1977	♀ 31 years	tumor of 6x3,5x3 cm (right), encapsulated, a few mitoses, rich vascularization, calcification, no capsule or vessel invasion, glomerulosa type cells	2 1/2 years	tumor recurrence in right adrenal region, metastases in liver, spleen and mesentery
Boers 1981	♀ 50 years	tumor of 3 cm, subcapsular in right kidney, cut surface bleedings and necroses, partial encapsulation, fibrous bands, atypical cells, frequent mitoses, vascular thrombi, vessel and capsule invasion	local recurrence one year after operation No signs of recurrence or metastasis up to 5 months after resection of the recurrent tumor	

lemic alkalosis occurred in many patients. There were no overt clinical symptoms of excessive production of other adrenal steroids, but urine metabolites of adrenal steroids other than aldosterone were regularly found in a number of patients (Crane et al. 1965, Brooks et al. 1972). The excretion of 17-ketosteroids was, with a single exception (Revach et al. 1977, Boers et al. 1981), practically always raised. Clinical symptoms that might indicate a malignant tumor as the cause of the primary aldosteronism in the patients mentoined in table VIII-5, were: emaciation, fever, pain in the upper abdomen or back, a palpable tumor in the upper abdomen and hepatomegaly. An intravenous pyelogram often showed a caudal shift of the kidney on the side where the adrenal tumor was lying. The diagnosis of carcinoma of the adrenal was subsequently made in most patients by anatomopathological examination of the extirpated tumor. It is well known that in assessing adrenal and other endocrine tumors, the histopathological criteria that in general are used for the establishment of the presence of malignancy, may not, without further consideration, be applied for this type of tumor. Thus, multiplicity of mitoses, invasion of the capsule and vessels, polymorphism of cells or nuclei, are not histological features that are found exclusively in malignant tumors, while their absence does not exclude malignancy (Hough et al. 1979). Absolute certainty about the malignancy of an adrenal tumor is obtained only by the demonstration of metastases some distance away (Symington 1969). Thus, the tumor removed by Revach et al. and described by them in the first instance as benign (1977) had to have its designation changed later on when metastases appeared. Some clinical and pathological findings in 11 patients with adrenal carcinoma producing aldosterone are reported in table VIII-5. Of the 11 patients – 4 men and 7 woman – 6 were found to be younger than 40 years of age. The tumor was mostly of considerable size (up to more than 2000 grams), but there were also small malignant tumors (Alterman et al. 1969, Boers et al. 1981). The most frequent pathological findings were: bleedings and necroses on the cut surface of the tumor, thickwalled vessels with thrombi, and invasion of the capsule and vessels. The tumors consisted of one or more of the 4 cell types, that are also found in benign aldosterone-producing adenomas. Metastases were met in the liver, lungs and bone marrow, while on several occasions recurrent tumor growth was observed. It is noteworthy that the average survival was generally less than six months, with the exception of the patients described by Revach et al. (1977) and Boers et al. (1981).

Without referring in detail to the discussion of the case of the woman patient L-v G as set forth in chapter IX (Boers et al. 1981), we can conclude in summary that this patient had in total developed the syndrome of primary aldosteronism 3 times; on 2 occasions this was

due to a malignant tumor. The case history differs in the following points from most of the cases of adrenal carcinomas producing aldosterone that have been described up till today.

1. No previous report has been made of an aldosterone-producing carcinoma that developed after removal of a benign aldosterone-producing adenoma.
2. There are arguments (see discussion in chapter IX) for the assumption that the carcinoma has developed from heterotopic adrenal tissue localized in the right kidney.
3. An adrenal carcinoma with, exclusively, overproduction of aldosterone, has so far been reported only twice in the literature (Santander et al. 1965, Revach et al. 1977). In both cases, however, the number of measured steroids was limited.
4. The clinical course seems up to the present time to be considerably more favourable than the cases of aldosterone-producing carcinoma reported in the literature.

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CHAPTER IX

HYPERALDOSTERONISM DUE TO AN ADRENOCORTICAL CARCINOMA 12 YEARS AFTER SURGICAL REMOVAL OF AN ALDOSTERONE PRODUCING ADRENOCORTICAL ADENOMA

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IX.1. Summary

To our knowledge only 3 patients with selective and excessive production of aldosterone due to a carcinoma of the adrenal gland have been reported. Heterotopic benign adrenal tissue inducing primary aldosteronism has been reported in one patient. In this paper, we describe a patient in whom the syndrome of primary aldosteronism recurred 12 years after removal of an aldosterone-producing adenoma of the right adrenal gland. Overproduction of 18-hydroxycorticosterone and aldosterone appeared to be due to an adrenal carcinoma located subcapsularly, at the upper pole of the right kidney. Removal of the tumor led to normalization of blood pressure, plasma potassium, 18-hydroxycorticosterone, and aldosterone.

IX.2. Introduction

The syndrome of primary aldosteronism in adult patients is in approximately 80 percent of cases due to a single adenoma of the adrenal cortex. In the remaining patients, the syndrome occurs in the presence of multiple, sometimes bilateral, adenomas, diffuse bilateral hyperplasia, or even in the presence of histologically normal adrenal glands (Conn et al. 1964 and 1971, Neville and Mackay 1972). Only 15 cases of primary aldosteronism due to an adrenal carcinoma are reported in the literature in detail (Santander et al. 1965, Alterman et al. 1969, Brooks et al. 1972, Filipecki et al. 1972, Revach et al. 1977, Vetter et al. 1978). In 12 of these patients clinical and laboratory data suggest hypersecretion of glucocorticoids, androgens, as well as aldosterone by the tumor. Therefore, these patients do not fulfill Conn's criteria of the syndrome of primary aldosteronism (Conn et al. 1964). In the remaining 2 cases, selective and excessive production of aldosterone was present (Santander et al. 1965, Revach et al. 1977), thus establishing Conn's syndrome. Two cases of primary aldosteronism in patients with virilizing carcinoma of the ovary are reported (Ehrlich et al. 1963, Todesco et al. 1975). The tumor of these patients contained areas of heterotopic, adrenocortical tissue. The syndrome has also been reported in 2 patients with metastases from a bronchial carcinoma in the adrenal gland (Mach et al. 1957, Spaulding et al. 1966). Adrenal hyperplasia without evidence of metastasis to the adrenal gland has been reported in a patient with advanced carcinoma of the prostate (Kohler 1959). Benign extra-adrenal tissue rarely produces the syndrome of primary aldosteronism. Only one case has been published, in whom the syndrome was due to a benign adrenocortical adenoma located in the kidney (Flanagan and McDonald 1967). We present a patient with the

syndrome of primary aldosteronism without evidence suggesting overproduction of other adrenal hormones, caused by an adrenal carcinoma. The carcinoma was attached subcapsularly to the right kidney. Twelve years earlier, the right adrenal gland had been removed because of hyperaldosteronism due to a pathologically and clinically benign adrenocortical adenoma.

IX.3. Methods

Aldosterone secretion rate (ASR) was measured by radioimmunoassay (Man de and Benraad 1977) in urine collected during 24 hours of recumbency after a dietary intake of 0, 6 and 18 grams of NaCl per day for at least 4 days. Plasma aldosterone (Man de et al. 1980), 11-deoxycorticosterone (DOC) and 18-hydroxy-11-deoxycorticosterone (18-OH-DOC (Hoefnagels et al. 1978)), 11-deoxycortisol (S (Smals et al. 1978)), cortisol (F (Man de et al. 1980)) were measured by radioimmunoassay. Corticosterone (B) and 18-hydroxycorticosterone (18-OH-B) were measured with the method described for 18-OH-DOC using specific antibodies for these hormones. Plasma renin activity (PRA) was measured by radioimmunoassay (Drayer and Benraad 1975), in blood collected at noon after 3 hours of ambulation during a dietary intake of 0 and 6 grams of NaCl per day for at least four days. Excretion of 17-hydroxysteroids and keto-steroids in 24 hours urine samples were measured by standard methods (Appleby et al. 1955). Plasma electrolytes and serum creatinine were measured using routine laboratory techniques. Adrenal scintigraphy was performed 1, 4 and 6 days after intravenous administration of 1.9 mCi ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol, after pretreatment with dexamethasone (0.5 mg qid for 3 weeks) and potassium perchlorate (0.2 g qid for one day). Dexamethasone and potassium perchlorate were continued throughout the scintigraphy study.

IX.4. Case report

The patient, a woman born in 1930, had a history of hypertension during pregnancies in 1960 and 1964. She was found to have sustained hypertension since her last pregnancy in 1966. She was referred to the hospital in 1967, at age 37, because of tiredness, headaches, dizziness, palpitations and uncontrollable hypertension. Her blood pressure was 160 over 105 mmHg. Physical examination was otherwise normal. Laboratory tests (table IX-1) revealed hypokalemia, alkalosis, and normal creatinine values. The ASR was clearly elevated and the PRA

Table IX-1.

Clinical and biochemical data at the time of the removal of the adrenal adenoma (1A), during the symptom-free follow-up (1B), and at the time of the removal of the adrenal carcinoma (1C)

	normal values		1967 prior to surgery 1A	1967 after surgery 1A	1969 1B	1976 1B	1979 prior to surgery 1C	1979 after surgery 1C
Blood pressure		mmHg						
supine			160/105	115/70	130/83	160/95	170/110	140/90
upright			180/120	125/75	140/85	155/105	175/110	130/80
Potassium	3 8-4 6	mmol/l	2 0	4 6	4 3	3 7	2 2	4 1
Bicarbonate	26-28	mmol/l	38 9	22 9	21 2	26	33 7	28 1
Creatinine	60-100	µmol/l	62	77	–	77	76	80
$ASR^{*}_{0\ g}$	200-500	µg/24 hr	3711	–	–	–	721	–
$ASR_{6\ g}$	75-175	µg/24 hr	1960	64	–	–	808	65
$ASR_{18\ g}$	30-80	µg/24 hr	–	–	–	–	683	–
$PRA^{**}_{0\ g}$	115-595	ng/10 ml/3 hr	0	320	–	193	6	–
$PRA_{6\ g}$	– –	–	0	5	–	–	12	179
Cortisol								
9 a m	0 19-0 55	µmol/l	0 40	0 40	–	–	0 25	0 28
5 p m	0 06-0 24	µmol/l	0 22	0 25	–	–	0 18	0 12
17-hydroxy-steroids	17-52	µmol/24 hr	46 5	–	–	–	35	40
17-keto-steroids	26-62	µmol/24 hr	35 4	–	–	–	32	23

* Aldosterone secretion rate measured during recumbency and after a dietary intake of 0 6 and 18 g NaCl

** Plasma renin activity measured at noon after 3 hr of ambulation and a dietary intake of 0 and 6 g NaCl per day for at least four days

undetectably low. Plasma cortisol levels were normal as was the excretion of 17-hydroxy- and keto-steroid compounds in the urine. Arteriography showed an enlarged right adrenal gland. Right lumbotomy was performed and an adrenal tumor was found. The tumor was removed as a whole and the remaining adrenal tissue for technical reasons in at least three pieces. The tumor weighed 6.3 g and the remaining right adrenal gland 4 g. Microscopic examination of the tumor (figure IX-1) revealed adrenal cortical tissue consisting of relatively large polygonal cells with abundant, mostly eosinophylic, sometimes vacuolated cytoplasm. The cells contained centrally located round nuclei, generally containing one or more small basophylic or eosinophylic nucleoli. The cells were growing in trabecular and alveolar structures, sometimes in sheets. Small conglomerates or ribbons of eosinophylic cells were seen in a rather loose connective tissue, surrounding wide endothelium lined lumina. Especially in these areas the tissue resembled the zona glomerulosa of a normal adrenal cortex. In other areas the typical structure of the zona fasciculata is seen. Scattered giant cells were present in the tumor, with large polyploid or multiple nuclei and some cells showed slight to moderate nuclear atypia with prominent nucleoli. Mitoses were scarce. There was no necrosis.

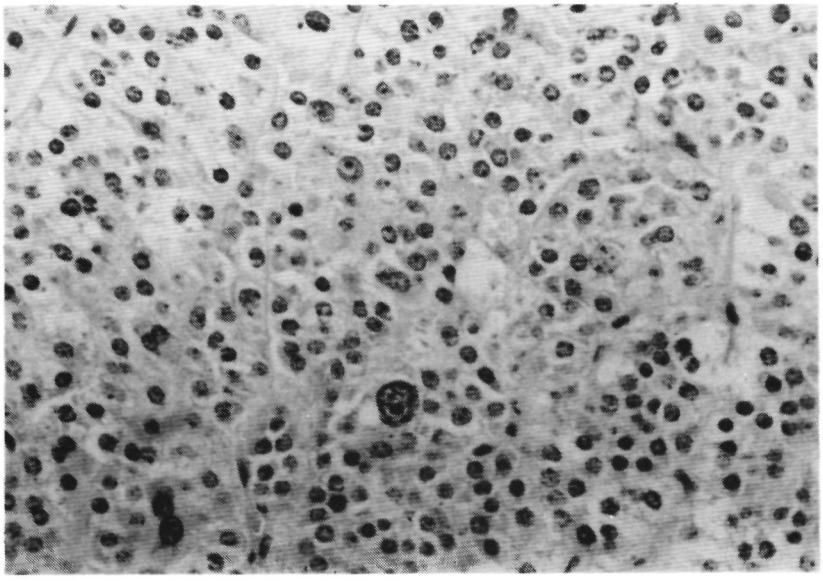

Figure IX-1. Adrenocortical adenoma. Although some small and large atypical cells with coarse nuclear chromatin and prominent nucleoli are found, the overall picture is rather monotonous. Mitoses are scarce (H&E. x78)

It is known to be often very difficult to predict the future behaviour of an adrenocortical tumor from its morphology as no definite criteria have emerged as diagnostic, but the absence of vascular or capsular invasion, necrosis and marked nuclear pleomorphism did seem to justify the diagnosis of adrenocortical adenoma. The remaining adrenal gland showed an atrophic cortex with a zona glomerulosa, fasciculata and reticularis in normal proportions. After surgery blood pressure, plasma potassium, bicarbonate, ASR and PRA normalized (table IX-1). The patient denied any symptoms. Symptoms recurred in 1976 and blood pressure was found to be elevated at that time. The oral contraceptive medication which she was using since 1968 was discontinued. However, blood pressure remained elevated. Plasma potassium was just below normal at that time, but plasma aldosterone and PRA were normal. Antihypertensive therapy was started using spironolactone and oxprenolol. Blood pressure fell to 130 over 85 mmHg. The patient was not without headaches during treatment. In the following years blood pressure rose to 170 over 110 mmHg and in 1979 antihypertensive treatment was discontinued to allow further evaluation. The patient had a hypokalemic alkalosis (table IX-1). The ASR was clearly

Table IX-2.

Adrenocortical hormone concentrations in plasma before and after surgery and the content of these hormones in the removed tumor

	normal values in plasma	plasma values		tumor values
		prior to surgery	after surgery	ng/g tumor tissue
Deoxycorticosterone (DOC)	4-14 ng/100 ml	15	2	24
18-hydroxydeoxycorticosterone (18-OH-DOC)	3-13 ng/100 ml	5	4	7
Corticosterone (B)	130-820 ng/100 ml	198	199	38
18-hydroxy-corticosterone (18-OH-B)	25-70 ng/100 ml	184	28	601
Aldosterone	3-25 ng/100 ml	134	7	336
11-deoxycortisol (S)	30-200 ng/100 ml	186	168	3
Cortisol (F)	0.19-0.55 µmol/l at 9 a.m.	0.25	0.29	21

elevated but to a lower level than the values measured in 1967. The PRA was low. Plasma cortisol and urinary excretion of 17-hydroxy- and keto-steroids were normal. Assays of adrenocortical hormones in blood taken prior to surgery (table IX-2) showed normal values except for plasma aldosterone and its immediate precursor 18-OH-B. Routine laboratory tests were normal, including ESR (8 mm) and serum creatinine. Chest X-ray and intravenous pyelography were normal. Adrenal scintigraphy showed poor concentration of radioactivity located above both kidneys. Again a right lumbotomy was performed and just below the diaphragma a very small (diameter 0.2 cm) nodule of macroscopically and histologically normal adrenal tissue was found. Moreover a tumor with a diameter of 3 cm was seen attached to the right kidney, located subcapsularly, about 4 cm from the upper pole of the kidney. The tumor could easily be isolated. After enucleation of the tumor, the adjacent kidney tissue was removed. The tumor consisted of a lobulated friable mass of soft yellow-brown tissue, containing areas of necrosis and hemorrhage. The tumor was partly surrounded by an irregular

fibrous capsule, which was continuous with fibrous strands between the lobuli. In certain parts of the tumor, the histology was similar to that of the adenoma which had been resected 12 years earlier. Other parts of the tumor showed predominantly atypical cells (figure IX-2) with very large nuclei, large eosinophylic nucleoli, and a coarse chromatin structure. Some of the large nuclei were vacuolated. In these areas frequent mitoses were seen up to 5 per high power field. In many parts of the tumor broad areas of necrosis and hemorrhage were present associated with trombosed blood vessels. Occasional giant cells were found, some with marked atypia. Between the noduli of tumor cells broad septa of fibrous tissue were present, invaded by groups and strands of proliferating cells. Infiltrative growth in vessel walls and peripheral capsular tissue could readily be found (figure IX-3). All signs indicative of malignancy (O'Hare et al. 1979, Hough et al. 1979) were present and the diagnosis of adrenal cortical carcinoma was made. The kidney tissue adjacent to the tumor showed microscopically formation of an irregular zone of fibrous tissue with scattered glomeruli and atrophic tubuli, surrounded by a diffuse and perivascular lymphocytic infiltration. More distally, signs of interstitial nephritis gradually decreased. The superficial renal cortex adjacent to the localization of the tumor was covered with capsular tissue which was not continuous with the pseudocapsular tissue of the tumor bed. In an extract of the tumor cells measurements of adrenocortical hormones were performed. The results are compared to those obtained in plasma taken before and after removal of the tumor (table IX-2). High levels of 18-OH-B and aldosterone were found both in plasma taken prior to surgery and in the extract of the tumor cells. After surgery blood pressure fell (table IX-1). Blood values of potassium, bicarbonate, PRA, 18-OH-B and plasma aldosterone normalized (table IX-1 and -2). During follow-up for 5 months, the patient did not reveal any symptoms.

IX.5. Discussion

The diagnosis of primary hyperaldosteronism was made in this patient at age of 37 and 12 years later at age 49. Signs and symptoms of the syndrome disappeared at both occasions after removal of an aldosterone-producing tumor. The firstly removed tumor did not show histopathological signs indicative of malignancy, although it has to be admitted that the pathological diagnosis of malignancy of adrenal tumors may be difficult (O'Hare et al. 1979, Hough et al. 1979). As mentioned before no definite single criterion for establishing the benign or malignant potential of adrenocortical tumors is available. Criteria as multiplicity of mitosis, invasion of the capsule and vessels,

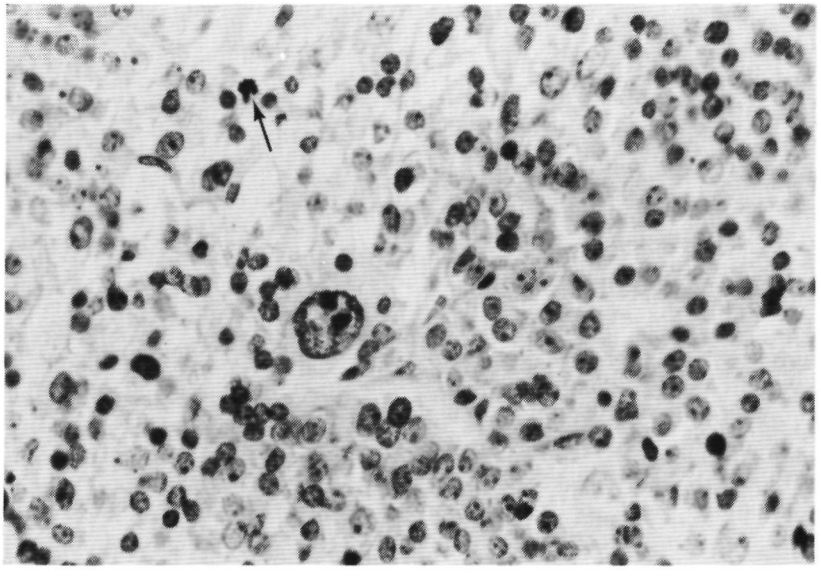

Figure IX-2. Adrenocortical carcinoma. The histologic appearance is essentially the same as that of the adenoma. However, atypia is more pronounced and mitoses (arrow) are easily found (H&E x125)

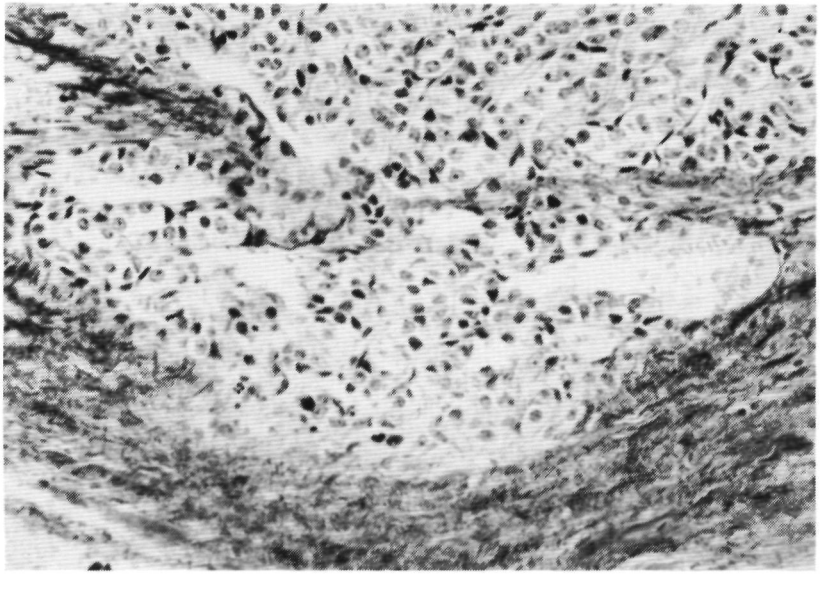

Figure IX-3. Adrenocortical carcinoma. Tumor cells invade a capsular vessel (Elastin von Gieson stain x78)

polymorphism of cells or nuclei, and necrosis are not histological features that are found exclusively in malignant tumors However, the occurrence of several of these histological features in the same tumor will be sufficient for a reliable diagnosis of malignancy The tumor removed 12 years later showed all histopathological features indicative of adrenocortical carcinoma The clinical follow-up after the first procedure could be an argument against the hypothesis that the second tumor was a metastasis of the first one Since the adrenal carcinoma developed after a total adrenalectomy at the same side, we have to face several possibilities with respect to the origine of the carcinoma As mentioned earlier, the right adrenal gland and the adenoma were removed in at least 3 pieces and not as one mass. Therefore, it seems not unlikely that an adrenal remnant was left in the right suprarenal area at that time. It is well known in experimental endocrinology that adrenal tissue will regenerate after adrenalectomy, when the adrenal capsule is left behind The localization of the carcinoma in this patient, subcapsularly attached to the right kidney, does not support the idea of regeneration and subsequently degeneration, of an adrenal remnant The remote possibility cannot completely ruled out that the second tumor was a metastasis grown via lymphatic and blood vessels into the subcapsular regio of the right kidney from adrenocortical cells dispersed in the area of the right adrenal during the adrenalectomy in 1967, which have shown malignant degeneration afterwards. Heterotopic adrenal tissue was found indeed in this patient, during the second surgical procedure, just below the diaphragma However, no signs of malignancy were found in this adrenal tissue Heterotopic, both cortical and medullary, adrenal tissue had been demonstrated to be present in up to 30% of random post mortem examinations (Flanagan and McDonald 1967) Accessory cortical tissue has been found in the peri-adrenal and peri-nephric area, along the great vessels, in the ovary, broad ligament, intestine, spermatic cord, pancreas and in the root of the mesentery Adrenal rests are found in 1% of kidneys studied at autopsy (Allen 1951) Usually, ectopic adrenal cortical tissue is hormonally inactive. Only one case has been reported of a benign adrenocortical adenoma in the kidney producing the syndrome of primary aldosteronism (Flanagan and McDonald 1967) We speculate that in this patient malignant degeneration of heterotopic adrenal tissue, located subcapsulary in the right kidney, caused the syndrome of recurrent primary aldosteronism, 12 years after removal of a benign aldosterone-producing adrenal adenoma of the right adrenal gland

In view of the developments that took place in this patient after the article of Boers et al. (1981) had gone to press, we give here the sequel of this clinical history.

After, in this patient on 11.10.79 an aldosterone-producing carcinoma localized subcapsularly in the right kidney had been removed operatively, the blood pressure and the mineral spectrum normalized completely, while the excretion of aldosterone in the 24 hours urine fell off to 1.9 μg/24 hours. At policlinical control on 6.8.80 the patient was found to be suffering from headaches, and edema of the ankles in the evening. But the plasma electrolytes and the plasma aldosterone values were entirely normal. On 8.10.80 the headache increased, there was intensification of the edema of the ankles and the blood pressure had risen to 180/110 mmHg. The mineral spectrum showed a serious hypokalemia of 1.8 mmol/l and the plasma concentration of aldosterone had risen to 60 ng/100 ml. On admission to hospital on 13.10.80 the blood pressure had slightly increased to 165/90 mmHg. The body weight was unchanged and was 48.1 kg. There were no edemas. Physical examination also revealed no further abnormal findings. Determination of the aldosterone secretion rates showed a recurrent primary aldosteronism (table IX-3).

The excretion of the 17-ketosteroids in the 24 hours urine was normal

Table IX-3.

Aldosterone secretion rates and additional clinical and biochemical findings in patient L-v G, one year after surgical removal of an aldosterone-producing carcinoma

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure		146/103 (n=9)	
Sodium (mmol/l)	139	145	143
Potassium (mmol/l)	2.2	1.9	1.6
Creatinine (μmol/l)	81	73	75
UV sodium (mmol/24 hr)	31	188	202
UV potassium (mmol/24 hr)	59	60	78
UV creatinine (mmol/24 hr)	10.4	10.5	10.2
PRA (ng/10 ml/3 hr)	43	33	–
ASR (μg/24 hr)	1087	642	740

on repetition, varying from 1.0 to 3.5 mmol/mmol creatinine (n=17). The BSE was 15 mm. The liver functions were normal. The Hgb was 8.5 mmol/l. For the detection of the aldosterone-producing tumor the following examinations were done: X-ray of the chest: no anomalies of heart or lungs. The heart-lung quotient was 12 : 37. IVP: partial nephrectomy of the right kidney. Normal position of the kidneys. CT scan: no indications of local recurrence of the tumor. No indications of metastases in the liver or retroperitoneally. Aortography, coeliacography and renal arteriography: no anomalies. Liver, spleen and skeleton scintigraphy: no anomalies. Adrenal scintigraphy with ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol: on the 2nd, 6th, 8th, 9th and 10th days after intravenous injection of the isotope at a dose of 2 mCi, no accumulation of the tracer inside or outside the adrenal region was observed. The examination was made after giving dexamethasone 2 mg/day for 3 weeks. Venous catheterization with blood sampling: the plasma aldosterone concentrations in blood samples that were collected at varying levels in the vascular area of the vena cava yielded no convincing indication of the localization of the tumor: peripheral vena cava inferior 28 ng/100 ml, proximal vena cava inferior 29 ng/100 ml, left renal vein 29 ng/100 ml, right renal vein 29 ng/100 ml, hepatic vein 31 ng/100 ml, right atrium 41 ng/100 ml. On 12.12.80 the right adrenal region was explored via a pararectal-thoracic, transabdominal incision. There was found a well encapsulated tumor of 4x3x2 cm, localized retroperitoneally, firmly adherent to the psoas muscles. The tumor lay 3 cm above and lateral to the upper pole of the right kidney, without being attached to it. The tumor could be easily removed in toto. The extirpated tumor weighed 8 grams and was entirely surrounded by a capsule. On the cut surface the tumor presented a nodular structure with local bleedings and areas of necrosis. On microscopic examination the tumor was seen to be made up of nodes of medium-size to large cells with eosinophile clear cytoplasm and atypical nuclei. The nodes were separated from each other by thin septa of connective tissue. Mitoses were easily found. Here and there, there was commencing necrosis and invasion of blood vessels. In the capsule of varying breadth (in which there was topically both fatty and muscular tissue) there were several tumor foci manifesting the picture of an infiltrative growth. Conclusion: adrenal cortex carcinoma.

Postoperatively the blood pressure fell to 120/85 mmHg. The mineral spectrum normalized and the plasma aldosterone concentration was lowered to 5 ng/100 ml. During a follow-up of 6 months no indications were found of recurrence of tumor or of metastases. The blood pressure remained entirely normal.

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SUMMARY

In this thesis some clinical and pathological aspects of "primary aldosteronism" are discussed on the basis of studies that were made in 28 patients. Attention has been devoted to both the individual clinical histories of these patients (Appendix) and to the summaries of the most important aspects they present (chapters III up to and including chapter IX). The patients were referred to the department of Internal Medicine in the period 1961 to 1979. The consequence of this long time interval is that a number of data (chapters III and VIII) could be compiled only by retrospective research, with all the shortcomings inherent in such investigations. On the other hand data of prospective research are set forth in chapters IV, V, VI and VII.

In chapter I there are a number of references to the literature about the diagnosis and treatment of the adenomatous and idiopathic forms of primary aldosteronism.

In chapter II a description is given of the methods by which the data were collected that concerned the aspects of "primary aldosteronism" that in this thesis receive special attention. These aspects were: "general clinical data", "the diagnosis of primary aldosteronism", "the day and night rhythm of the plasma aldosterone concentration", "adrenal scintigraphy", "medicamentous treatment", "operation", "pathology of the adrenals" and "clinical follow-up".

In chapter III anamnestic data about the patients studied are reported, with some emphasis on the first complaints and signs with which the illness was initiated. A remarkable feature is the number of patients who had already a raised blood pressure for a long time before the diagnosis of "primary aldosteronism" was definitely made. The blood pressure was mostly seriously raised as was apparent from the frequent occurrence of complications, that were the sequel of the hypertension. The theme then dwells upon the influence of deprivation or loading of salt upon the electrolytes in plasma and urine. The adenomatous form, in comparison with the idiopathic form, shows clearer signs of aldosteronism, with which the difference in plasma renin activity between the two groups is in agreement. From the comparison of the effectiveness of medicamentous treatment by spironolactone and by surgery, it became apparent in our study that the effect produced by spironolactone was of prognostic value with regard to the results to be expected from treatment by surgery. The results of surgical treatment in this group of patients show that the operation, according to a long-lasting

follow-up, leads to a permanent normal blood pressure in only a minority of the patients.

In chapter IV, the importance of salt loading for the diagnosis of "primary aldosteronism" is elucidated. Measurements of aldosterone in the 24 hours urine under various conditions – after salt loading, changing of body posture, administration of dexamethasone – however, prove not to contribute to a differentiation between idiopathic and adenomatous aldosteronism. On the contrary it did prove possible to differentiate the two forms of primary aldosteronism on the basis of measuring aldosterone in blood during the night and the day. We summarize these data on the basis of the article published in chapter V. Also in chapter IV a report is made on the fact that the regulation of aldosterone in the blood in patients "after removal of an adenoma", measured under varying circumstances – night versus day, basally versus dexamethasone, standing up versus lying down – is essentially different from the regulation of aldosterone in patients before the removal of an adenoma. Moreover it was found that there is a striking agreement in the behaviour of aldosterone in patients "after removal of an adenoma" and that in patients with idiopathic aldosteronism.

In chapter V the differences in the diurnal plasma aldosterone concentrations in 8 patients with adenomatous (APA) and 4 with idiopathic aldosteronism (IHA), were featured by the following findings. During the night the plasma aldosterone concentration in patients with APA was noticeably higher than in patients with IHA, and also during the day if the patients were resting in bed. But if the patients were out of bed by day there was no difference in the height of the aldosterone level in the two groups. In patients with APA the concentration of aldosterone in the plasma was especially under the influence of ACTH. This became clear from the day and night rhythms of the aldosterone concentrations that manifested a significant correlation with the concentrations of plasma cortisol. In patients with IHA on the contrary, the values of aldosterone and cortisol in the plasma were significantly correlated solely during the night. The values of aldosterone in the plasma were, during the day, significantly correlated with the renin activity in the plasma and, during the days on which the patients were out of bed, manifested significantly higher values than on the days when the patients were resting in bed. Therefore, plasma aldosterone concentrations in patients with IHA were during daytime predominantly under control of the renin angiotensin system.
The influence of short-lasting administration of dexamethasone on the day and night variations of aldosterone showed that, as was to be expected, the nocturnal aldosterone values in both groups were redu-

ced in particular The findings after administration of dexamethasone yielded no additional data that can contribute to a further differentiation between adenomatous and idiopathic aldosteronism Yet, in this connection an exception must be made. The influence of change of body posture from lying down to standing up during the morning of day 1, did not lead in the group with APA to a rise of the plasma aldosterone concentration, on the contrary, to what was observed in patients with IHA However, during administration of dexamethasone there was seen, under the influence of the same stimulus, for unexplained reasons, a definite rise of the plasma aldosterone concentration, comparable with that in patients with IHA

In chapter VI the value is assessed of short and long-lasting administration of dexamethasone for the scintigraphic localization of aldosterone-producing adenomas With the aid of the radiocholesterol compound ^{131}I-19-Iodocholesterol and short-lasting dexamethasone administration the adenoma was correctly localized in only 3 out of 8 patients, whereas with the more recent radiocholesterol compound ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol and long-lasting pretreatment with dexamethasone the adenoma was correctly localized in 8 out of the 9 patients, including 3 patients in whom, with the former procedure, no lateralization was established The importance of a long-lasting administration of dexamethasone resides in the fact that thereby an uptake of the radiocholesterol compound into the "normal" adrenal is blocked in a more effective manner than after short-lasting dexamethasone administration The uptake of radioactivity into the adrenal containing the adenoma has been found to be not blocked by long-lasting administration of dexamethasone

In chapter VII the results of treatment with the aldosterone antagonist spironolactone were compared with those of the weak potassium-saving diuretic amiloride, in order to gain more insight into the hypotensive action of spironolactone. Spironolactone (400 mg/day) and amiloride (40 mg/day) were given to 10 patients with primary aldosteronism (group I) and 10 patients with essential hypertension (group II). In patients with primary aldosteronism a greater fall of blood pressure occurred after treatment with spironolactone than after treatment with amiloride, whereas in patients with essential hypertension a comparable slight fall of blood pressure occurred. The decrease of body weight – as a measure for the depletion of volume – was greater after treatment with spironolactone than after treatment with amiloride in both group I and group II. In patients with primary aldosteronism, after both medicaments, qualitatively and quantitatively comparable changes of the plasma sodium and the plasma potassium were obser-

ved, which point to a similar degree of antimineralocorticoid activity. In group II the changes of plasma sodium and potassium were only small. Furthermore, it was noticed that in the group with primary aldosteronism the aldosterone excretion after treatment with spironolactone displayed a rise that was comparable with the aldosterone excretion after treatment with amiloride. This was remarkable as after treatment with spironolactone the plasma renin activity showed a considerably greater rise than after treatment with amiloride. This finding was interpreted as the consequence of a relative inhibition of the secretion of aldosterone by interference with the biosynthesis of this hormone. In the discussion the question is debated of to what extent the hypotensive action of spironolactone as well as having a diuretic and antimineralocorticoid effect, is also based on a specific antialdosterone effect.

In chapter VIII the morphological anomalies in the adrenals of patients with primary aldosteronism are discussed. The macroscopic adrenal pathology, measured by the weight of the adrenal and/or the size of the adenoma – showed only little agreement with the functional pathology, as measured by the secretion rate of aldosterone. The microscopic architecture of the adrenal adenomas was assayed according to the classical description of Neville and Symington. In 15 of the 19 adenomas the histological pattern was dominated by the zona fasciculata type of cells, while the most frequent anomaly in the adrenals of patients with idiopathic aldosteronism consisted of a focal or diffuse broadening of the zona glumerulosa. Also a remarkable finding was that the zona glomerulosa of the adrenal cortex lying outside the adenoma in the majority of the adrenals examined presented a diffuse broadening. In 4 of the 18 patients who were treated preoperatively with spironolactone the presence of intracellular eosinophile inclusion bodies ("spironolactone bodies") was demonstrated. There are good indications that these "spironolactone bodies" are the morphological expression of an inhibition of the biosynthesis of aldosterone under the influence of spironolactone. The presence of "spironolactone bodies" in the adrenal tissue of only 4 of the 18 patients who were treated with spironolactone, is possibly explained by differences in the duration in time of treatment and the time interval before the adrenal was removed. Finally, in this chapter, at the instigation of a woman patient with an aldosterone-producing carcinoma (chapter IX) a review is given of the pathological findings in this rare variant of primary aldosteronism.

In chapter IX a case report is presented of a woman patient with an aldosterone-producing carcinoma. This patient has in total developed on 3 occasions the syndrome of primary aldosteronism, 2 of which were

the sequel of a malignant tumor. In the literature no earlier report has been made of an aldosterone-producing carcinoma that has developed after removal of an aldosterone-producing adenoma. There are indications that the malignant tumor arose from heterotopic adrenal tissue localized in the right kidney.

In the Appendix the case histories of the patients are reported.

SAMENVATTING

In dit proefschrift worden enkele klinische en pathologische aspecten van „primair aldosteronisme" besproken aan de hand van studies die werden verricht bij 28 patienten. Er werd aandacht besteed aan zowel de individuele ziektengeschiedenissen van deze patienten (Appendix) als aan de samenvattingen van de belangrijkste aspecten daarvan (hoofdstukken III tot en met IX) De patienten werden verwezen naar de afdeling Inwendige Geneeskunde in de periode 1961-1979 Dit lange tijdsinterval heeft tot gevolg, dat een aantal gegevens (hoofdstukken III en VIII) slechts door retrospectief onderzoek verzameld kon worden, met alle beperkingen die aan dit soort van onderzoek inherent zijn. Anderzijds werden gegevens van prospectief onderzoek neergelegd in de hoofdstukken V, VI en VII

In hoofdstuk I zijn een aantal literatuurverwijzingen bijeengezet over de diagnostiek en behandeling van de adenomateuze en idiopathische vorm van primair aldosteronisme.

In hoofdstuk II wordt een beschrijving gegeven van methoden waarmee de gegevens werden verzameld betreffende die aspecten van „primair aldosteronisme" die in dit proefschrift bijzondere aandacht kregen Deze aspecten waren: „algemene klinische gegevens", „de diagnose primair aldosteronisme", „het dag en nacht rithme van de plasma aldosteron concentratie", „bijnier scintigraphie", „medicamenteuze behandeling", „operatie", „pathologie van de bijnier" en „klinische follow-up".

In hoofdstuk III worden anamnestische gegevens van de bestudeerde patienten vermeld, met enige nadruk op de eerste klachten en verschijnselen waarmee de ziekte debuteerde Het is opvallend dat een aantal patienten reeds langdurig een verhoogde bloeddruk hadden, alvorens de diagnose „primair aldosteronisme" definitief werd gesteld De bloeddruk was meestal ernstig verhoogd, zoals bleek uit het frequent optreden van complicaties, die daarvan het gevolg waren. Vervolgens wordt stilgestaan bij de invloed van zoutonthouding en zoutbelasting op de electrolyten in plasma en urine De adenomateuze vorm toont in vergelijking met de idiopathische, duidelijker tekenen van aldosteronisme waarmee ook het verschil in plasma renine activiteit tussen beide groepen in overeenstemming is. Uit vergelijking van effectieve medicamenteuze behandeling door spironolacton en door chirurgie bleek ook in onze studie dat het bloeddrukverlagend effect door spironolacton een voorspellende waarde heeft voor het te ver-

wachten behandelingsresultaat door chirurgie. De resultaten van chirurgische behandeling in deze groep patiënten tonen aan dat de ingreep, bij een langdurige follow-up, slechts bij een minderheid van de patiënten tot een blijvende normale bloeddruk leidt.

In hoofdstuk IV wordt het belang van zoutbelasting voor de diagnostiek van ,,primair aldosteronisme" aangetoond. Metingen van aldosteron in de 24-uurs urine onder diverse omstandigheden – na zoutbelasting, verandering van lichaamshouding, toediening van dexamethason – bleken echter niet bij te dragen tot een differentiatie tussen idiopathisch en adenomateus aldosteronisme. Het bleek daarentegen wel mogelijk om beide vormen van primair aldosteronisme te onderscheiden op basis van metingen van aldosteron in bloed gedurende de nacht en de dag. Deze gegevens vatten wij samen aan de hand van het gepubliceerde artikel in hoofdstuk V. In hoofdstuk IV wordt voorts melding gemaakt van het feit dat de regulatie van aldosteron in bloed bij patiënten ,,na verwijdering van een adenoom", gemeten onder verschillende omstandigheden – nacht vs dag, basaal vs dexamethason, staand vs liggend – essentiëel verschillend is met de regulatie van aldosteron bij patiënten vóór verwijdering van een adenoom. Bovendien bleek er een opvallende overeenkomst in het gedrag van aldosteron bij patiënten ,,na verwijdering van een adenoom" en dat bij patiënten met idiopathisch aldosteronisme.

In hoofdstuk V worden de verschillen in de diurnale plasma aldosteronconcentraties bij 8 patiënten met adenomateus (APA) en 4 met idiopathisch aldosteronisme (IHA), gemarkeerd door de volgende bevindingen. Gedurende de nacht was de plasma aldosteron concentratie bij patiënten met APA aanmerkelijk hoger dan bij patiënten met IHA, evenals gedurende de dag wanneer de patiënten bedrust hadden. Wanneer de patiënten echter gedurende de dag ,,op" waren was er geen verschil in de hoogte van aldosteronspiegels in de beide groepen. Bij patiënten met APA bleek de concentratie van aldosteron in plasma vooral onder invloed te staan van ACTH. Dit werd duidelijk uit het dag- en nachtritme van de aldosteronconcentraties, die een significante correlatie toonden met de concentraties van plasma cortisol. Bij patiënten met IHA, daarentegen, waren de waarden van aldosteron en cortisol in plasma, uitsluitend gedurende de nacht significant gecorreleerd. De waarden van aldosteron in plasma waren gedurende de dag significant gecorreleerd aan de renine activiteit in het plasma en toonden gedurende de dag waarop de patiënten ,,op" waren significant hogere waarden, dan op de dag waarop de patiënten bedrust hadden. De invloed van kortdurende toediening van dexamethason op de dag- en nachtvariaties van aldosteron toonde aan dat overeenkomstig de

verwachting, vooral de nachtelijke aldosteronwaarden in beide groepen werden gereduceerd. De bevindingen na toediening van dexamethason leverden geen additionele gegevens op die kunnen bijdragen tot een verdere differentiatie tussen adenomateus en idiopatisch aldosteronisme. In dit verband moet echter één uitzondering worden gemaakt. De invloed van verandering van lichaamshouding van liggen naar staan gedurende de ochtend van dag 1, leidde in de groep met APA niet tot een stijging van de plasma aldosteronconcentratie, in tegenstelling tot hetgeen bij patiënten met IHA werd waargenomen. Echter, tijdens de toediening van dexamethason werd onder invloed van dezelfde stimulus, om onverklaarde redenen, wel een stijging van de plasma aldosteronconcentratie gezien, vergelijkbaar met die bij patiënten met IHA.

In hoofdstuk VI wordt de waarde geëvalueerd van kort- en langdurige toediening van dexamethason voor scintigrafische localisering van aldosteronproducerende adenomen. Met behulp van de radiocholesterolverbinding ^{131}I-19-Iodocholesterol en kortdurende dexamethasontoediening werd bij slechts 3 van de 8 patiënten het adenoom correct gelocaliseerd, terwijl met de nieuwere radiocholesterolverbinding ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol en langdurige voorbehandeling met dexamethason het adenoom bij 8 van de 9 patiënten correct werd gelocaliseerd, inclusief 3 patiënten bij wie met de eerste procedure geen lateralisatie was vastgesteld. Het belang van een langdurige toediening van dexamethason is gelegen in het feit dat hierdoor een opname van de radiocholesterolverbinding in de „normale" bijnier op een meer effectieve wijze wordt geblokkeerd dan na kortdurende dexamethason toediening. De opneming van radioactiviteit in de adenoomhoudende bijnier blijkt door langdurige toediening van dexamethason niet te worden geblokkeerd.

In hoofdstuk VII werden de resultaten van behandeling met de aldosteron-antagonist spironolacton vergeleken met die van het zwakke kaliumsparende diureticum amiloride, teneinde meer inzicht te verkrijgen in de bloeddrukverlagende werking van spironolacton. Spironolacton (400 mg/dag) en amiloride (40 mg/dag) werden gegeven aan 10 patiënten met primair aldosteronisme (groep I) en 10 patiënten met essentiële hypertensie (groep II). Bij patiënten met primair aldosteronisme trad een grotere bloeddrukdaling op na behandeling met spironolacton dan na behandeling met amiloride, terwijl bij patiënten met essentiële hypertensie een vergelijkbaar geringe bloeddrukdaling optrad. De daling van het lichaamsgewicht – als een maat voor de volumedepletie – was na behandeling met spironolacton groter dan na behandeling met amiloride zowel in groep I als in groep II. Bij patiënten met primair aldosteronisme werden na beide medicamenten

kwalitatief en kwantitatief vergelijkbare veranderingen van het plasma natrium en het plasma kalium waargenomen die duidden op eenzelfde mate van antimineralocorticoide activiteit In groep II waren de veranderingen van plasma natrium en kalium slechts gering Voorts werd geconstateerd dat in de groep met primair aldosteronisme de aldosteronexcreties na behandeling met spironolacton een stijging vertoonden die vergelijkbaar was met de aldosteronuitscheiding na behandeling met amiloride Dit gegeven was opmerkelijk omdat na behandeling met spironolacton de plasma renine activiteit een aanzienlijk grotere stijging toonde dan na behandeling met amiloride Deze bevinding werd geduid als het gevolg van een relatieve inhibitie van de secretie van aldosteron door interferentie met de biosynthese van dit hormoon In de discussie wordt ingegaan op de vraag in hoeverre de bloeddrukverlagende werking van spironolacton, behalve op een diuretisch en antimineralocorticoid effect, ook berust op een specifiek anti-aldosteron effect

In hoofdstuk VIII worden de morfologische afwijkingen aan de bijnieren van patienten met primair aldosternisme besproken De macroscopische bijnierpathologie, gemeten aan het gewicht van de bijnier en/of grootte van het adenoom – toonde maar weinig overeenkomst met de functionele pathologie, zoals gemeten aan de secretie snelheid van aldosteron De microscopische architectuur van de bijnieradenomen werd getoetst aan de klassieke beschrijving van Neville en Symington In 15 van de 19 adenomen werd het histologisch beeld beheerst door cellen van het zona fasciculatatype, terwijl de meest frequente afwijking in de bijnieren van patienten met idiopathisch aldosteronisme bestond uit een focale of diffuse verbreding van de zona glomerulosa Een opmerkelijke bevinding was voorts dat de zona glomerulosa van de bijnierschors gelegen buiten het adenoom bij het merendeel van de onderzochte bijnieren een diffuse verbreding vertoonde Bij 4 van de 18 patienten die pre-operatief waren behandeld met spironolacton werd het voorkomen van intracellulaire eosinophiele insluitsels (spironolactone bodies") aangetoond Er zijn goede aanwijzingen dat deze „spironolactone bodies" de morfologische expressie zijn van een inhibitie van de biosynthese van aldosteron onder invloed van spironolacton Het voorkomen van „spironolactone bodies" in het bijnierweefsel van slechts 4 van de 18 patienten die met spironolacton werden behandeld, wordt mogelijk verklaard door verschillen in tijdsduur van behandeling en het tijdsinterval voordat de bijnier werd verwijderd Tenslotte wordt in dit hoofdstuk, naar aanleiding van een patiente met een aldosteronproducerend carcinoom (hoofdstuk IX) een literatuur overzicht gegeven van de pathologische bevindingen bij deze zeldzame variant van primair aldosteronisme

In hoofdstuk IX wordt een case report weergegeven van een patiënte met een aldosteronproducerend carcinoom. Deze patiënte heeft in totaal 3 maal het syndroom van primair aldosteronisme ontwikkeld, waarvan 2 maal tengevolge van een maligne tumor. In de literatuur werd niet eerder melding gemaakt van een aldosteronproducerend carcinoom dat zich heeft ontwikkeld na verwijdering van een aldosteronproducerend adenoom. Er zijn aanwijzingen dat de maligne tumor is ontstaan uit heterotopisch bijnierweefsel gelocaliseerd in de rechter nier.

In de Appendix worden de ziektegeschiedenissen van de patiënten vermeld.

APPENDIX

Patient 1 (♀, G-J, 17 10 25)

1 The patient is a 38 years old woman, who was referred to the department of internal medicine in May 1964, because of hypertension and spontaneous hypokalemia Two months earlier the patient was admitted to the department of neurology of a hospital elsewhere after a sudden loss of consciousness Examination had revealed a marked hypertension with blood pressure values varying from 220/120 to 280/180 mmHg A neurosurgical decompression was performed for a left sided intracerebral hemorrhage Hypokalemia, with plasma potassium values as low as 2 2 mmol/l, was repeatedly found and primary aldosteronism was suspected The patient's history did not reveal the presence of hypertension during any of her 3 pregnancies (1952, 1954, and 1958) She had been without complaints until a few months before the cerebrovascular accident, when she developed headache, fatigue, polyuria and nycturia Medical treatment with rauwolfia alkaloids at the department of neurology had decreased blood pressure to 165/105 mmHg Physical examination revealed a hemiparesis of the right arm and leg and an expressive aphasia Blood pressure was 175/105 mmHg Fundoscopy did not disclose the presence of exudates or hemorrhages Central venous pressure was normal (R-5 cm H_2O) No edema was found The heart was slightly enlarged Abdominal vascular bruits were absent Laboratory Urinalysis did not reveal glucosuria or proteinuria Plasma electrolytes sodium 141 mmol/l, potassium 3 2 mmol/l, chloride 105 mmol/l, and bicarbonate 26 9 mmol/l Renal function was unimpaired Roentgenography X-rays of the chest showed a slight increase of the heart size Intravenous pyelography did not disclose any abnormalities Seldinger arteriography of the renal arteries did not show abnormalities of the renal arteries After presacral gas insufflation, both adrenal glands were visualized the right adrenal gland appeared normal, while the left gland appeared to contain a round tumor with a diameter of 2 5 cm

2 Aldosterone secretion rates were measured before and after moderate sodium loading (table A-1) Assay for determination of PRA was not yet available in 1964 However, aldosteronism in the absence of known causes of secondary aldosteronism strongly suggested the presence of primary aldosteronism

Table A-1

Aldosterone secretion rates and additional clinical and biochemical findings in patient G-J

	SODIUM INTAKE	
	15 mmol/24 hr	115 mmol/24 hr
Blood pressure (mmHg)	172/114 (n=50)	
Sodium (mmol/l)	144	145
Potassium (mmol/l)	3 4	3 1
Creatinine (μmol/l)	–	58
UV sodium (mmol/24 hr)	5	42
UV potassium (mmol/24 hr)	37	51
ASR (μg/24 hr)	396	370

6 On September 8th 1964, the adrenal glands were surgically explored via a median abdominal incision The left adrenal gland appeared to contain a tumor and was removed in toto The gallbladder was also removed because of a cholelithiasis

7 The surgically removed adrenal gland contained a yellow tumor whose greatest diameter was 2 cm The tumor was sharply separated from the surrounding adrenal cortex Light microscopy the tumor was composed of large clear cells with vacuolated cytoplasm and round nuclei, which varied in size The cells were arranged in solid fields, separated by thin septa of connective tissue, or in columns Focally, cells with a more eosinophilic and nonvacuolated cytoplasm were found The adjacent adrenal cortex showed an atrophic zona glomerulosa Conclusion Adrenocortical adenoma composed of zona fasciculata-type cells Focally, zona reticularis-type cells Atrophy of the zona glomerulosa in the adjacent cortex

8 Aldosterone secretion rates were measured clinically, one month after operation ASR measured

during a sodium-restricted diet was 292 µg/24 h Blood pressure decreased to 105-120/70-95 mmHg and remained normal without the use of antihypertensive medicaments In 1969, 5 years after operation, blood pressure was 130/95 mmHg and the patient was discharged from further control visits At that time her neurologic symptoms had markedly improved

Patient 2 (♂, Br, 31 05 17)

1 The patient is a man aged 44 years, who in November 1961 was referred to the department of internal medicine Since five years he had a history of severe, increasing hypertension, for which he had received no medicamentous treatment He had been admitted to a hospital elsewhere on account of dizziness, headache and a transitory motor aphasia At that time the blood pressure was 240/110 mmHg and the renal function had deteriorated The patient complained of headache and pain in the chest on effort He also had a period of visual disturbances and difficulty in walking The blood pressure was 245/115 mmHg On fundoscopy exudates and retinal edema were found The plasma mineral spectrum showed hypernatremia (150 and 146 mmol/l) and hypokalemia (2 6 and 3 0 mmol/l) The IVP and the lumbar aortography revealed no anomalies in the kidneys or the renal arteries During treatment with guanethidine and reserpine (1962-1964) the blood pressure fell off to 150/110 in the supine and 100/80 mmHg in the upright position In 1964 the patient was admitted to the clinic for determinations of the aldosterone secretion rate and for retroperitoneal insufflation of gas In the latter examination suspicion of a tumor of 3 5 cm in the left adrenal was expressed

2 The aldosterone secretion rate was measured during continuous use of antihypertensive medication (reserpine and hydralazine) In the table A-2 are arranged the values of the aldosterone secretion rate, determined during the taking of 0 and 6 grams of salt, and presented together with some other parameters The very high secretion values during a salt-restrictive diet were found to be not suppressible after moderate salt loading so that the diagnosis of primary aldosteronism was made

Table A-2

Aldosterone secretion rates and additional clinical and biochemical findings in patient Br

	SODIUM INTAKE	
	15 mmol/24 hr	115 mmol/24 hr
Blood pressure (mmHg)	225/136 (n=33)	
Sodium (mmol/l)	139	142
Potassium (mmol/l)	3 0	2 5
Creatinine (µmol/l)	221	248
UV sodium (mmol/24 hr)	17	67
UV potassium (mmol/24 hr)	29	60
ASR (µg/24 hr)	1255	1257

6 On December 16th 1964 both adrenals were explored by operation through a median incision in the upper abdomen The left adrenal was found to contain an adenoma 2 cm in size and the left adrenal was removed in toto

7 The weight of the adrenal was 30 grams On dissection a second node 2 mm in size was found in the adrenal cortex Light microscopy the adenoma was composed of large cells with foamy cytoplasm and a small round nucleus The cells were indistinguishable from the type that is encountered in a normal zona fasciculata Sections of the adrenal cortex lying outside the adenoma showed a narrow zona glomerulosa The zonae fasciculata and reticularis ranged from normal to widened Conclusion adenoma consisting of cells of the zona fasciculata-type

8 The blood pressure remained raised after operation During the stay in the clinic, one month after operation, an average value of 178/127 mmHg was found The plasma mineral spectrum was normalized and the aldosterone secretion rate had fallen to normal values (225 and 154 µg/24 hr, during salt-free diet and with 6 grams of salt respectively) At the policlinical controls from 1964 to 1971 the blood pressure remained seriously raised in spite of the medicamentous treatment At the

end of 1970 the patient was admitted to the clinic because of repeated subcoma with transitory paralyses, speech disorders and a rapidly deteriorating renal function Death occurred on June 14th 1971.

Patient 3 (♂ v W, 19 07 22)

1. The patient is a man aged 49 years, who was referred to the department of nephrology in February 1971 for analysis and treatment of hypertension Blood pressure was found to be raised in 1967, when he complained of fatigue From 1961 on he had developed complaints of headache in the early morning Hypertension analysis by another internist had revealed a marked hypertension (230/140 mmHg), an impairment of renal function (creatinine 206 µmol/l), an increase of heart size (heart-to-lung quotient: 18.35) and hypertensive retinopathy (hemorrhages) Antihypertensive treatment with rauwolfia alkaloids, had been unsuccessful In January 1971 the patient developed a transient ischemic attack with speech disturbances and paresis of the right arm and leg. On admission the patient complained of fatigue, headache, drowsiness, polydipsia and nycturia Physical examination Blood pressure 260/170 mmHg Central venous pressure was R-6 cm H_2O No edema was found Fundoscopy revealed arteriovenous nicking and segmental constriction of the arterioles Hemorrhages and exudates were absent There were no abdominal bruits Laboratory. Urinalysis revealed a mild proteinuria of less than 1 g/24 hr Urine sediment was normal Urine culture remained sterile Plasma electrolytes sodium 143 mmol/l, potassium 2 5 mmol/l, chloride 98 mmol/l and bicarbonate 33 2 mmol/l Creatinine 268 µmol/l The endogenous creatinine clearance was diminished to 38 ml/min. An oral glucose tolerance test showed a decreased carbohydrate tolerance. Roentgenography X-rays of the chest showed a heart-to-lung quotient of 15 5:34 5. An intravenous pyelogram revealed a diminished excretion of the contrast material on both sides The left kidney measured 12 5x6 cm and the right kidney 12x5 5 cm Seldinger arteriography disclosed no abnormalities of the renal arteries. Electrocardiography sinus rhythm with signs of left strain, ST-segment depression and T-inversion in leads I, II, AVL, AVF and V1-V4

2. Aldosterone secretion rates were measured before and after moderate sodium loading (table A-3). For the interpretation of the results it should be noted that the measurements were performed during the use of antihypertensive treatment (rauwolfia alkaloids, guanethidine, methyldopa and chlorthalidone) The findings were in accordance with the diagnosis of primary aldosteronism An impairment of renal function of unknown origin, might also have contributed to the development and maintenance of hypertension.

Table A-3.

Aldosterone secretion rates and additional clinical and biochemical findings in patient v W

	SODIUM INTAKE	
	15 mmol/24 hr	115 mmol/24 hr
Blood pressure (mmHg)	186/123 (n=10)	
Sodium (mmol/l)	142	144
Potassium (mmol/l)	3 8	3 0
Creatinine (µmol/l)	197	200
UV sodium (mmol/24 hr)	27	153
UV potassium (mmol/24 hr)	130	163
UV creatinine (mmol/24 hr)	17.3	18 9
PRA (ng/10 ml/3 hr)	<15	-
ASR (µg/24 hr)	1750	429

5 Clinical treatment with spironolactone 400 mg/day for 3 weeks resulted in an increase of blood pressure from 186/123 mmHg (= the mean blood pressure value that was reached with other antihypertensive agents) to 203/141 mmHg (n=6).

6 On May 4th 1971 the right adrenal gland was surgically explored by a right lumbotomy The gland had to be detached from the perirenal adipose tissue and from the diaphragm No adrenal tumor was

found on palpation of the gland Subsequently the left adrenal gland was explored by a left lumbotomy The left gland was normal in size and a tumor could be easily palpated The left gland was surgically removed

7 The adrenal gland measured 7x4x1 5 cm and weighed 9 gram The cut surface showed, besides a yellow tumor of 1 4 cm, several other small adrenocortical nodules Light microscopy The adrenal adenoma was neither surrounded by a capsule nor sharply separated from the surrounding tissue The tumor was composed of small eosinophilic cells with an alveolar arrangement These cells frequently contained spironolactone bodies Large clear cells, as found normally in the zona fasciculata, were located in the periphery of the tumor The tumor gradually shaded off into the adjacent adrenal cortex The adrenal cortex was widened and composed of zona fasciculata and zona reticularis cells, while the zona glomerulosa was only focally present

8 The postoperative period was complicated by clinical shock and anuria on the day after operation, most probably caused by mineralocorticoid deficiency Plasma sodium was 127 mmol/l and plasma potassium 6 0 mmol/l The patient was successfully treated with massive doses of mineralocorticoids Subsequently the patient developed prolonged fever and, probably, pulmonary embolism, for which he was treated with heparin and oral anticoagulants On discharge from hospital, blood pressure values were still raised 152/117 mmHg (n=7) Urinary aldosterone excretion, measured on the fifth day after operation had decreased to 1 5 γ/24 hr Subsequently, blood pressure responded satisfactorily to medical treatment with chlorthalidone, hydralazine and propranolol Plasma creatinine showed a gradual decrease to 155 μmol/l On January 14th 1977, 6 years after operation, the patient died suddenly Post mortem examination was not performed Blood pressure, measured one month before death, was 112/95 mmHg

Patient 4 (♂, F. 11 04 26)

1 The patient is a 46 years old medical doctor, who visited the department of nephrology in August 1972 Hypertension had been detected in 1970 (160/120 mmHg) He had taken many antihypertensive medicaments (chlorthalidone, alprenolol, propranolol, oxprenolol, clonidine, methyldopa), without any effective decrease of blood pressure, but with many side effects The patient had also taken prednisone 10 mg/day for several months, because he supposed himself to be suffering from a temporal arteritis A biopsy taken from a temporal artery however, had been completely normal During prednisone treatment he had experienced a marked subjective improvement and a decrease of blood pressure to levels as low as 130/80 mmHg, with a return of hypertension after discontinuation of this therapy His previous history revealed a hepatitis-B infection in 1953, and a laminectomy in 1963 for a hernia nuclei pulposi Antihypertensive therapy at his first visit chlorthalidone 100 mg/day, triamterene 50-100 mg/day and prednisone 5-10 mg/day He complained of fatigue and headache Nycturia, polydipsia, tetany, muscle weakness and paresthesia were absent At the first visit blood pressure was 190/110 mmHg He had a slight Cushing face The pulse rate was irregular, due to premature beats Central venous pressure was normal No edema was found The heart was not enlarged No abdominal vascular bruits were heard over the abdomen Fundoscopy revealed no

Table A-4

Aldosterone secretion rates and additional clinical and biochemical findings in patient F

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		155/103 (n=13)	
Sodium (mmol/l)	143	146	144
Potassium (mmol/l)	3 2	3 5	3 5
Creatinine (μmol/l)	84	84	86
UV sodium (mmol/24 hr)	52	220	196
UV potassium (mmol/24 hr)	110	123	195
UV creatinine (mmol/24 hr)	20	18 6	18 3
PRA (ng/10 ml/3 hr)	15	–	–
ASR (μg/24 hr)	–	516	408

abnormalities Laboratory Urine negative for protein and glucose Urine culture remained sterile Plasma electrolytes sodium 144 mmol/l potassium 2 4 mmol/l chloride 96 mmol/l and bicarbonate 24 2 mmol/l Renal function was unimpaired Electrocardiography showed a sinus rhythm with U-waves Premature beats arising from two different ventricular foci were seen Roentgenography of the chest showed a heart-to-lung quotient of 13 5 33 5 The IVP was normal Seldinger arteriography of the renal arteries showed a minimal stenosis of the right renal artery at 3 cm from its origin This stenosis was considered to be of no hemodynamic importance

2 The finding of elevated aldosterone secretion rates before and after sodium loading, concurrent with a low PRA, confirmed the diagnosis of primary aldosteronism (table A-4)

3 Diurnal rhythms of plasma aldosterone (figure A-1) were determined, 6 years after resection of a small adrenocortical adenoma of 0 8 cm Plasma aldosterone values were low and showed only slight variations during the night and during daytime The correlation coefficients between the basal values of the three adrenocortical hormones showed an almost equal influence of ACTH on the regulation of the three hormones, both during the night and during the night, days 1 and 2

		night (n=11)		night days 1 and 2 (n=17)	
Aldosterone	vs cortisol	0 85	(p<0 001)	0 81	(p<0 001)
Aldosterone	vs 18-OH-DOC	0 91	(p<0 001)	0 76	(p<0 001)
Cortisol	vs 18-OH-DOC	0 93	(p<0 001)	0 95	(p<0 001)

Dexamethasone treatment only slightly reduced the mean nocturnal plasma aldosterone value from 5 7 ng/100 ml to 4 3 ng/100 ml Daytime aldosterone values remained essentially unchanged under dexamethasone

5 Treatment with spironolactone 400 mg/day for 4 weeks, resulted in a normalization of blood pressure Blood pressure measurements at the weekly control visits showed the following values 170/110, 160/105, 120/85, 125/80 mmHg *

6 On August 16th 1973 the right adrenal gland was explored via a right lumbotomy and appeared normal on palpation Half of the right adrenal gland was resected Subsequently, the left adrenal gland was removed in toto via a left lumbotomy, although no tumor could be palpated

7 On dissection of the left adrenal gland, a small adrenocortical adenoma was found, with a maximal diameter of 0 8 cm The tissue removed from the right adrenal gland looked normal upon dissection Light microscopy the adrenocortical adenoma was sharply separated from the adjacent cortex and was composed of relatively small eosinophilic cells arranged in alveolar fields Almost every cell contained one or two laminated cytoplasmic inclusions, surrounded by a clear halo (spironolactone bodies) The adrenal cortex outside the tumor showed a slightly nodular architecture caused by an increase of both the zona glomerulosa and the zona fasciculata The zona glomerulosa cells of the adjacent cortex also contained spironolactone bodies but less abundantly than the tumor did
The adrenal tissue from the right adrenal gland showed an adrenal cortex varying in width, with a normal zonation into three layers At several places the zona glomerulosa cells contained spironolactone bodies Conclusion Adrenocortical adenoma composed of zona glomerulosa-type cells A slightly nodular hyperplasia of the adjacent adrenal cortex of the left gland Spironolactone bodies in the tumor cells and, to a lesser extent, in the zona glomerulosa cells of the left and the right adrenal cortex

* Spironolactone was withdrawn on August 6th 1973 and on August 10th the patient was admitted to hospital Plasma aldosterone values were determined on August 15th after 5 days of a 115 mmol sodium diet At that time blood pressure was normal (130/80 mmHg) plasma sodium was 147 mmol/l and plasma potassium 4 5 mmol/l Remarkably plasma aldosterone values were low both at 09 00 hr in the supine position (4 9 ng/100 ml) and after 3 hours of ambulation at 12 00 hr (12 6 ng/100 ml) It might be that these low aldosterone values were caused by an interference of aldosterone biosynthesis with spironolactone The finding of spironolactone bodies in the adrenal glands, surgically removed on August 16th (see also 7) is in accordance with this supposition, as has been discussed in chapter VIII

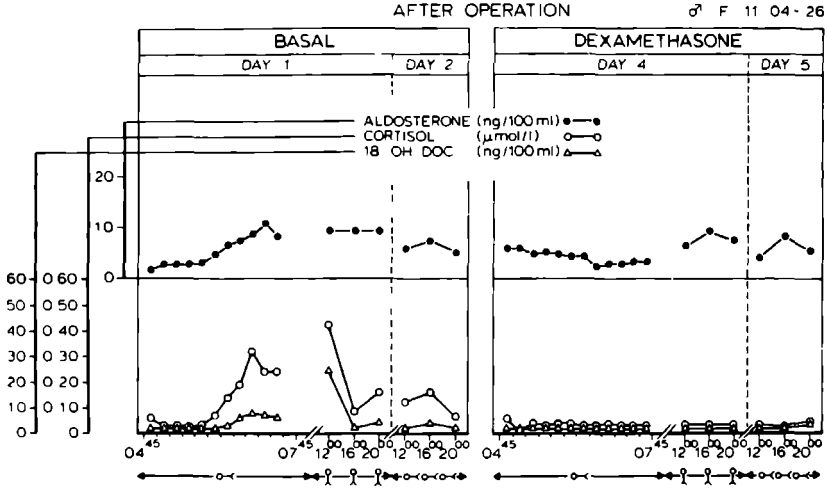


Figure A-1 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient F, 6 years after resection of an adenoma

8 Six weeks after operation, the patient was admitted to hospital for postoperative evaluation Blood pressure was 134/88 mmHg, plasma sodium 140 mmol/l, and potassium 4 2 mmol/l Aldosterone secretion rate measured after a 115 mol sodium diet for 5 days, was 32 µg/24 hr Blood pressure values measured during a clinical observation in 1979, 6 years after operation (see also 4), were normal (132/89 mmHg, n=7) without antihypertensive treatment

Patient 5 (♀, Ba, 29 12 20)

1 The patient is a 46 years old woman, who was referred to the department of internal medicine in September 1966 A few months earlier she had visited a cardiologist elsewhere complaining of backache Physical examination had revealed hypertension (190/115 mmHg) and enlargement of the thyroid gland The patient was referred to our institute for evaluation of thyroid function At her first visit she complained of nervousness and weight loss of 9 kg in the last 6 months, despite a good appetite She had a marked polyuria, polydipsia and nycturia For 3 years she had had ankle edema in the evening There were no complaints of headache paresthesia or muscle weakness Her previous history recorded an orthopedic operation of the lumbar spine in 1950 and an appendectomy in 1964 She had never been pregnant and had not used oral contraceptive agents Physical examination revealed a nervous woman without overt signs of hyperthyroidism Body weight 82 3 kg Height 1 70 m Central venous pressure was R-6 5 cm H_2O No edema was found Blood pressure was 190/105 mmHg The thyroid gland was not enlarged but contained a small solitary nodule No pathologic lymph nodes were found The heart was slightly enlarged and an early systolic souffle was heard over the apex Abdominal bruits were absent Fundoscopy revealed no signs of hypertensive retinopathy Laboratory Urinalysis no abnormalities Plasma electrolytes sodium 143 mmol/l, potassium 2 8 mmol/l, chloride 103 mmol/l, bicarbonate 30 3 mmol/l Renal function was unimpaired PBI was normal After oral glucose loading a slightly diminished carbohydrate tolerance was detected Roentgenography of the chest showed a heart-to-lung quotient of 13 5 28 5 The IVP revealed a normal excretion of the contrast material on both sides In both kidneys small renal calculi were found The adrenal glands were not visualized after presacral insufflation of gas Electrocardiography sinus rhythm with ST T depressions in leads I, AVL, and V4-V6 No signs of left ventricular hypertrophy

2 Aldosterone secretion rates were measured
a In February 1967
b In April 1967 after surgical removal of the left adrenal and half of the right adrenal gland

c In August 1967 before cholecystectomy and exploration of the remaining half of the right adrenal gland
d In September 1967 after cholecystectomy and surgical failure to remove the adrenal remnant
e In February 1974 before pyelotomy of the right kidney (for obstructive renal disease) and successful removal of an aldosterone-producing adenoma
The results of the clinical evaluation in February 1967 (table A-5) revealed a mild hypertension, hypokalemia, hyporeninemia and aldosteronism after moderate sodium loading These findings were in accordance with the diagnosis of primary aldosteronism For a comment on the findings mentioned under the headings b, c, d and e, see "follow-up" (8)

5 Medical treatment with aminoglutethimide (an inhibitor of adrenal steroidogenesis) at a dosage of 750 mg/day was given from October 1967 to February 1974 Aminoglutethimide as used in this dosage did not significantly lower the blood pressure Plasma potassium values however, were markedly higher during treatment

	without treatment (during stay in the clinic from August to October 1967)	aminoglutethimide 750 mg/day (from October 1967 to February 1974)
P systolic	156 6(130 190)n=24	153 3(125-185)n=48
P diastolic	103 5(85-130)n=24	99 2(85-120)n=48
Plasma Na^+	142 8(140 145)n=10	143 1(137-149)n=35
Plasma K^+	2 2(1 7 2 7)n=10	3 4(2 7-4 6)n=35

Absence of a significant blood pressure lowering effect during this treatment was acceptable in view of the relatively mild hypertension There were no side effects Polydipsia nycturia and muscle weakness disappeared during treatment

6 a On February 24th 1967 both adrenal glands were explored through a transverse abdominal incision The right adrenal gland was normal in size and no tumor could be palpated Subsequently the left adrenal gland was explored and appeared also to be normal in appearance and on palpation The left adrenal was removed in toto while half of the right gland was resected
b On August 8th 1967 a cholecystectomy was performed because of cholelithiasis, recurrent gallstone colics and jaundice The surgeon was asked to remove the remnant of the right adrenal gland A tissue fragment suspected of adrenal tissue was resected
c On February 14th 1974 a pyelotomy of the right kidney was performed after a lumbotomy below the 12th rib Two renal calculi were removed Subsequently the suprarenal region was explored and adrenal tissue containing a tumor was found just below the liver The removed adrenal tissue contained a classical yellow tumor

7 a After dissection of the left adrenal gland and the partially resected right adrenal gland, no tumor was found The macroscopic aspect of the adrenal cortex was normal Light microscopy The adrenal cortex of the left gland did not show the characteristics of micronodular hyperplasia Focally, however the zona glomerulosa was widened extending inward in a tongue-like manner The microscopic findings of the right gland were identical with those of the left gland
b The removed fragments did not contain adrenal tissue
c Macroscopy a yellow tumor with a maximal diameter of 1 cm and several adrenal tissue fragments, together measuring 10x8x6 mm Inspection of the lamellated gland showed a diffuse adrenocortical hyperplasia Light microscopy The fragmented adenoma was partially surrounded by a thin capsule and was composed of clear cells of the zona fasciculata-type In between these cells, so-called "hybrid cells were found while focally also zona glomerulosa cells were present At several levels, a gradual transition of clear cells into dark eosinophilic cells (zona reticularis-type cells) was noted The adrenal cortex outside the tumor showed a normal architecture with a focal widening of the zona glomerulosa Conclusion Adrenocortical adenoma of the right gland composed of four different cell types

8 The effects of subtotal adrenalectomy were evaluated in March-April 1967 Clinical and biochemical data are presented in table A 5b Although blood pressures were somewhat lower than before operation aldosterone secretion rates were still markedly elevated, concurrently with hypernatremia,

Table A-5

Aldosterone secretion rates and additional clinical and biochemical findings in patient Ba

	a January 1967 sodium intake		b April 1967 sodium intake	
	15 mmol/24 hr	115 mmol/24 hr	15 mmol/24 hr	115 mmol/24 hr
Medicaments	–	–	–	–
Blood pressure (mmHg)	151/96 (n=8)		127/84 (n=6)	
Sodium (mmol/l)	142	144	145	141
Potassium (mmol/l)	3 2	2 3	3 3	3.4
Creatinine (μmol/l)	64	–	54	44
UV sodium (mmol/24 hr)	29	89	14	144
UV potassium (mmol/24 hr)	60	74	73	97
UV creatinine (mmol/24 hr)	11 5	10 7	8 8	8 6
PRA (ng/10 ml/3 hr)	57	<28	86	43
ASR (μg/24 hr)	732	551	617	329

Table A-5 (continued)

Aldosterone secretion rates and additional clinical and biochemical findings in patient Ba

c August 1967 sodium intake		d September 1967 normal diet			e February 1974 sodium intake
15 mmol/24 hr	115 mmol/24 hr				115 mmol/24 hr
–	–	–	dexametha-sone 2 mg/day	amino-glutethimide 750 mg/day	–
141/95 (n=6)		160/107 (n=3)	172/115 (n=3)	172/115 (n=2)	173/102 (n=2)
141	143	143	140	143	140
2 4	2 4	2 3	1 8	3 0	2 6
–	–	–	–	–	52
18	90	215	194	70	117
57	119	–	–	–	90
9 3	9 5	–	–	–	13 2
–	–	–	–	–	31
788	864	466	375	236	835

hypokalemia and hyporeninemia In August 1967 the patient was admitted to the hospital for observation of unexplained abdominal pain Signs and symptoms of primary aldosteronism were unaltered (table A -5c) Subsequently, a cholecystectomy was performed, after the patient had developed typical gallstone colics and jaundice Unfortunately, the surgeon could not trace the remnant of the right adrenal gland, despite a careful exploration of the right suprarenal region The failure was apparent on histologic examination of the removed tissue and the postoperative determination of aldosterone secretion rate (table A-5d) It was therefore decided to treat the patient medically with aminoglutethimide The presence of glucocorticoid remediable aldosteronism was excluded, since treatment with dexamethasone 2 mg/day for 10 days did not reduce the aldosterone secretion rate to normal values (table A-5d) In February 1974 the patient was admitted to hospital because of recurrent renal colics After discontinuation of aminoglutethimide, the aldosterone secretion rate appeared still markedly elevated (table A-5e) One month after operation aldosterone secretion rate was measured during a 115 mmol sodium diet and concurrent adrenal substitution therapy with cortisone 25 mg/day and 9-α-fluorohydrocortisone 0 1 mg/day The findings of a low secretion rate (4 μg/24 hr), a normal blood pressure (117/78 mmHg, n=3) and normal plasma electrolytes were in accordance with the successful resection of an aldosterone-producing adenoma Blood pressure values remained normal during the follow-up period of 6 years (averaging 138/84 mmHg, n=32)

Patient 6 (♀, vd V, 18 05 41)

1 The patient is a woman aged 32 years who was referred to the department of endocrinology on March 20th 1973 A tentative diagnosis of primary aldosteronism had been made by an internist elsewhere On December 7th 1972 the patient was admitted to a hospital elsewhere because of headache, vomiting and tetany Blood pressures varied from 180/100 to 200/120 mmHg Hypernatremia (140-147 mmol/l) and hypokalemia (2 8-3 3 mmol/l), resistent to potassium suppletion, were repeatedly found On admission to our institute the patient complained of headache and nycturia (2-3x) She had no edema or muscle weakness Her previous history was uneventful She had never been pregnant and she had never used oral contraceptives Physical examination Blood pressure on admission was 210/140 mmHg Central venous pressure R-4 cm H_2O No edema The heart was not enlarged Fundoscopy except for a few crossing phenomena, no abnormalities Vascular bruits over the abdomen were not found Laboratory no proteinuria or glucosuria was found Urine culture remained sterile Sodium 144 mmol/l potassium 2 7 mmol/l Renal function was unimpaired An oral glucose tolerance test showed a diminished carbohydrate tolerance, probably as a result of hypokalemia Roentgenography The heart-to-lung quotient was normal The IVP showed no abnormalities Seldinger arteriography of the renal arteries did not reveal renal artery stenosis The adrenal glands were not visualized Adrenal venography Catheterization of the right adrenal vein was unsuccessful, while venography of the left adrenal gland did not reveal the presence of a tumor After retroperitoneal gas insufflation the right adrenal gland was visualized and appeared to be normal The left adrenal gland was not visualized

2 The elevated aldosterone secretion rates measured at a sodium intake of 115 mmol/day (1973 and 1974) and at a sodium intake of 315 mmol/day (1974) concurrently with hypertension, hypokalemia and hyporeninemia, established the diagnosis of primary aldosteronism (table A-6)

Table A-6

Aldosterone secretion rates and additional clinical and biochemical findings in patient vd V

		March 1973 sodium intake		Jan 1974 sodium intake	April 1974 sodium intake
	15 mmol/ 24 hr	115 mmol/ 24 hr	315 mmol/ 24 hr	115 mmol/ 24 hr	315 mmol/ 24 hr
Blood pressure (mmHg)		184/125 (n=12)		158/108 (n=13)	162/113
Sodium (mmol/l)	146	148	149	145	143
Potassium (mmol/l)	3 2	2 7	2 7	3 7	3 2
Creatinine (μmol/l)	55	56	46	96	70
UV sodium (mmol/24 hr)	4	224	400	121	260
UV potassium (mmol/24 hr)	41	55	91	96	59
UV creatinine (mmol/24 hr)	8 2	9 0	11 0	12 6	7 6
PRA (ng/10 ml/3 hr)	21	–	–	58	–
ASR (μg/24 hr)	–	248	–	281	555

3 Three years after resection of the right adrenal gland diurnal rhythms of plasma aldosterone were determined (figure A-2) Plasma aldosterone levels during the night averaged 6 4 ng/100 ml Aldosterone showed an increase in response to ambulation in the morning Daytime supine aldosterone values were lower than the corresponding daytime upright values The correlation coefficients between the basal values of the three adrenocortical hormones showed that ACTH played an important role in the regulation of aldosterone concentration during the night, not, however, during night, days 1 and 2

		night (n=12)		night, days 1 and 2 (n=18	
Aldosterone	vs cortisol	0 67	(p<0 01)	0 27	(n s)
Aldosterone	vs 18-OH-DOC	0 85	(p<0 001)	0 35	(n s)
Cortisol	vs 18-OH-DOC	0 85	(p<0 001)	0 95	(p<0 001)

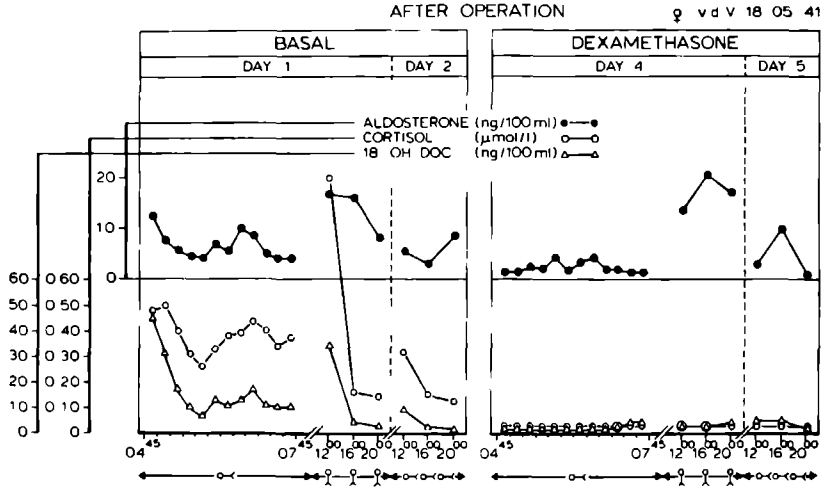


Figure A-2 Diurnal variations of plasma aldosterone, cortisol and 18-OH DOC in patient vd V 3 years after resection of an adenoma

Dexamethasone treatment reduced mean nocturnal aldosterone concentration to 2 4 ng/100 ml Daytime aldosterone values remained essentially unchanged during dexamethasone treatment

4 Adrenal scintigraphy was performed with ^{131}I-19-Iodocholesterol during suppression with dexamethasone Dexamethasone was given at a dose of 4 mg/day starting 3 days before injection of the radiopharmaceutical which was given at a dose of 2 1 mCi Accumulation of radioactivity in the right adrenal gland was found on the 3rd 5th and 6th days after injection The left adrenal gland was not visualized

5 Clinical treatment with spironolactone 400 mg/day resulted in a decrease of blood pressure from 184/125 (n=12) to 130-140/90-100 mmHg After discharge from hospital the dosage of spironolactone was reduced to 200 mg/day Blood pressure was maintained at a level of 140-150/100-105 mmHg during a treatment period of 5 months The patient experienced no side effects of spironolactone treatment

6 On April 4th 1974, the right adrenal gland was explored by lumbotomy at the height of the 12th rib which had to be surgically removed The right adrenal gland was resected after palpation of a large adenoma

7 The right adrenal gland harbored a yellow-green adenoma with a maximal diameter of 2 cm The adrenal gland weighed 11 5 g Lightmicroscopy the large nodule was partly encapsulated and at some levels not clearly separated from the surrounding adrenal tissue Peripherally the tumor was composed of large clear polygonal cells Towards the middle of the tumor the cells showed a more eosinophilic and foamy cytoplasm containing pigment granulae The nuclei of these cells showed a marked anisokaryosis Spironolactone bodies were not found Mitoses were sporadically present The adrenal cortex outside the tumor showed focally a nodular architecture Both clear cells and small eosinophilic cells were found Conclusion adrenocortical adenoma composed of zona fasciculata and zona reticularis cells Micronodular hyperplasia of the adrenal cortex outside the tumor

8 Blood pressure and aldosterone secretion rate were evaluated during a clinical observation 3 weeks after operation Blood pressure had decreased to 130/94 mmHg (n=7) Plasma electrolytes were normal and aldosterone secretion rate measured during a 115 mmol sodium diet, was 39 µg/24 hr At regular control visits during a follow-up period of three years diastolic blood pressures measured without antihypertensive treatment, remained slightly elevated, varying form 90 to 105 mmHg

Patient 7 (♀, O-K, 25 02 19)

1 The patient woman was referred to the department of endocrinology in March 1974, when she was 55 years old She was known to have been hypertensive for 18 years and had been treated with methyldopa and chlorthalidone In 1973 she was referred to an internist elsewhere, because of progressive fatigue and an unsatisfactory response of blood pressure to medical treatment Hypertension analysis had revealed a blood pressure of 170/120 mmHg, persistent hypokalemia (2 2 and 2 8 mmol/l), hypernatremia (146 and 147 mmol/l) and a suppressed plasma renin activity Treatment with spironolactone 200 mg/day had resulted in a fall of blood pressure to 135/95 mmHg The tentative diagnosis of primary aldosteronism was made and the patient was referred to our institute for further analysis and treatment Her previous history recorded recurrent epileptic insults since the age of 21, and urinary tract infections with roentgenologic characteristics of a chronic pylonephritis of the right kidney Blood pressure had been normal during each of her four pregnancies At her first visit she complained of headache, fatigue, muscle weakness, ankle edema, nycturia, paresthesia and palpitations In 1973 a cholecystectomy was performed with postoperative paroxysmal atrial fibrillation Blood pressure at the first visit was 180/120 mmHg Fundoscopic examination revealed no signs of hypertensive retinopathy Central venous pressure was normal (R-5 cm H_2O) and edema was absent The heart was slightly enlarged No vascular abdominal bruits were heard Laboratory Urine culture remained sterile The urine contained no protein or glucose Plasma electrolytes were markedly disturbed sodium 146 mmol/l potassium 2 1 mmol/l Renal function was unimpaired Electrocardiography sinus rhythm with marked U-waves Roentgenography of the chest gave a heart-to-lung quotient of 14 5 29 Intravenous pyelography showed a dilation of pelvis and calyces on either side The renal parenchyma, however, was not reduced and both kidneys were of normal size

2 Clinical measurements of aldosterone secretion rates before and after sodium loading established unequivocally the diagnosis of primary aldosteronism (table A 7)

Table A-7

Aldosterone secretion rates and additional clinical and biochemical findings in patient O-K

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol 24 hr
Blood pressure (mmHg)		154/100 (n=10)	
Sodium (mmol/l)	143	144	145
Potassium (mmol/l)	2 2	1 9	2 2
Creatinine (µmol/l)	61	67	62
UV sodium (mmol/24 hr)	10	118	341
UV potassium (mmol/24 hr)	63	92	153
UV creatinine (mmol/24 hr)	11 1	10 1	11 0
PRA (ng/10 ml/3 hr)	25	–	–
ASR (µg/24 hr)	–	1944	1721

3 Diurnal rhythms of plasma aldosterone (figure A 3) were determined in 1978, 4 years after surgical resection of an aldosterone-producing adenoma of the left adrenal gland and subsequent disappearance of signs and symptoms of primary aldosteronism Plasma aldosterone values during the night averaged 13 1 ng/100 ml and showed little variation A slight increase of aldosterone in response to upright posture was observed Daytime supine values were lower than the corresponding upright values The correlation coefficients between the basal values of aldosterone cortisol and 18-OH-DOC did not show any significant influence of ACTH on the regulation of aldosterone during the night, nor during the night days 1 and 2

		night (n=11)		night, days 1 and 2 (n=17)	
Aldosterone	vs cortisol	0 27	(n s)	0 31	(n s)
Aldosterone	vs 18-OH-DOC	0 22	(n s)	0 24	(n s)
Cortisol	vs 18-OH-DOC	0 71	(p<0 01)	0 53	(p<0 05)

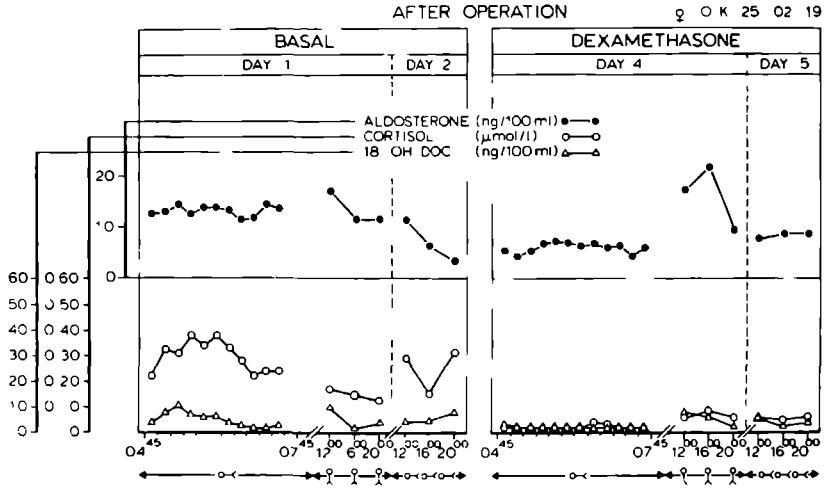


Figure A-3 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient O-K 4 years after resection of an adenoma

Dexamethasone treatment reduced the mean nocturnal aldosterone value from 13 1 ng/100 ml to 6 1 ng/100 ml Daytime upright and supine aldosterone values did not show a reduction during dexamethasone treatment

4 Adrenal scintigraphy was performed with ^{131}I-19-Iodocholesterol 2 2 mCi i v after 8 days pretreatment with dexamethasone 4 mg/day Adrenal scintigrams were obtained on the 2nd, 4th, 5th and 7th days after injection On the 7th day p i the left adrenal gland showed an accumulation of radioactivity, while the right gland was not visualized These findings suggested the presence of an aldosterone-producing adenoma in the left adrenal gland

6 On June 6th 1974 the left adrenal gland was explored by a lumbotomy on the left side at the height of the 12th rib An adrenal adenoma could be easily palpated The adenoma was freed from the surrounding adrenal tissue and surgically removed

7 The adrenocortical adenoma measured 2 cm and was surrounded by a thin capsule Some subcapsular hemorrhages were found Light microscopy the tumor was largely composed of large polygonal cells with a clear cytoplasm and a round nucleus The cells located peripherally in the tumor were generally smaller and contained hyperchromatic nuclei Conclusion Adrenocortical adenoma composed of zona fasciculata type cells

8 Postoperatively, blood pressure values decreased to 118/88 mmHg (n=6), measured during clinical admission 3 weeks after operation Plasma electrolytes were restored to normal During a 6-years follow-up period, blood pressures remained normal without antihypertensive treatment, varying from 130 to 140/85 to 95 mmHg

Patient 8 (♀, vd K-M, 14 11 26)

1 The patient is a woman aged 48 years who in September 1974 was referred by an internist elsewhere to the department of endocrinology, because of hypertension and hypokalemia A tentative diagnosis of primary aldosteronism had been made The patient was found to be hypertensive during each of her three pregnancies in 1955, 1957 and 1959 In 1961 she had been treated medically for hyperthyroidism Blood pressures at that time were occasionally high and varied from 150 to 170/90 to 100 mmHg In 1964 the patient had an abortion Blood pressure, measured shortly afterwards was 200/120 mmHg From 1964 to 1974 the patient did not receive any medical antihypertensive treatment In 1974 a blood pressure of 230/110 mmHg was found at a routine medical examination Treatment was started with

methyldopa and chlorthalidone 100 mg twice a week After one week of medical treatment the patient had to be admitted to another hospital as she had developed severe muscle weakness and even intermittent paralysis Blood pressure was 200/140 mmHg Laboratory findings revealed hypernatremia (153 mmol/l), hypokalemia (1 7 mmol/l) resistent to potassium suppletion, and marked elevations of the enzyme activities of SGOT, SGPT and CPK, probably due to hypokalemic myopathy On admission to our hospital the patient complained of fatigue, headache, muscle weakness, paresthesia and nycturia Blood pressure on admission was 225/110 mmHg No edema Central venous pressure R-5 cm H_2O The heart was not enlarged No abdominal bruits were heard

2 Aldosterone secretion rates and other relevant clinical and biochemical data are given in table A-8 These findings were in accordance with the diagnosis of primary aldosteronism

Table A-8

Aldosterone secretion rates and additional clinical and biochemical findings in patient vd K-M

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		212/127 (n=15)	
Sodium (mmol/l)	142	142	144
Potassium (mmol/l)	2 8	2 7	2 7
Creatinine (µmol/l)	84	70	68
UV sodium (mmol/24 hr)	9	50	192
UV potassium (mmol/24 hr)	56	56	95
UV creatinine (mmol/24 hr)	11 1	10 5	9 9
PRA (ng/10 ml/3 hr)	53	–	–
ASR (µg/24 hr)	–	851	981

3 The diurnal rhythms of plasma aldosterone (figure A-4) were determined 3 years after removal of the left adrenal gland, which contained a classical aldosterone-producing adenoma Plasma aldosterone concentrations during the night were considerably lower than during the day and upright posture (day

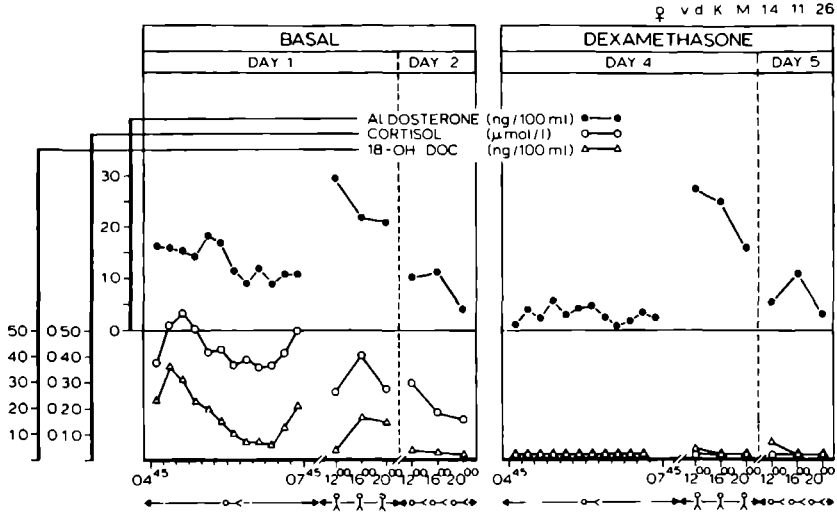


Figure A-4 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient vd K-M, 3 years after resection of an adenoma

1) Daytime recumbent values (day 2) were about comparable to the nightly aldosterone values Plasma aldosterone increased markedly in response to ambulation in the morning The correlation coefficients between the basal values of the three adrenocortical hormones demonstrate that the influence of ACTH on the regulation of plasma aldosterone is only limited

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0 32	(n s)	0 16	(n s)
Aldosterone	vs 18-OH-DOC	0 61	(p<0 05)	0 31	(n s)
Cortisol	vs 18-OH-DOC	0 79	(p<0 01)	0 91	(p<0 001)

Dexamethasone treatment reduced the mean nocturnal aldosterone value from 13 5 ± 3 2 ng/100 ml to 3 2 ± 1 6 ng/100 ml Daytime aldosterone concentrations were not influenced by dexamethasone treatment

4 Adrenal scintigraphy using ^{131}I-19-Iodocholesterol was performed during treatment with dexamethasone 4 mg/day Dexamethasone treatment was started 2 days before intravenous injection of 2 mCi ^{131}I-19-Iodocholesterol Accumulation of radioactivity in the adrenal glands was found on the 6th day after injection Although radioactivity showed an asymmetrical distribution (more accumulation in the left than in the right adrenal gland), the results were considered not to be conclusive with respect to the presence or absence of an adrenal adenoma The adrenal scintigrams were therefore repeated in 1975 ^{131}I-19-Iodocholesterol at a dose of 1 5 mCi was injected on the 4th day of treatment with dexamethasone 4 mg/day On the 4th and 5th days after injection of the radiopharmaceutical, uptake of radioactivity was found in the left adrenal gland and virtually no uptake in the right adrenal gland These findings led to the tentative diagnosis of adenoma of the left adrenal gland

5 The effect on blood pressure of treatment with high doses of spironolactone (400 mg/day) was evaluated during a 3 months treatment period Blood pressure measurements at monthly control visits showed slowly decreasing values 208/130 mmHg, 190/122 mmHg and 160/112 mmHg Remarkably, only after 3 months treatment blood pressure responded favourably to spironolactone treatment, although the values did not return to normal Side effects of spironolactone treatment included menstrual irregularities and Raynaud's phenomenon

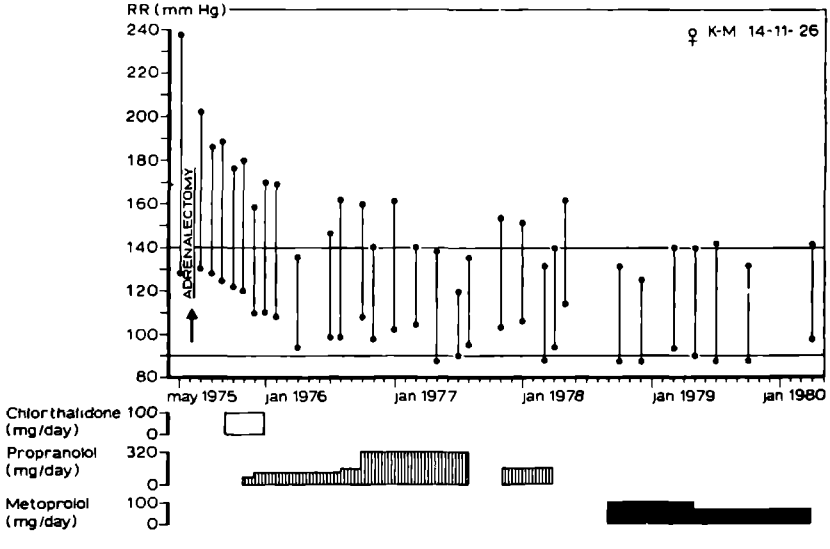


Figure A-5 Response of blood pressure values to medicamentous treatment during 5 years after resection of an adenoma in patient vd K-M

6 On June 6th 1975 the left adrenal gland was surgically removed through a flank incision A typical yellow adrenocortical adenoma measuring 3x2x1 cm protruded above the surface of the gland

7 Adrenal pathology the adrenal cortex adjacent to the tumor was relatively narrow and showed a normal zonation in three layers The zona glomerulosa was broad while both the zona fasciculata and the zona reticularis were decreased in size The tumor was not sharply separated from the surrounding adrenocortical tissue It was composed of polygonal cells, which were arranged in alveoli, trabeculae or nodules The cytoplasm was eosinophilic and showed a fine granulation Spironolactone bodies were not found Conclusion adrenocortical adenoma composed of cells of the zona fasciculata-type

8 Postoperatively, plasma electrolytes normalized within 5 days after adrenalectomy (sodium 140 mmol/l, potassium 4 1 mmol/l) Urinary aldosterone excretion decreased to 1 7 µg/24 hr, measured on the 8th day after surgery On discharge from hospital blood pressure was still markedly elevated (190/118 mmHg) Aldosterone secretion rate, measured one month after adrenalectomy during a sodium intake of 115 mmol/day was 31 µg/24 hr and still well below values found in normal individuals Blood pressures measured during a 5 years follow-up, are depicted in figure A 5 Because of a persistent high blood pressure, antihypertensive treatment with chlorthalidone and subsequently propranolol, reduced blood pressure to near-normal values Finally, blood pressure normalized during a relatively small dose of metoprolol of 50-100 mg/day

Patient 9 (♀, W-S, 29 12 58)

1 The patient is a girl 16 years old, who was referred by an internist elsewhere to the department of nephrology on October 10th 1974 Hypertension was detected in September 1974 at a routine medical examination Subsequent analysis in another hospital had revealed a marked hypertension (190/145 mmHg), normal renal function and a normal intravenous pyelogram The patient was referred to our hospital for further analysis and treatment At her first visit she was free of complaints Her previous history was uneventful, except for a paresis of the nervous facialis at the age of seven Blood pressure on admission was 200/135 mmHg Body weight 67 kg Height 1 73 m Fundoscopic examination did not reveal hemorrhages, exudates or other signs of hypertensive retinopathy The heart was not enlarged Vascular abdominal bruits were absent Laboratory urine negative for protein and glucose Plasma electrolytes sodium 142 mmol/l potassium 3 2 mmol/l, chloride 102 mmol/l, and bicarbonate 25 2 mmol/l Renal function was unimpaired creatinine 60 µmol/l Electrocardiogram sinus rhythm U-waves No signs of left ventricular hypertrophy An X-ray of the chest showed a heart-to-lung quotient of 12 28 Seldinger arteriography of the renal arteries excluded the presence of renal artery stenosis

2 Aldosterone secretion rates before and after sodium loading are presented in table A-9 Hypertension hypokalemia, hyporeninemia and elevated aldosterone secretion rates established the diagnosis of primary aldosteronism Aldosterone secretion rates were repeatedly measured in August 1975, 7 months after surgical resection of the right adrenal, which, unfortunately, had not contained an

Table A-9

Aldosterone secretion rates and additional clinical and biochemical findings in patient W-S

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		193/127 (n=9)	
Sodium (mmol/l)	145	143	144
Potassium (mmol/l)	3 7	2 9	3 2
Creatinine (µmol/l)	–	60	54
UV sodium (mmol/24 hr)	9	76	339
UV potassium (mmol/24 hr)	106	78	135
UV creatinine (mmol/24 hr)	15 5	12 0	12 0
PRA (ng/10 ml/3 hr)	44	–	–
ASR (µg/24 hr)	–	440	455

Table A-10

Aldosterone secretion rates and additional clinical and biochemical findings in patient W S, 7 months after surgical resection of the right adrenal gland

	SODIUM INTAKE		
	15 mmol 24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		185/120 (n=10)	
Sodium (mmol/l)	140	139	144
Potassium (mmol/l)	3 4	2 8	2 9
Creatinine (μmol/l)	70	75	65
UV sodium (mmol/24 hr)	20	205	375
UV potassium (mmol/24 hr)	85	122	129
UV creatinine (mmol/24 hr)	11 1	11 3	12 3
PRA (ng/10 ml/3 hr)	25	–	–
ASR (μg/24 hr)	–	348	301

adrenocortical adenoma (see also 6 and 7) The results of these determinations indicate that signs and symptoms of primary aldosteronism were still present after resection of the right adrenal (table A-10)

4 Adrenal scintigraphy was performed, using ^{131}I-19-Iodocholesterol, which was given intravenous at a dose of 1 9 mCi on the 3rd day of treatment with dexamethasone 4 mg/day On the 6th and 7th days after injection, accumulation of radioactivity was found in the right adrenal gland, while the left adrenal gland was completely suppressed These findings were considered to be due to an aldosterone-producing adenoma in the right adrenal gland The right adrenal gland was therefore surgically removed (see also 6) The uptake of radioactivity measured in the removed gland, was about 1 μCi One year after operation a second adrenal scintigram – using ^{131}I-19-Iodocholesterol – was performed because of persistent hyperaldosteronism ^{131}I-19-Iodocholesterol was injected intravenously at a dose of 2 mCi on the third day of dexamethasone 4 mg/day Adrenal scintigrams on the 2nd, 5th and 7th days did not show any accumulation of radioactivity in the left adrenal gland

5 The effects on blood pressure of successive treatment with spironolactone, and amiloride were evaluated by automated blood pressure recordings which showed a favourable response to spironolactone, and a moderate response to amiloride

spironolactone 400 mg/day (4 wks)	no medication	amiloride 40 mg/day (4 wks)
158/94 (n=7)	191/115 (n=8)	171/101 (n=7)

6 On January 2nd 1975 the right adrenal gland was explored through a right lumbotomy Although the right adrenal did not contain a palpable tumor, it was resected The decision to remove this gland was based on the unequivocal accumulation of radioactivity in the right adrenal gland as seen on the adrenal scintigram No tumor, however, was found on dissection of the gland On December 11th 1975 the left adrenal gland was explored via a lumbotomy and an adenoma with a diameter of 1 5 cm was resected from the left adrenal gland

7 Light microscopy of the right adrenal gland, which weighed 2 6 g, showed a normal zonation of the adrenal cortex in three layers The width of the zona glomerulosa was focally increased The tumor, resected from the left gland weighed 1 6 g and was surrounded by a thin connective tissue capsule It was composed of different cell types Peripherally, polygonal cells with clear and vacuolated cytoplasm were found, arranged in solid trabeculae Centrally in the tumor the cells were smaller and contained an eosinophilic granulated cytoplasm and a relatively large nucleus Forms intermediate between both cell types were found Conclusion adrenocortical adenoma composed of zona fasciculata-type zona glomerulosa-type and hybrid cells

8 After right adrenalectomy, signs and symptoms of primary aldosteronism were unaltered (see also 2)

After resection of the adenoma from the left adrenal plasma electrolytes normalized within a few days Aldosterone excretion decreased to 0 9 μg/24 hr on the ninth postoperative day On discharge from hospital, blood pressure was 130/90 mmHg At the subsequent control visits, however, blood pressure remained slightly elevated After a follow-up of five years, blood pressure was 138/98 mmHg during treatment with chlorthalidone

Patient 10 (♀, S-R, 21 10 31)

1 This patient is a woman aged 42 years who was referred to the department of internal medicine in May 1974 because of hypertension and hypokalemia Hypertension had been found for the first time 2 months earlier when she visited her family doctor as she had developed ankle edema Subsequent examination by an internist elsewhere had revealed marked hypernatremia (145 and 147 mmol/l) and hypokalemia (2 6 and 3 1 mmol/l) Besides ankle edema she complained of headache and fatigue There was no muscle weakness or polyuria or nycturia The previous history was uneventful During the first of her three pregnancies (1958, 1960 and 1963), she had taken a salt-restricted diet on account of a slight hypertension Menstrual cycles were regular She had never taken oral contraceptives Physical examination at the first visit revealed severe hypertension (240/125 210/140 210/140 mmHg), slight edema of the left ankle and a slight increase of the heart size Examination of the fundus oculi disclosed neither hemorrhages nor exudates X-rays of the chest manifested a heart-to-lung quotient of 15 30 Intravenous pyelography was normal Seldinger arteriography showed no abnormalities of the renal arteries The right and left adrenal glands were incompletely visualized (via the right arteria phrenica dextra and the left arteria suprarenalis inferior, respectively) Electrocardiogram showed U-waves, abnormal repolarisations in leads I II, V5 and V6 and no signs of left ventricular hypertrophy

2 Some of the relevant clinical and biochemical data are summarized in table A-11 Remarkably the aldosterone secretion rate was suppressible by increasing the dietary sodium intake, although aldosterone secretions were elevated for each of the three levels of sodium intake It should be noted, however, that the collections of the 24 hours urine were not optimal, as can be derived from the urinary creatinine excretions

Table A-11

Aldosterone secretion rates and additional clinical and biochemical findings in patient S-R

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		198/121 (n=16)	
Sodium (mmol/l)	140	143	145
Potassium (mmol/l)	2 8	2 9	2 9
Creatinine (μmol/l)	86	82	69
UV sodium (mmol/24 hr)	37	83	235
UV potassium (mmol/24 hr)	75	54	84
UV creatinine (mmol/24 hr)	15 5	11 0	8 4
PRA (ng/10 ml/3 hr)	20	–	–
ASR (μg/24 hr)	920	544	266

3 The diurnal plasma aldosterone pattern (figure A-6) showed high values during the late night (mean 36 9 ± 5 0 ng/100 ml) with a subsequent decline during the day (to 14 6 ng/100 ml at 08 00 hr p m) Plasma aldosterone failed to increase during ambulation in the morning The diurnal decline of plasma aldosterone occurred also in the supine position (day 2) Dexamethasone treatment induced a fall of mean nocturnal plasma aldosterone from 36 9 to 23 6 ng/100 ml During dexamethasone, a diurnal fall of plasma aldosterone was observed only during the supine position (day 2) Remarkably, plasma aldosterone increased during dexamethasone and upright posture (day 1) Correlation coefficients between the basal values of the three adrenocortical hormones plasma aldosterone, cortisol and 18-OH-DOC were as follows

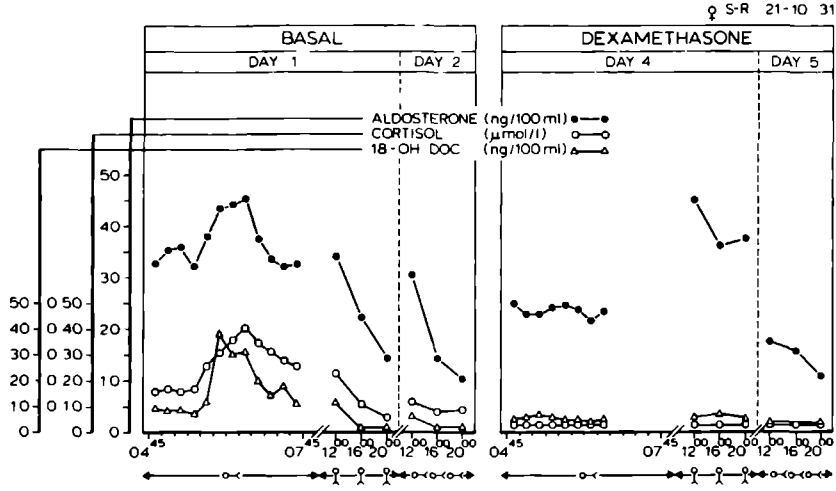


Figure A-6 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient S-R with an aldosterone-producing adenoma

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0 58	(p<0 05)	0 82	(p<0 001)
Aldosterone	vs 18-OH-DOC	0 67	(p<0 05)	0 85	(p<0 001)
Cortisol	vs 18-OH-DOC	0 88	(p<0 001)	0 95	(p<0 001)

These correlation coefficients suggest an important role for ACTH in the secretion of aldosterone in this patient

4 During suppression with dexamethasone adrenal scintigraphy was performed, using ^{131}I-19-Iodocholesterol Dexamethasone was given at a dose of 4 mg per day, starting one day before the intravenous administration of 1 mCi of the radiopharmaceutical The adrenal scintigrams on the 5th and 6th days after the injection showed an almost equal accumulation of radioactivity in the two adrenal glands Adrenal scintigrams were repeated 3 years later after the newer radiopharmaceutical ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol had become available Adrenal scintigraphy was performed during dexamethasone treatment, which was started 13 days before administration of the radiopharmaceutical The adrenal scintiscans obtained on the 5th, 7th and 9th days after injection of the radiopharmaceutical at a dose of 1 9 mCi, showed accumulation of radioactivity in the left adrenal gland and only minimal accumulation in the right adrenal gland

5 Medical treatment with spironolactone at a dose of 300 mg per day resulted in a good, but slowly initiating effect on blood pressure Blood pressure values measured at monthly intervals during this treatment were 180/110, 160/120, 160/110, 146/96, 142/105, 150/98 mmHg Side effects of spironolactone treatment were nausea and irregular menstrual cycles A low dose of spironolactone (50-100 mg/day) combined with propranolol 3x80 mg also had a favourable effect on blood pressure (134/82, 130/80 and 140/90 mmHg) The effects of spironolactone 400 mg/day compared with amiloride 40 mg/day, on blood pressure and some biochemical parameters are shown in table A-12 Amiloride had a marked lowering effect on blood pressure, almost comparable to that of spironolactone and without side effects The increase of aldosterone excretion after amiloride treatment is probably caused by the increase of potassium, since PRA and body weight remained essentially unchanged

6 On March 10th 1978, the left adrenal gland was surgically removed The adrenal gland was explored via a left sided lumbotomy between the 10th and 11th ribs The adrenal gland weighed 3 85 g and contained a round yellow tumor with a maximal diameter of 1 5 cm, and an additional cortical nodule of 3 mm

Table A 12

Comparison of the effects of treatment with spironolactone versus amiloride on some clinical and biochemical findings in patient S R

	spironolactone 400 mg/day (6 wks)	placebo (6 wks)	amiloride 40 mg/day (6 wks)
Body weight (kg)	62 0	65 5	66 0
Blood pressure (mmHg)*	123/91	179/114	139/95
Sodium (mmol/l)	139	144	137
Potassium (mmol/l)	4 1	2 2	4 3
Creatinine (μmol/l)	95	61	75
PRA (ng/10 ml/3 hr)	331	94	84
Aldosterone excretion (μg/24 hr)	38	25	71

* Measured by arteriosonde

7 Adrenal pathology a well defined cortical tumor protruding above the surface of the gland The tumor was composed of clear polygonal cells with a fine vacuolated cytoplasm Mitoses were absent The adrenal cortex outside the tumor showed a normal architecture Only at one level a nodular proliferation was found composed of clear cells comparable to those found in the tumor Conclusion a large and a small adrenal adenoma composed of cells as found normally in the zona fasciculata

8 On the first day after operation urinary aldosterone excretion decreased to 1 3 μg/24 hr Blood pressure during the first 10 days after operation varied from 135/90 to 180/120 mmHg At the monthly visits during the first half year after operation blood pressures remained slightly elevated (160/110 182/122 146/106 154/106 156/108 170/120 mmHg) During treatment with metoprolol 2x100 mg/day and chlorthalidone 100 mg/day blood pressure decreased gradually to 124/86 mmHg in April 1980 2 years after operation

Patient 11 (♀ S Kr 10 11 31)

1 This woman was 41 years old when she was referred by her family doctor to the department of internal medicine in July 1972 because of hypertension Treatment of hypertension with methyldopa and rauwolfia alkaloids had not resulted in a satisfactory response of blood pressure Hypertension was detected for the first time during her second pregnancy in 1965 She was also found to be hypertensive during her third pregnancy in 1966 and the blood pressure remained elevated after the delivery She had complaints of fatigue palpitations occasionally headache in the morning nycturia 2 3 times and paresthesia She had neither muscle weakness nor edema There was a history of asthmatic bronchitis psoriasis and low back pain At her first visit she was not having any medication From 1968 to 1969 she had taken oral contraceptives Blood pressure values at the first visit showed a moderate hypertension 200/120 170/120 170/120 and 200/120 mmHg Fundoscopy revealed no signs of hypertensive retinopathy Central venous pressure was R 4 cm H_2O No edema was found The heart size was just within normal limits An early systolic murmer at the apex was noted No vascular bruits were heard over the abdomen Several psoriatic skin manifestations were found Laboratory no proteinuria Urine culture remained sterile Endogenous creatinine clearance was 130 ml/min A glucose tolerance test was normal X rays of the chest showed a heart of normal size The heart to-lung quotient was 12 5 28 Intravenous pyelography was normal Seldinger arteriography demonstrated 2 renal arteries on each side without abnormalities CT scanning of the adrenals (performed in 1978) visualized the left adrenal gland which was normal with respect to size and shape The right adrenal gland was not visualized The electrocardiogram demonstrated a sinus rhythm flattening of the ST T segments in all leads and U waves No signs of left ventricular hypertrophy were found

2 Aldosterone secretion rates were measured at two different levels of sodium intake The results in combination with other relevant clinical and biochemical data are presented in table A 13 With these clinical and biochemical data the diagnosis of primary aldosteronism was established

Table A-13

Aldosterone secretion rates and additional clinical and biochemical findings in patient S-Kr

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		174/110 (n=9)	
Sodium (mmol/l)	142	143	140
Potassium (mmol/l)	3 7	3 3	3 2
Creatinine (µmol/l)	76	62	66
UV sodium (mmol/24 hr)	41	197	348
UV creatinine (mmol/24 hr)	12 9	13 5	13 4
PRA (ng/10 ml/3 hr)	29	–	–
ASR (µg/24 hr)	–	862	793

3 Plasma aldosterone values (figure A-7) during the late night were high and showed marked fluctuations After ambulation in the morning plasma aldosterone increased from 32 2 ng/100 ml to 54 6 ng/100 ml Since plasma cortisol concentration decreased in the morning (from 07 45 hr to 12 00 hr noon), it might be that this increase of plasma aldosterone occurred in response to upright posture Plasma aldosterone decreased from 12 00 to 20 00 hr both on day 1 and day 2 The correlation coefficients between the basal values of the three adrenocortical hormones aldosterone, cortisol and 18-OH-DOC, showed poor correlations between aldosterone and each of the ACTH-dependent hormones

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0 48	(n s)	0 57	(p<0 05)
Aldosterone	vs 18-OH-DOC	0 27	(n s)	0 45	(n s)
Cortisol	vs 18-OH-DOC	0 24	(n s)	0 76	(p<0 001)

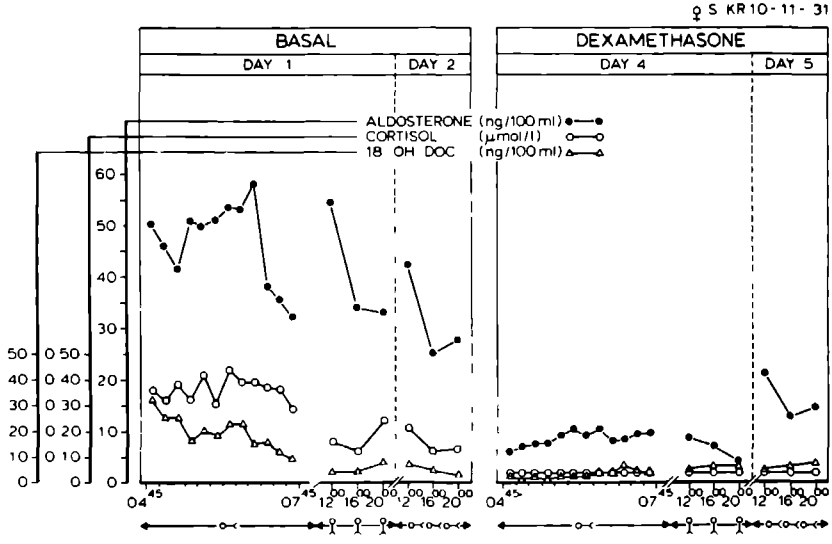


Figure A-7 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient S-Kr with an aldosterone-producing adenoma

Although these correlation coefficients suggest that aldosterone in this patient is relatively ACTH-independent, dexamethasone reduced the mean nocturnal plasma aldosterone from 46 7 ng/100 ml to 8 6 ng/100 ml The rise of plasma aldosterone values on day 2, suggest an escape from the suppressive action of dexamethasone

4 Adrenal scintigraphy using ^{131}I-19-Iodocholesterol was performed in 1976 Dexamethasone treatment was started one day before administration of the tracer at a dose of 2 mg/day and continued during the investigations Adrenal scintigrams on the 5th, 6th, 7th and 8th days after injection of 2 mCi of the radiopharmaceutical, were of poor quality Accumulation of radioactivity in the right adrenal, and to a lesser degree in the left adrenal, was noted The investigations were inconclusive with respect to the presence or absence of an adrenal adenoma One year later, adrenal scintigrams were repeated, using the newer radiopharmaceutical ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol Dexamethasone was administered at a dose of 2 mg/day, starting 9 days before injection of the tracer at a dose of 1 7 mCi Adrenal scintigrams on the 5th, 7th and 9th days showed unequivocal visualization of the right adrenal gland and almost complete suppression of the left adrenal gland

5 Antihypertensive treatment with spironolactone in doses gradually increasing from 100 to 400 mg/day, resulted in a stepwise decrease of blood pressure from 180/120 to 130/80 mmHg after 2 months treatment Medical treatment with spironolactone was continued for more than three years Blood pressure remained under good control after the dose of spironolactone had been reduced to 50 mg/day With the higher spironolactone doses (more than 200 mg/day) the patient experienced side effects, including itching and dead fingers Comparison of the effects of spironolactone and amiloride on blood pressure and other parameters, yielded the following results (table A-14) Amiloride caused a decrease of blood pressure comparable to the decrease of blood pressure observed after spironolactone treatment Urinary aldosterone excretion increased to a greater extent after amiloride than after spironolactone treatment, despite (1) the finding that spironolactone caused a greater volume depletion (body weight[1]) than amiloride and (2) the absence of an increase of PRA after amiloride

Table A-14

Comparison of the effects of treatment with spironolactone versus amiloride on some clinical and biochemical findings in patient S-Kr

	spironolactone 400 mg/day (6 wks)	placebo (6 wks)	amiloride 40 mg.day (6 wks)
Body weight (kg)	63 3	68 2	65 0
Blood pressure (mmHg)*	106/73	141/92	113/79
Sodium (mmol/l)	136	142	137
Potassium (mmol/l)	3 8	2 7	4 3
Creatinine (μmol/l)	88	68	83
PRA (ng/10 ml/3 hr)	306	75	61
Urinary aldosterone excretion (μg/24 hr)	68	59	90

* Measured by arteriosonde

6 On March 31st 1978 the right adrenal gland was surgically removed Adrenal exploration was performed via a lumbotomy between the 10th and 11th ribs on the right side An adrenal adenoma could be easily palpated The surgical procedure was without complications

7 The adrenal gland weighed 4 1 g An oval yellow tumor, measuring 13x8 mm, was located at one side of the gland The cut surface of the adrenal cortex outside the tumor was thin and did not show any abnormalities Light microscopy the tumor was well defined and partially surrounded by a thin capsule The tumor was composed of large polygonal clear cells with a fine vacuolated cytoplasm The adrenal cortex adjacent to the tumor showed a normal zonation of a relatively atrophic cortex Conclusion Adrenocortical adenoma composed of cells of the zona fasciculata-type

8 The urinary aldosterone excretion decreased to 1 4 µg/24 hr on the first day after operation The aldosterone secretion rate, measured 10 days after operation during a 115 mmol sodium diet, was 29 µg/24 hr Blood pressure decreased to 136/80 on the third postoperative day and to 118/80 mmHg on discharge from hospital Blood pressure remained normal at regular control visits during a follow-up period of 2 years

Patient 12 (♀, H-S, 24 08 19)

1 This patient, a woman aged 57 years, was referred to the department of endocrinology on January 7th 1977, for evaluation of primary aldosteronism During each of her 10 pregnancies (1945-1959) she was found to be hypertensive, but only after her last delivery in 1959 did her blood pressure remain elevated She was treated with mefruside In 1976 severe hypokalemia was found, during her stay in a hospital elsewhere for surgical treatment of a breast carcinoma stage T_1NoMo After operation (left ablatio mammae) and parasternal irradiation, hypertension analysis was performed Mild hypertension (160/90-180/110 mmHg), hypokalemia (2 2-2 7 mmol/l) hypernatremia (147-149 mmol/l) and hyporeninemia (84 ng/10 ml/3 hr after ambulation during sodium restriction) suggested the presence of primary aldosteronism At her first visit she complained of fatigue and nycturia (5 times/night) She had no muscle weakness, edema or headache Previous history 1970, diabetes mellitus, treated with oral antidiabetics until 1975 and with diet thereafter From 1968 to 1976 she had been under the control of a neurologist because of epileptic manifestations, for which she had been treated with prominal up to 1976 The patient was not under any medication at her first visit Physical examination Blood pressure at the first visit was 240/120 mmHg Body weight 54 2 kg Height 1 63 m Central venous pressure R-6 cm H_2O No edema Normal size of heart No abdominal bruits were heard Laboratory no proteinuria or glucosuria Blood glucose 6 2 mmol/l Endogenous creatinine clearance was diminished to 62 ml/min Electrocardiography regular sinus rhythm Prominent U-waves No signs of left ventricular hypertrophy X-rays of the chest no abnormalities of heart or lungs Intravenous pyelography a slight disparity in renal size was found the left kidney measured 11 cm and the right 13 cm There was a delayed appearance of the contrast medium on the left side The left renal cortex was reduced as compared to the right

2 Table A-15 presents the values of the aldosterone secretion rates together with other relevant clinical and biochemical data From these results the diagnosis of primary aldosteronism was established

Table A-15

Aldosterone secretion rates and additional clinical and biochemical findings in patient H-S

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		183/106 (n=24)	
Sodium (mmol/l)	141	144	142
Potassium (mmol/l)	2 5	2 8	1 9
Creatinine (µmol/l)	–	–	96
UV sodium (mmol/24 hr)	36	123	340
UV potassium (mmol/24 hr)	56	97	117
UV creatinine (mmol/24 hr)	6 0	8 3	7 3
PRA (ng/10 ml/3 hr)	63	–	–
ASR (µg/24 hr)	–	642	1079

3 The plasma aldosterone concentrations (figure A-8) showed a diurnal rhythm with markedly elevated plasma aldosterone values during the late night, declining during the day to a normal value of 7 ng/100 ml at 20 00 hr on day 1 A diurnal fall of plasma aldosterone was also observed during the recumbent position (day 2) Plasma aldosterone did not response with a postural increase after ambulation in the morning The correlation coefficients between the basal values of the adrenocortical hormones aldosterone, cortisol and 18-OH-DOC suggested that the role of ACTH in the regulation of aldosterone was of only little importance

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0.52	(n.s.)	0 44	(n s)
Aldosterone	vs 18-OH-DOC	0.27	(n.s)	0.72	(p<0 001
Cortisol	vs 18-OH-DOC	0 73	(p<0 01)	0 63	(p<0.01

Short term treatment with dexamethasone resulted in a marked reduction of the nocturnal level of plasma aldosterone. The diurnal fall of plasma aldosterone during the taking of dexamethasone was preserved, although at a lower level of plasma aldosterone concentrations.

4. Adrenal scintigraphy was performed with ^{131}I-19-Iodocholesterol during dexamethasone treatment. Dexamethasone 2 mg/day was started 6 days before administration of the radiopharmaceutical. The scintigrams obtained on the 5th, 6th, 7th and 8th days after injection of 2 mCi ^{131}I-19-Iodocholesterol, showed accumulation of radioactivity in both adrenal glands. The tentative diagnosis of "primary aldosteronism due to bilateral adrenal hyperplasia" was therefore made One year later, in 1978, adrenal scintigraphy was repeated, using the newer radiocholesterol ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol Adrenal scintigraphy was performed during treatment with dexamethasone 2 mg/day, which was started 13 days before injection of the isotope On the 5th, 7th, 9th and 12th days after injection of the radiopharmaceutical at a dose of 1 8 mCi, a marked asymmetrical distribution of radioactivity in favour of the left adrenal gland, was found. These results were considered to be in accordance with a left adrenal adenoma

5. The effects on blood pressure and other parameters of medical treatment with high doses of spironolactone for 6 weeks were compared with the effects of 6 weeks treatment with high doses of amiloride The results are presented in table A-16 Treatment with spironolactone reduced blood pressure to normal values Remarkably, urinary aldosterone excretion decreased, despite a marked volume depletion (body weight reduction), a rise of PRA and a rise of plasma potassium. Amiloride treatment induced only a slight reduction of blood pressure. Aldosterone excretion also decreased after amiloride treatment despite a concomitant rise of plasma K^+ and PRA. No side effects of amiloride treatment were observed Spironolactone temporarily caused abdominal discomfort and diarrhea

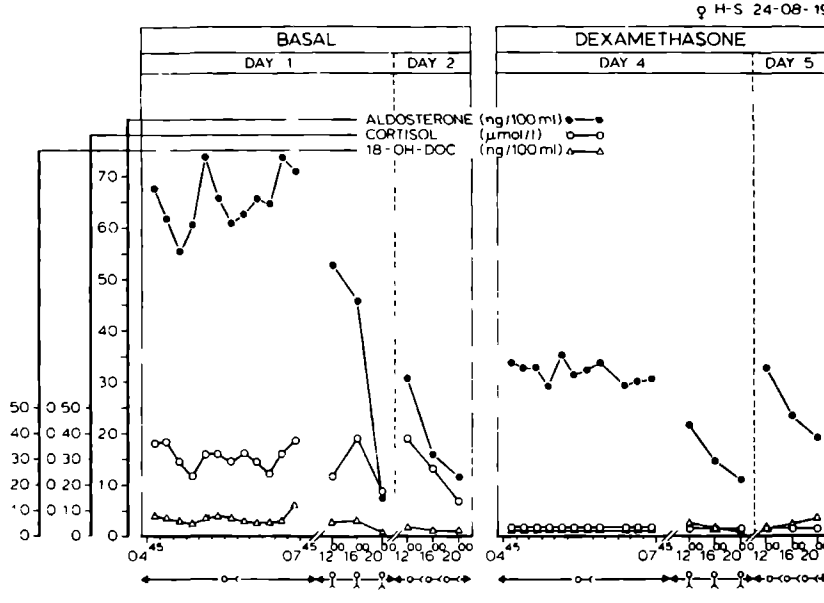


Figure A-8 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient H-S with an aldosterone-producing adenoma

Table A-16

Comparison of the effects of treatment with spirolactone versus amiloride on some clinical and biochemical findings in patient H-S

	spironolactone 400 mg/day (6 wks)	placebo (6 wks)	amiloride 40 mg/day (6 wks)
Body weight (kg)	56 4	58 2	59 5
Blood pressure (mmHg)*	125/87	168/102	152/97
Sodium (mmol/l)	135	147	137
Potassium (mmol/l)	4 6	3 3	3 8
Creatinine (μmol/l)	153	86	107
PRA (ng/10 ml/3 hr)	91	59	109
Aldosterone excretion (μg/24 hr)	14	26	19

* Measured by arteriosonde

6 On April 14th 1978 the left adrenal gland was surgically removed, after lumbotomy on the left side between the 10th and 11th ribs an adrenal adenoma could be easily palpated The adrenal gland weighed 8 4 g and harbored an adenoma with a maximal diameter of 2 cm

7 The circumscribed encapsulated tumor was composed of large polygonal cells arranged in alveoli or solid fields The centrally located nuclei exhibited some pleomorphism Mitoses were absent The cells were indistinguishable from normal zona fasciculata cells Locally, the cells were smaller with a dark and eosinophilic cytoplasm The adrenal cortex outside the tumor showed locally a nodular broadening caused by an increase of both clear large cells and smaller eosinophilic cells Conclusion adrenocortical adenoma composed of cells normally found in the zona fasciculata Nodular hyperplasia of the adjacent adrenal cortex

8 Postoperatively, urinary aldosterone excretion decreased to 0 51 μg/24 hr, measured on the second day after operation Aldosterone secretion rate on the 10th postoperative day measured during a 115 mmol sodium diet, was only 7 5 μg/24 hr Plasma electrolytes on that day were in accordance with a mineralocorticoid deficiency plasma sodium 133 mmol/l, plasma potassium 5 3 mmol/l Blood pressure on discharge from hospital was still slightly elevated, 158/100 mmHg

Patient 13 (♀ K-H, 27 02 45)

1 This woman was 28 years old in November 1973, when she was referred by the department of gynecology to the department of cardiology of this institute At that time she was 15 weeks pregnant In March 1972 she had been operated elsewhere for an atrial septum defect Blood pressure was elevated on admittance to that hospital in March 1972 (180/120 mmHg) but normal on discharge (125/90 mmHg) Plasma sodium and potassium concentrations were normal During her pregnancies in 1969 and 1970 blood pressures were normal She had taken oral contraceptives from 1970 to February 1972 Blood pressure at the first visist in 1973 was 130/80 mmHg Cardiologic examination revealed no abnormalities except for evidence of a right bundle branch block on the electrocardiogram The pregnancy and delivery were uneventful However, blood pressures appeared to be elevated at the control visits to the out-patient department of cardiology in 1974 (170/110 mmHg), 1975 (150/100 mmHg) and 1976 (165/110 mmHg) Diuretic treatment with chlorthalidone had to be suspended, because of severe muscle weakness and paresis of the lower limbs Antihypertensive therapy with propranolol 240 mg/day did not result in a significant decrease of blood pressure After discontinuation of antihypertensive therapy, the patient was admitted to the department of internal medicine in November 1977 At that time she had no complaints Fundoscopic examination was normal X-rays of the chest revealed that the heart-to-lung-quotient, which was normal in 1974, had increased to 16 27 5 The urogram was normal Seldinger arteriography showed no stenosis of the renal arteries

2 Aldosterone secretion rates obtained at three different levels of sodium intake, were in accordance with the diagnosis of primary aldosteronism (table A-17)

Table A-17

Aldosterone secretion rates and additional clinical and biochemical findings in patient K-H

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		177/115 (n=17)	
Sodium (mmol/l)	143	143	147
Potassium (mmol/l)	2 8	2 4	3 0
Creatinine (µmol/l)	58	58	54
UV sodium (mmol/24 hr)	26	114	209
UV potassium (mmol/24 hr)	35	53	95
UV creatinine (mmol/24 hr)	9 8	9 7	10 0
PRA (ng/10 ml/3 hr)	38	–	–
ASR (µg/24 hr)	400	331	459

3 The nocturnal and diurnal plasma aldosterone, cortisol and 18-OH-DOC patterns before and during dexamethasone, are depicted in figure A-9 Plasma aldosterone values were high, especially in the night, and showed marked fluctuations The highest aldosterone value was found during the night (66 0 ng/100 ml) and the lowest during the recumbent position at 16 00 hr (10 2 ng/100 ml) Aldosterone decreased during the upright posture in the morning from 47 5 to 18 3 ng/100 ml Dexamethasone treatment induced a marked fall of mean plasma aldosterone during the night, from 51 3 ± 11 3 ng/100 ml to 7 9 ± 1 7 ng/100 ml Daytime aldosterone values were slightly lower during dexamethasone as compared with the basal daytime values The basal values of the three adrenocortical hormones were significantly correlated with each other

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0 80	(p<0 001)	0 90	(p<0 001)
Aldosterone	vs 18-OH-DOC	0 89	(p<0 001)	0 96	(p<0 001)
Cortisol	vs 18-OH-DOC	0 77	(p<0 001)	0 89	(p<0 001)

These figures suggest a marked influence of ACTH on the regulation of aldosterone Plasma cortisol and 18-OH-DOC were normally suppressed during dexamethasone treatment Diurnal and nocturnal plasma aldosterone patterns were repeatedly assessed 6 months after surgical removal of an aldosterone-producing adenoma (figure A-10) The mean plasma aldosterone concentration during the night was 11 4 ± 2 3 ng/100 ml There was a postural increase of plasma aldosterone after ambulation in the morning, from 7 4 to 13 1 ng/100 ml The highest aldosterone value was found after ambulation at 16 00 hr Dexamethasone treatment induced a fall of mean plasma aldosterone during the night from 11 4 ± 2 3 ng/100 ml to 2 2 ± 0 6 ng/100 ml The correlation coefficients between the three adrenocortical hormones under basal conditions did not reveal a role for ACTH in the control of plasma aldosterone

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	−0 42	(n s)	0 02	(n s)
Aldosterone	vs 18-OH-DOC	0 41	(n s)	0 40	(n s)
Cortisol	vs 18-OH-DOC	0 07	(n s)	0 70	(p<0 001)

4 Adrenal scintigrams using ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol as radiopharmaceutical, were performed after long-term dexamethasone treatment Dexamethasone was given at a dose of 2 mg/day, starting 3 weeks before injection of the tracer The scintigrams made on the third day after injection showed a discernable accumulation of activity in the left adrenal gland The scintigrams on the 6th and 8th days after injection, showed an unmistakable accumulation in the left adrenal region The right adrenal gland was almost completely suppressed

5 Medical treatment of blood pressure with chlorthalidone 50 mg/day and amiloride 15 mg/day for 3 weeks resulted in a decrease of blood pressure from 158/111 mmHg (n=16) to 113/88 mmHg

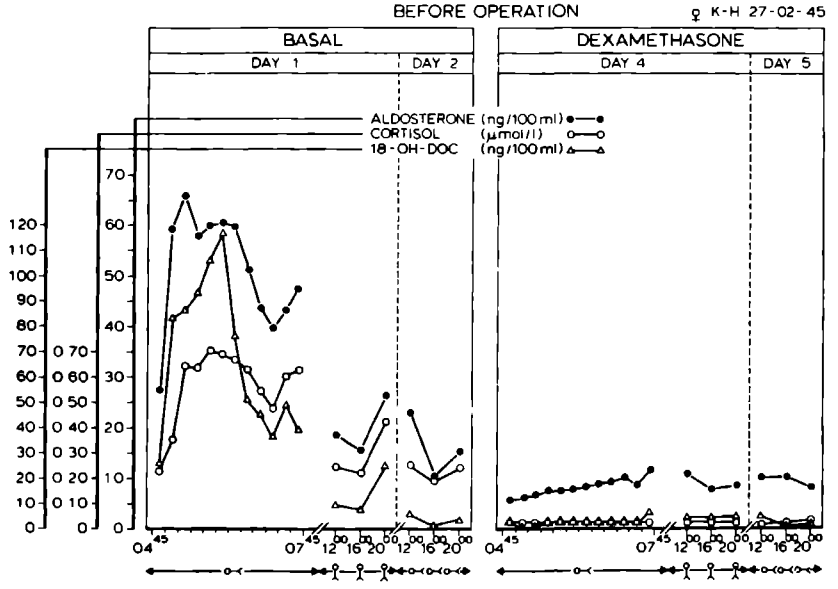


Figure A-9. Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient K-H with an aldosterone-producing adenoma

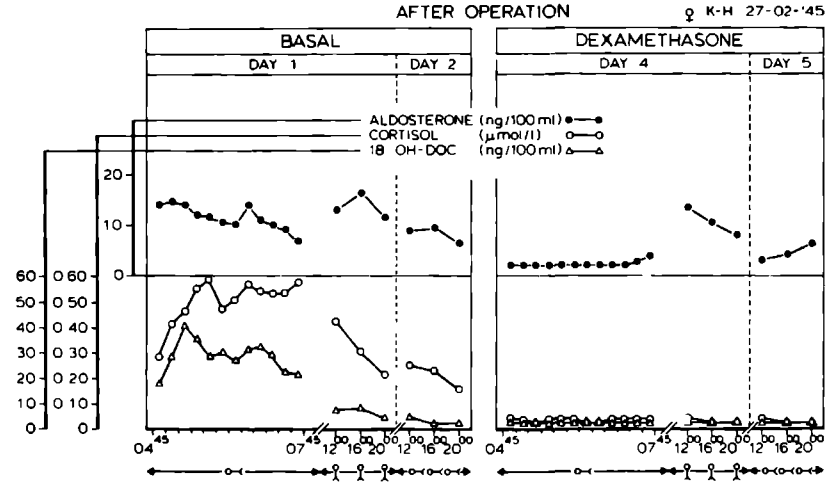


Figure A-10. Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient K-H, 6 months after resection of an adenoma

(n=30), as measured by arteriosonde. This antihypertensive treatment was given concomitantly with the dexamethasone treatment (see 4). Therapy with spironolactone, 400 mg/day for 3 weeks, resulted in a decrease of blood pressure to 117/80 mmHg (n=25) During this medication the patient developed a transient eruption of the skin accompanied by itching. In addition she had irregularities of the menstrual cycle

6 On April 28th 1978, the left adrenal gland was explored by a lumbotomy between the 10th and 11th ribs on the left side The left adrenal gland was removed and weighed 7 35 g A circumscribed yellow tumor with a maximal diameter of 1 4 cm was found after dissection of the gland

7 The adrenal cortex adjacent to the tumor showed no abnormalities The tumor was composed for the greater part of large polygonal cells with foamy cytoplasm and centrally located nuclei The nuclear chromatin was finely dispersed and regularly contained a large nucleolus There were only few mitoses In the more peripheral areas and sub-capsularly, the cells were smaller, without eosinophilic cytoplasm These cells had the appearance of zona glomerulosa cells In the adrenal cortex adjacent to the tumor, a normal zonation was found with only local broadening of the zona fasciculata Conclusion an adrenocortical adenoma, for the greater part composed of zona fasciculata-type cells

8 The aldosterone secretion rate decreased to 8 µg/24 hr on the 10th day after operation Plasma sodium and potassium were restored within 9 days to 140 and 4 4 mmol/l, respectively Blood pressure was 126/88 on discharge and remained normal at regular control visits thereafter, throughout a 2 years follow-up period

Patient 14 (♂, H, 07 01 41)

1 This patient was referred to the departement of endocrinology in January 1976, when he was 35 years old Eight months previously he had been found to be hypertensive (240/130 mmHg), while in 1974 his blood pressure was normal (140/75 mmHg) Since 1975 he had had complaints of severe headache Antihypertensive treatment with chlorthalidone 100 mg/day did not result in a significant fall of blood pressure However, plasma potassium levels during this treatment decreased to values as low as 2 1 mmol/l, despite the use of potassium supplements Since plasma potassium was not restored to normal after discontinuation of diuretic treatment, the presumptive diagnosis of primary aldosteronism was made Hypertension analysis, performed in a hospital elsewhere, yielded the following results PRA, measured after 5 days chlorthalidone 100 mg/day was 53 ng/10 ml/3 hr Renal function unimpaired X-rays of the chest and urogram were normal Seldinger arteriography showed a slight, hemodynamically insignificant stenosis of the main right renal artery Adrenal scintigrams performed with ^{131}I-19 Iodocholesterol showed an equal accumulation of radioactivity in both adrenal regions The scintigrams repeated after pretreatment with dexamethasone, did not show any accumulation of activity in the adrenal glands Antihypertensive treatment with spironolactone 450 mg/day and propranolol 240 mg/day resulted in a decrease of blood pressure to 140/100 mmHg During this treatment the patient began to have a loss of potency and developed gynecomastia On March 5th 1976, he was admitted to our hospital for measurements of aldosterone secretion rates Antihypertensive treatment was withheld for one month In that time he developed headache, fatigue and nycturia Blood pressure on admission was 230/140 mmHg Fundoscopic examination was normal The electrocardiogram showed prominent U-waves The radiological heart-to-lung quotient was 14 31

2 The aldosterone secretion rates were markedly elevated at three different levels of sodium intake (table A-18)

Table A-18

Aldosterone secretion rates and additional clinical and biochemical findings in patient H

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		199/125 (n=16)	
Sodium (mmol/l)	142	141	143
Potassium (mmol/l)	2 7	3 0	2 9
Creatinine (µmol/l)	72	75	72
UV sodium (mmol/24 hr)	16	37	403
UV potassium (mmol/24 hr)	38	33	90
UV creatinine (mmol/24 hr)	9 9	8 7	13 0
PRA (ng/10 ml/3 hr)	53	32	–
ASR (µg/24 hr)	908	702	666

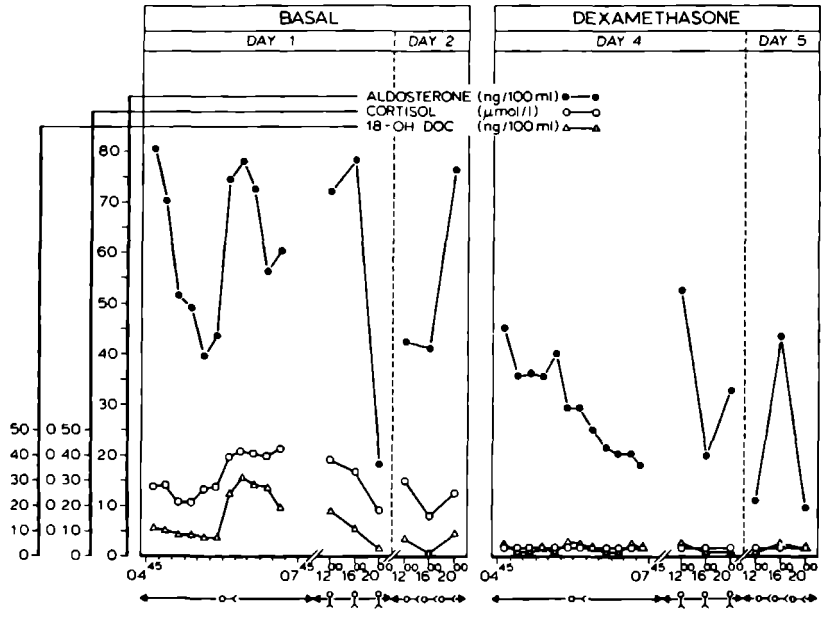


Figure A-11 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient H with an aldosterone-producing adenoma

3 The nocturnal and diurnal variations of plasma aldosterone in relation to plasma cortisol and 18-OH-DOC are depicted in figure A-11 Aldosterone values were markedly elevated and showed a wide variation during the night and the day The highest aldosterone value (80 7 ng/100 ml) was found during the night and the lowest (17 8 ng/100 ml) during daytime at 20 00 hr There was a slight increase of aldosterone in the morning during upright posture (from 60 7 to 72 1 ng/100 ml) Dexamethasone treatment suppressed the mean aldosterone value during the night from 61 5 ± 14 5 ng/100 ml to 29 4 ± 9 0 ng/100 ml The daytime values were slightly suppressed by dexamethasone The correlation coefficients between the basal concentrations of the three adrenocortical hormones demonstrate that ACTH plays an important role in the regulation of aldosterone in this patient

		night (n=11)		night, days 1 and 2 (n=17)	
Aldosterone	vs cortisol	0 56	(p<0 05)	0 53	(p<0 05)
Aldosterone	vs 18-OH-DOC	0 75	(p<0 01)	0 72	(p<0 001)
Cortisol	vs 18-OH-DOC	0 79	(p<0 01)	0 85	(p<0 001)

4 The dexamethasone suppression scintigrams of the adrenal glands, performed on the 6th, 7th and 8th days after intravenous administration of 1 9 mCi ^{131}I-19-Iodocholesterol, did not show any appreciable accumulation of radioactivity over either adrenal gland Dexamethasone was administered at a dose of 4 mg/day, starting 3 days before administration of the tracer When the isotope ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol became available, the adrenal scintigrams were repeated After two weeks pretreatment with dexamethasone 2 mg/day, the isotope was administered at a dose of 1 6 mCi Scintigrams on the 3rd, 4th, 5th and 6th days after injection did not show any accumulation of radioactivity in the adrenal glands

5 The results of 6 weeks medical treatment with spironolactone 400 mg/day, compared to 6 weeks treatment with amiloride 40 mg/day are presented in table A-19 In contradistinction to treatment with spironolactone, blood pressure did not respond to amiloride Plasma potassium and aldosterone

Table A-19

Comparison of the effects of treatment with spironolactone versus amiloride on some clinical and biochemical findings in patient H

	spironolactone 400 mg/day (6 wks)	placebo (6 wks)	amiloride 40 mg/day (6 wks)
Body weight (kg)	62 9	65 1	64 3
Blood pressure (mmHg)*	137/91	172/110	172/112
Sodium (mmol/l)	138	145	138
Potassium (mmol/l)	3 8	2 5	3 7
Creatinine (μmol/l)	89	72	79
PRA (ng/10 ml/3 hr)	216	75	103
Aldosterone excretion (μg/24 hr)	52	32	46

* Measured by arteriosonde

excretions were comparable after either treatment PRA increased markedly after spironolactone, not however after amiloride Serious side effects were noted only after spironolactone treatment such were gynecomastia and stomach complaints The patient was subsequently treated for one year with spironolactone 100 mg/day in combination with methyldopa, propranolol and prasozine With this therapeutic regimen, blood pressure remained slightly elevated (140/100 mmHg)

6 At operation on June 23rd 1978, a lumbotomy between the 10th and 11th ribs was performed on the left side (because of the statistical preference of aldosterone-producing adenomas for localization in the left adrenal gland) A 1 5 cm nodule was palpable in the left adrenal, which was subsequently removed in toto During surgery, the left pleural cavity was accidently opened Postoperatively, X-rays of the chest showed a pneumothorax, for which the patient was treated successfully with suction drainage

7 The tumor that was partly surrounded by a thin capsule, compressed the adjacent adrenocortical tissue The tumor cells were arranged in alveoli and showed, in the peripheral areas, a clear and foamy cytoplasm However, also smaller tumor cells with a more eosinophilic cytoplasm were noted There was little or no anisokaryosis No areas with bleeding or necrosis were found The adjacent adrenal cortex showed a normal zonation with a relatively broad zona glomerulosa The adrenal medulla was normal Conclusion a solitary adrenocortical nodule, composed of zona fasciculata- and zona reticularis-type cells

8 After operation, the aldosterone secretion rate fell to 19 μg/24 hr (measured on the 10th day after operation, during a sodium intake of 115 mmol/24 hr) Plasma sodium and potassium were restored spontaneously to normal values within one week Blood pressures, however, remained markedly elevated during the postoperative period (152 to 200/100 to 120 mmHg), and slightly elevated at the control visits during the first year after operation (146 to 150/96 to 104 mmHg) Treatment with propranolol 80 mg/day lowered blood pressure to almost normal values (124 to 142/92 to 96 mmHg) during a follow-up period of 2 years

Patient 15 (♀, M-G, 13 06 20)

1 The patient is a woman aged 57 years, who was referred to the department of endocrinology on December 13th 1977 She was known to have been hypertensive for 15 to 20 years Blood pressure was normal during her 7 pregnancies of which two terminated with an abortion In 1975 she developed complaints of angina pectoris for which she was examined in the department of internal medicine of another hospital Marked hypertension, concomitant with hypokalemia were repeatedly found From 1975 to 1977 she was admitted 5 times to that hospital for further examinations During these observations the clinical and biochemical findings were not always in favour of the diagnosis of primary aldosteronism Plasma potassium varied from 1 9 mmol/l to normal values PRA was low and unresponsive to stimulation with sodium restriction and ambulation Urinary aldosterone excretion

was normal on several occasions Adrenal scintigraphy with ^{131}I 19 Iodocholesterol showed an equal uptake of radioactivity in both adrenal glands However after pretreatment with dexamethasone an asymmetrical uptake was found with a more pronounced accumulation in the right adrenal gland The patient was referred to the endocrine unit of this institute for further evaluation of primary aldosteronism or other syndromes of mineralocorticoid excess At the first visit she complained of low back pain headache nycturia muscle weakness and muscle cramps Further she had atypical angina pectoris palpitations and profuse perspirations Part of the complaints resulted from the taking of spironolactone 200 mg/day Because of severe headache she had abused analgetics and tranquilizers for many years She smoked 30 cigarettes per day Her family history recorded a high prevalence of hypertension mother and 2 sisters developed a cerebral vascular accident At the first visit the blood pressure was 225/130 mmHg Pulse rate 74/min with frequent premature beats Central venous pressure was normal No edema Fundoscopic examination showed a venous occlusion in the right fundus oculi with several small hemorrhages The heart was enlarged and an atherosclerotic souffle was heard over the aorta The electrocardiogram showed pathologic repolarisations in leads I AVL V5 V6 and left ventricular hypertrophy The heart to lung quotient on an X ray of the chest was 16 5 29 5

2 Figure A-12 presents the most relevant clinical and biochemical data obtained at three different levels of sodium intake The findings are in accordance with the diagnosis of primary aldosteronism hypertension increase of kaliuresis and hypokalemia after sodium loading low PRA unresponsive to stimulation and a lack of aldosterone suppressibility after sodium loading It is to be noted that the aldosterone secretion rate during sodium restriction is within the lower range of normal

3 Plasma aldosterone concentrations showed high values during the late night with a subsequent fall during the day despite the stimulus of upright posture (figure A 13) The highest aldosterone value was found during the night (37 9 ng/100 ml) and the lowest during day 1 at 16 00 hr (6 8 ng/100 ml) The correlation coefficients between the basal values of the three adrenocortical hormones show that the plasma aldosterone concentrations are not significantly influenced by ACTH

		night (n=11)		night days 1 and 2 (n=17)	
Aldosterone	vs cortisol	0 21	(n s)	0 34	(n s)
Aldosterone	vs 18 OH DOC	0 28	(n s)	0 28	(n s)
Cortisol	vs 18 OH DOC	0 90	(p<0 001)	0 82	(p<0 001)

Dexamethasone treatment however reduced mean nocturnal PA values from 32 3 ± 4 0 ng/100 ml to 9 4 ± 2 8 ng/100 ml Daytime aldosterone values were slightly lower than under basal circumstances The plasma aldosterone concentrations were repeatedly assessed 5 months after right adrenalectomy and subsequent recurrence of biochemical characteristics of primary aldosteronism (see also 8) The diurnal pattern of aldosterone (figure A 14) appeared unchanged as compared to the findings before operation There was a diurnal fall of aldosterone despite upright posture Nocturnal aldosterone values were even higher than before operation (51 7 ± 6 6 vs 32 3 ± 4 0 ng/100 ml) Aldosterone did not correlate significantly with cortisol during the night (r=0 57 n=8 n s) nor during the night days 1 and 2 (r=0 34 n=14 n s) Dexamethasone reduced mean nocturnal aldosterone from 51 7 ± 6 6 ng/100 ml to 31 6 ± 2 0 ng/100 ml

4 Adrenal scintigraphy using ^{131}I 6β Iodomethyl-19 Nor Cholesterol was performed after 2 weeks pretreatment with dexamethasone 2 mg/day The radiopharmaceutical was administered at a dose of 2 mCi On the 6th and 7th days after injection the right adrenal gland was clearly visualized The left adrenal gland showed almost absent accumulation of radioactivity

5 Treatment with spironolactone at a dose of 400 mg/day for 4 weeks resulted in only a slight decrease of blood pressure from 207/123 mmHg (mean value during clinical admission) to 178/112 mmHg Long-term treatment with dexamethasone 2 mg/day for 3 weeks exerted no influence on blood pressure level (216/122 mmHg before and 215/120 after dexamethasone treatment) although urinary aldosterone excretion decreased from 25 0 to 8 3 µg/24 hr

6 On June 2nd 1978 the right adrenal gland was surgically removed by lumbotomy between the 10th and 11th ribs The gland removed weighed 9 5 g and contained an adenoma with a maximum diameter of 2 5 cm

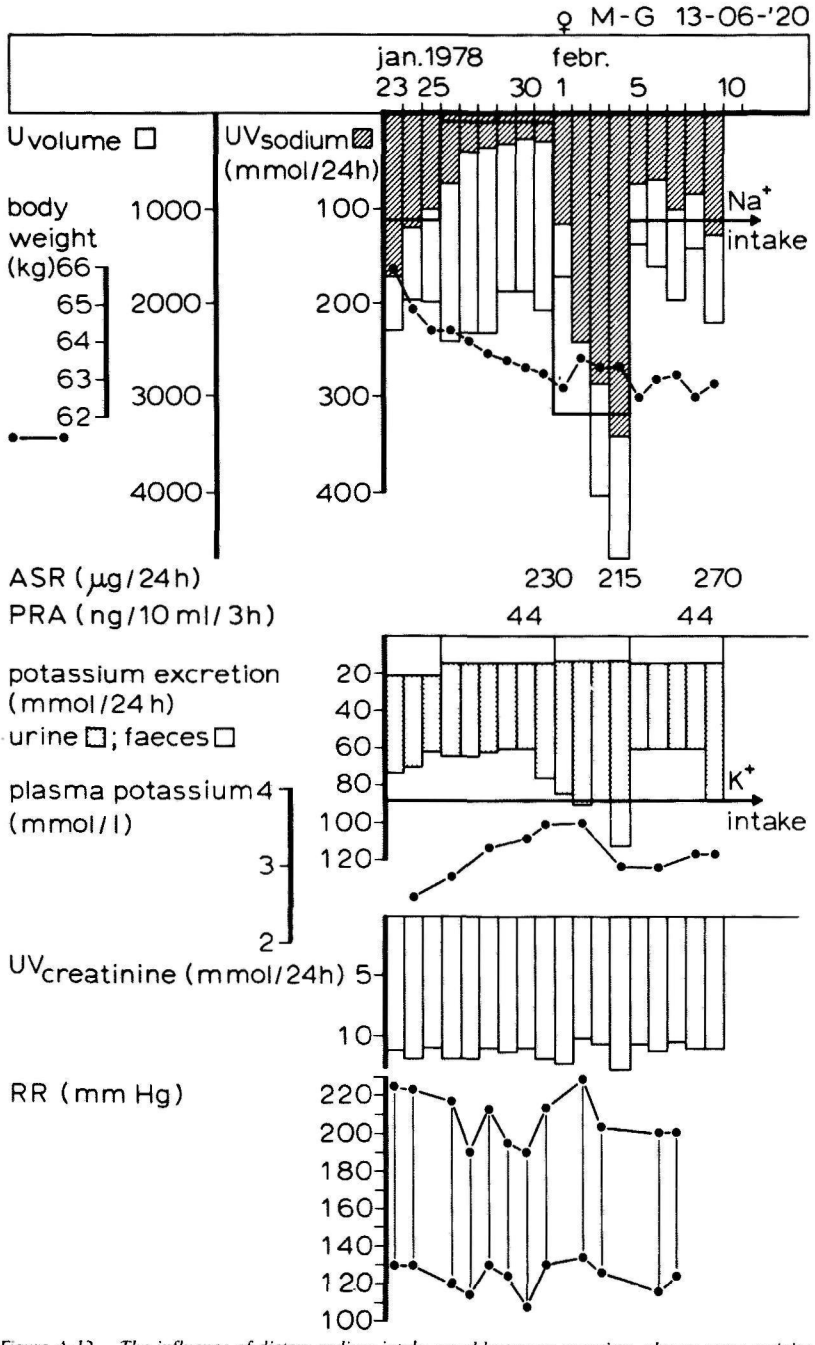


Figure A-12. The influence of dietary sodium intake on aldosterone secretion, plasma renin activity and plasma- and urinary electrolytes in patient M-G

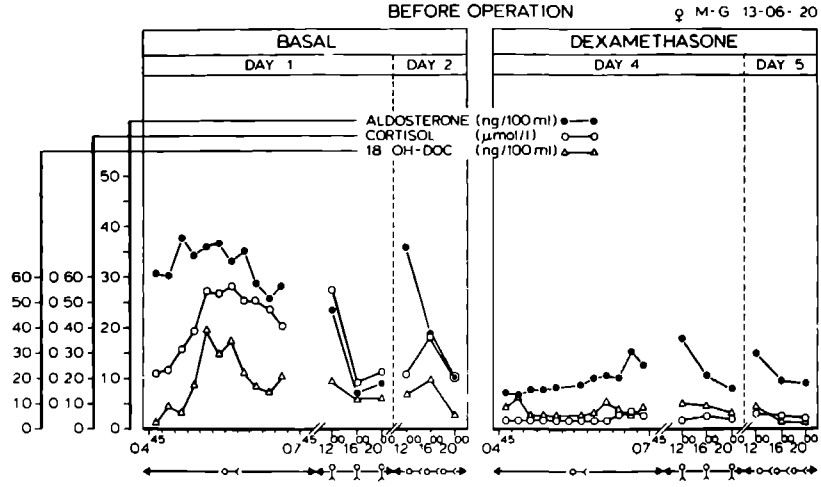


Figure A-13 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient M-G with an aldosterone-producing adenoma

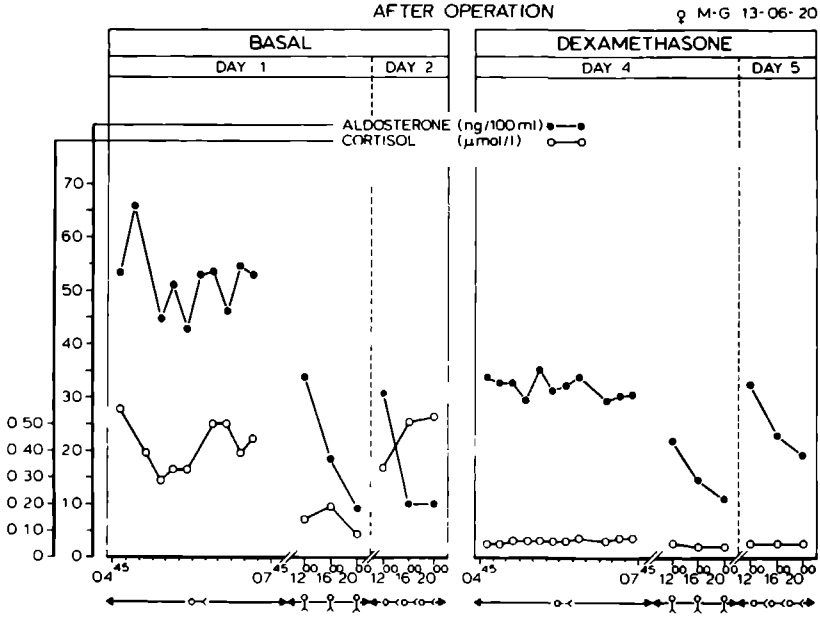


Figure A-14. Diurnal variations of plasma aldosterone and cortisol in patient M-G, 5 months after resection of an adenoma and recurrence of primary aldosteronism

7 The adrenal cortex surrounding the tumor showed a macronodular hyperplasia Dissection of the gland demonstrated besides a classical yellow adenoma, partly atrophic and partly hypertrophic areas in the attached adrenal cortex Microscopy the adenoma was not sharply separated from the adjacent adrenal tissue The adenoma was composed of predominantly clear cells, arranged in cords, trabeculae and acini There was no cellular nor nuclear polymorphism In some transverse sections the adjacent cortex showed a nodular hyperplasia caused by an increase of alveolarly or trabecularly arranged clear cells Conclusion adrenocortical adenoma and macro- and micronodular hyperplasia At postmortum examination the left adrenal gland appeared to contain a yellow tumor measuring 18 mm in diameter Besides, a small white tumor of 6 mm was found after dissection of the gland Light microscopy of the adrenal revealed a normal zonation of the cortex At one level a nodular proliferation of large clear cells with an alveolar arrangement was found Within this proliferation many capillaries were present At another level a proliferation of atypical glandular and alveolar structures with a central necrosis and a proliferation of connective tissue were found The cells did show a marked atypia and nuclear polymorphism Mitoses were numerous Conclusion adrenocortical adenoma and a metastasis of an adenocarcinoma

8 Postoperatively, urinary aldosterone excretion fell to 1 5 µg/24 hr on the second day after operation Aldosterone secretion rate measured on the 10th day after operation during a 115 mmol sodium diet, was 78 µg/24 hr Blood pressure however, remained elevated 192/122 mmHg and 170/130 mmHg, measured at 6 weeks and 3 months respectively, after operation
Surprisingly two months postoperatively plasma sodium values were found to be increased (142-144 mmol/l) with low plasma potassium values (2 5-2 9 mmol/l) Recurrence of hyperaldosteronism was suspected and the patient was readmitted to the hospital in November 1978 She complained of headache and low back- and muscle pains Blood pressure on admission was 218/130 mmHg Physical examination yielded no additional new findings as compared with earlier examinations Radiography of the chest revealed a round lesion 3 cm in diameter located in the left lung adjacent to the arch of the aorta On mediastinoscopy, several paratracheal and tracheobronchial lymph nodes were found Pathologic examination of biopsies revealed lymph node metastases of an adenocarcinoma Cytologic examination of sputum raised the suspicion of an adenocarcinoma Bronchoscopic examination was negative On bronchography, a compression of the dorsal branch of the left apico-posterior branch was detected The tentative diagnosis was made of a bronchial carcinoma with mediastinal lymph node metastases As described in the section "diurnal rhythms of plasma aldosterone", the patient had a recurrence of primary aldosteronism The profile of the diurnal plasma aldosterone concentrations was in accordance with the presence of an aldosterone-producing adenoma in the remaining left adrenal gland However, it was decided not to explore the left adrenal gland because of the patient's poor clinical prognosis On September 18th 1980 she died At autopsy, extensive tumor growth in the right and left lung with metastases in the mediastinal and parabronchial lymph nodes were found The left adrenal cortex contained a classical adenoma with a diameter of 1 8 cm

Patient 16, (♀, N-M, 02 01 23)

1 The patient is a 54 years old woman, who was referred to the department of nephrology of our institute on September 27th 1977, because of hypertension and pathology of the right kidney The patient had a history of hypertension during each of her 5 pregnancies (1946, 1951, 1953 1957, 1961) Blood pressure returned to normal after each delivery In 1961 she developed unexplained ankle edema Blood pressure at that time was 120/80 mmHg In 1971 hypertension was detected, when she was admitted to a hospital for a cholecystectomy Antihypertensive treatment with various medicaments did not result in a satisfactory response of blood pressure During treatment with clonidine, methyldopa and triamterene a moderate hypokalemia was found Intravenous pyelography had revealed a deformation of the calyces and pyelum of the right kidney, probably caused by chronic pyelonephritis Because of a diabetes mellitus, established in 1971 the patient took a sugar-free diet and tolbutamide 500 mg b i d The patient had no complaints of muscle weakness, nycturia, edema, palpitations or headache Blood pressure measured at her first visit, during medication with clonidine 150 γ b i d , methyldopa 250 mg q i d and triamterene 50 mg, was markedly elevated 240/125 mmHg Central venous pressure was R-6½ cm H_2O No edema Examination of the fundus oculi revealed no signs of hypertensive retinopathy The heart size was slightly increased A systolic bruit was heard over the left abdomen Laboratory slight proteinuria (0 2-0 6 g/24 hr) Urine culture remained sterile Plasma electrolytes sodium 130 mmol/l, potassium 3 3 mmol/l, chloride 97 mmol/l, bicarbonate 33 0 mmol/l Renal function was unimpaired Plasma creatinine 64 µmol/l Blood sugar slightly elevated to 11 8 mmol/l Electrocardiography regular sinus rhythm Prominent U-waves No

signs of left ventricular hypertrophy X-ray of the chest showed a heart-to-lung quotient of 14 5 26 5 Seldinger arteriography of the renal arteries showed normal renal arteries on both sides The right renal cortex showed a scar retraction On computer assisted tomography neither of the adrenal glands could be visualized

2 Aldosterone secretion rates were measured at three different levels of sodium intake The results are presented in table A-20 together with additional relevant data The aldosterone secretion rate was elevated during a sodium intake of 115 and 315 mmol/24 hr, but normal during a sodium free-diet The suppressibility of aldosterone after sodium loading was partially preserved although ASR's were elevated for each level of sodium intake With these results the diagnosis of primary aldosteronism was established

Table A-20

Aldosterone secretion rates and additional clinical and biochemical findings in patient N-M

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol 24 hr
Blood pressure (mmHg)		237/138 (n=19)	
Sodium (mmol/l)	143	143	139
Potassium (mmol/l)	3 1	2 3	2 0
Creatinine (µmol/l)	62	58	64
UV sodium (mmol/24 hr)	34	140	272
UV potassium (mmol/24 hr)	86	99	66
UV creatinine (mmol/24 hr)	9 6	9 7	11 0
PRA (ng/10 ml/3 hr)	66	-	-
ASR (µg/24 hr)	470	353	253

3 Plasma aldosterone concentrations during the late night (figure A-15) varied from 15 5 to 26 8 ng/100 ml The mean nocturnal aldosterone concentration was 19 6 ± 3 5 ng/100 ml A diurnal fall of plasma aldosterone concentration was observed on day 1 and day 2 Plasma aldosterone did not respond to the stimulus of 4 hours of ambulation in the morning (day 1) The correlation coefficients between the basal values of plasma aldosterone cortisol and 18-OH-DOC strongly suggest an influence of ACTH on the regulation of plasma aldosterone concentrations

		night (n=12)		night days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0 67	(p<0 05)	0 44	(n s)
Aldosterone	vs 18-OH-DOC	0 84	(p<0 001)	0 65	(p<0 01)
Cortisol	vs 18-OH-DOC	0 84	(p<0 001)	0 92	(p<0 001)

Dexamethasone treatment did not result in a reduction of the nocturnal aldosterone concentration On the contrary mean plasma aldosterone was even higher (25 7 ± 2 4 ng/100 ml) than under basal circumstances (19 6 ± 3 5 ng/100 ml) The diurnal decline of aldosterone remained preserved during dexamethasone treatment Determination of the diurnal rhythm of aldosterone was repeated 2 months after surgical resection of the right adrenal gland, which contained a classical adrenal adenoma Mean nocturnal aldosterone concentration (figure A-16) had decreased from 19 6 ± 3 5 ng/100 ml before to 10 5 ± 4 9 ng/100 ml after operation Plasma aldosterone increased markedly in response to 4 hours of ambulation in the morning The correlation coefficients between the basal values of aldosterone, cortisol and 18-OH-DOC demonstrate that the influence of ACTH on the control of plasma aldosterone was apparent only during the night

		night (n=12)		night days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0 63	(p<0 05)	0 10	(n s)
Aldosterone	vs 18-OH-DOC	0 66	(p<0 05)	- 0 03	(n s)
Cortisol	vs 18-OH-DOC	0 75	(p<0 01)	0 85	(p<0 001)

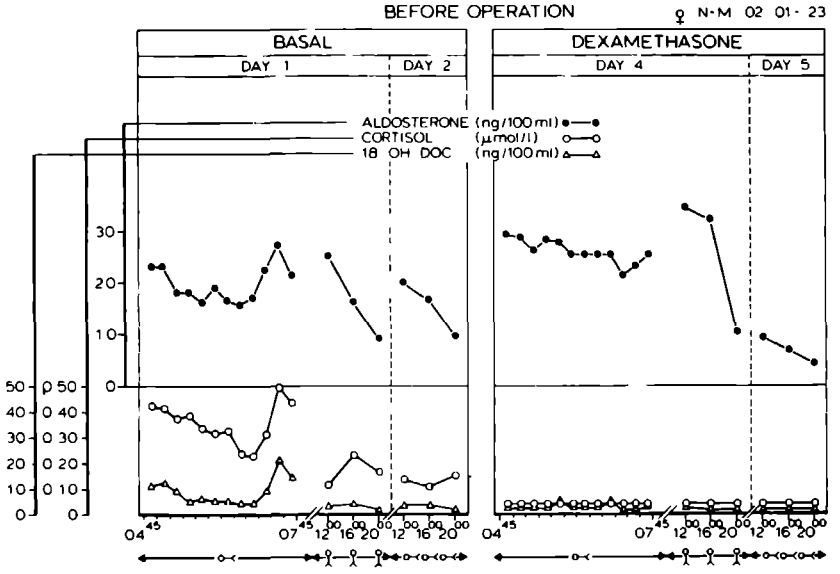


Figure A-15 Diurnal variations of plasma aldosterone, cortisol and 18 OH-DOC in patient N-M with an aldosterone-producing adenoma

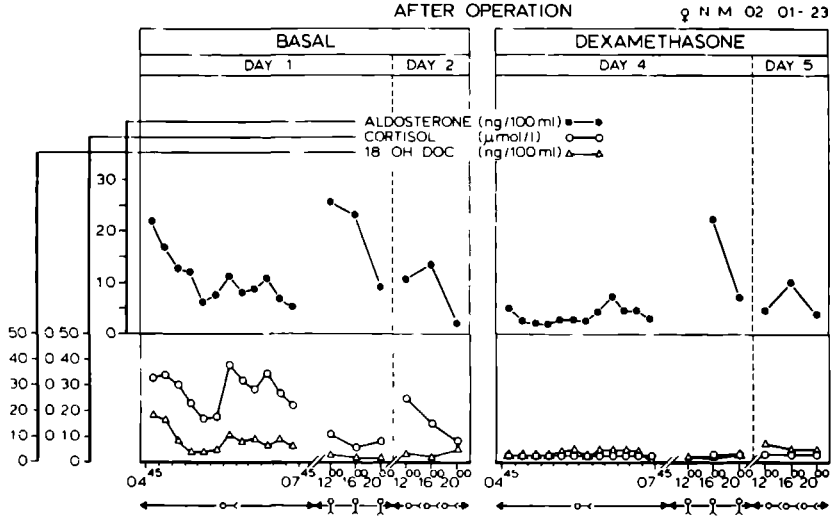


Figure A-16 Diurnal variations of plasma aldosterone cortisol and 18-OH-DOC in patient N-M, 2 months after resection of an adenoma

Dexamethasone treatment reduced mean nocturnal plasma aldosterone from 10 5 ± 4 9 ng/100 ml to 3 6 ± 1 6 ng/100 ml Aldosterone values during the day remained unchanged during dexamethasone

4 Adrenal scintigraphy was performed using the radiopharmaceutical ^{131}I 6β-Iodomethyl-19-Nor-Cholesterol during dexamethasone suppression Dexamethasone was given in a dose of 2 mg/day starting 14 days before injection of the isotope The dose administered was only 0 6 mCi, because the patient felt unwell during injection Scintigrams on the 6th 7th and 8th days showed an accumulation of radioactivity over the right adrenal region Only a minimal accumulation was found on the left side These findings were indicative of the presence of a right adrenal adenoma

5 Treatment with spironolactone 400 mg/day did not result in a significant fall of blood pressure 237/138 mmHg (mean value during stay in the clinic) to 199/116 mmHg after 1 month treatment Dexamethasone administered during 3 weeks, caused a fall of aldosterone excretion to 5 1 µg/24 h Blood pressure however remained unchanged A few days after withdrawal of dexamethasone, the patient was admitted to the hospital because of visus complaints Ophthalmologic examination of the fundus oculi revealed several cotton wool exudates and small hemorrhages A rapid decrease of blood pressure was achieved by treatment with diazoxide infusion and subsequently with spironolactone 400 mg/day and propranolol 240 mg/day The fundoscopy showed a marked improvement after 2 weeks treatment Treatment with spironolactone and propranolol was continued during 6 months Blood pressures during this medication varied from 170 to 196/98 to 116 mmHg

6 On July 27th 1978 the right adrenal gland was surgically removed and appeared to contain an eccentrically located adenoma measuring 1 cm

7 The adrenal gland weighed 12 6 g Locally macronodular hyperplasia was noted in the adrenal cortex, adjacent to the tumor Light microscopy the adenoma partially surrounded by a capsule, was composed of different cell types large and small cells with a clear or eosinophilic cytoplasm, identified as so called 'hybride cells' and large cells with a clear cytoplasm and a small nucleus, identified as zona fasciculata-type cells The adrenal cortex adjacent to the tumor showed locally, a micronodular hyperplasia Conclusion adenoma composed of 'hybride' cells and zona fasciculata-type cells Focally micro- and macronodular hyperplasia of the adrenal cortex

8 Aldosterone excretion decreased to 4 2 µg/24 hr on the second day after operation ASR, measured on the 10th day after operation during a sodium intake of 115 mmol/day, was 63 µg/24 hr Plasma electrolytes normalized within a few days Blood pressure values, however remained elevated varying from 170 to 190/100 to 110 mmHg Blood pressures measured at regular control visits from July 1978 to April 1981 varied from 164 to 200/96 to 120 mmHg, during various antihypertensive treatment regimens

Patient 17 (♀ P R, 13 05 31)

1 A 48 years old woman was referred to the department of internal medicine of our institute on January 17th 1979 because of hypertension Blood pressure was first found to be elevated in 1976 Antihypertensive treatment with propranolol 120 mg/day and chlorthalidone 100 mg twice a week, had not resulted in a decrease of blood pressure For 10 years she had suffered from severe attacks of migraine with nausea and emesis At the first visit she had no complaints There was no nycturia or muscle weakness but she had a slight ankle edema in the evening Menstrual cycles were regular She had never taken oral contraceptives Hypertension did not occur during her two pregnancies in 1957 and 1961 At the first visit she had not any antihypertensive treatment Physical examination blood pressure 200/120 mmHg Fundoscopic examination did not reveal exudates or hemorrhages Pulse rate 68 regular No edema Venous insufficiency of the legs was noted Laboratory slight to marked hypokalemia (2 1 to 3 3 mmol/l) and hypernatremia (142 to 144 mmol/l) Plasma renin activity after 5 days chlorthalidone 100 mg/day was lowered to 38 ng/10 ml/3 hr Electrocardiography sinus rhythm with prominent U-waves X-ray of the chest heart-to-lung quotient was normal

2 The most relevant clinical and biochemical data found during three different levels of sodium intake are summarized in table A-21 The elevated ASR without suppressibility after sodium loading along with a low PRA after stimulation with a sodium restricted diet, confirmed the diagnosis of primary aldosteronism

Table A-21

Aldosterone secretion rates and additional clinical and biochemical findings in patient P-R

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		185/121 (n=21)	
Sodium (mmol/l)	139	141	144
Potassium (mmol/l)	3 4	3 3	3 2
Creatinine (μmol/l)	69	68	72
UV sodium (mmol/24 hr)	32	93	267
UV potassium (mmol/24 hr)	86	90	122
UV creatinine (mmol/24 hr)	16 0	12 0	16 2
PRA (ng/10 ml/3 hr)	26	–	–
ASR (μg/24 hr)	–	385	387

3 The diurnal and noctural plasma aldosterone concentrations (figure A-17) showed wide variations with a tendency to fall during the day High values were found during the night, averaging 36 4 ± 5 9 ng/100 ml Aldosterone decreased during the morning, despite upright posture, from 35 9 to 13 0 ng/100 ml Dexamethasone treatment induced a fall of mean plasma aldosterone during the night from 36 4 ± 5 9 ng/100 ml to 20 7 ± 3 2 ng/100 ml The effects of dexamethasone on daytime aldosterone values were inconsistent Contrary to the findings before dexamethasone, plasma aldosterone increased during ambulation in the morning from 22 0 to 40 0 ng/100 ml From the correlation coefficients between the values of the three adrenocortical hormones, as found under basal conditions, no conclusions can be drawn with respect as to the role of ACTH in the regulation of plasma aldosterone in this patient The correlation coefficients between aldosterone and cortisol on the one hand, and aldosterone and 18-OH-DOC on the other hand, revealed contradictory results, which is probably related to the fact that the ACTH-dependent hormones cortisol and 18-OH-DOC also did not show a strong correlation

		night (n=11)		night, days 1 and 2 (n=17)	
Aldosterone	vs cortisol	0 25	(n s)	0 21	(n s)
Aldosterone	vs 18-OH-DOC	0 68	(p<0 05)	0 70	(p<0 001)
Cortisol	vs 18-OH-DOC	0 36	(n s)	0 56	(p<0 05)

4 Adrenal scintigraphy was performed with ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol Treatment with dexamethasone 2 mg/day was started three weeks before injection of the isotope The radiopharmaceutical was administered at a dose of 1 9 mCi On the 7th day after injection, a clear visualization of the left adrenal gland was obtained The right adrenal gland was almost completely suppressed

5 Two weeks treatment with amiloride 20 mg/day and chlorthalidone 50 mg/day, given concurrently with the dexamethasone treatment, resulted in a decrease of blood pressure to 140/88 mmHg in the recumbent and 100/80 mmHg in the upright position The patient developed complaints of orthostatic hypotension, which disappeared after withdrawal of the chlorthalidone medication Blood pressure after 2 weeks amiloride treatment was 171/108 mmHg

6 On June 6th 1979, the left adrenal gland was surgically removed by way of a left lumbotomy between the 10th and 11th ribs The adrenal gland weighed 11 5 g and contained an adenoma with a maximal diameter of 1 8 cm

7 A circumscript adenoma protruded above the surface of the gland The adenoma was predominantly composed of large polygonal clear cells with small vesicles as found in a normal zona fasciculata There was a slight anisokaryosis and hyperchromasia of the nuclei Small, dark eosinophilic cells, located centrally and in the periphery of the adenoma were also found Locally, a beginning infiltration of the thin capsule by clear cells was noted Mitotic activity was found only sporadically Necrosis, hemorrhages or infiltrations of vessels were absent The adrenal tissue outside the tumor, however, showed an irregular broadening of the cortex with a nodular hyperplasia of the zona

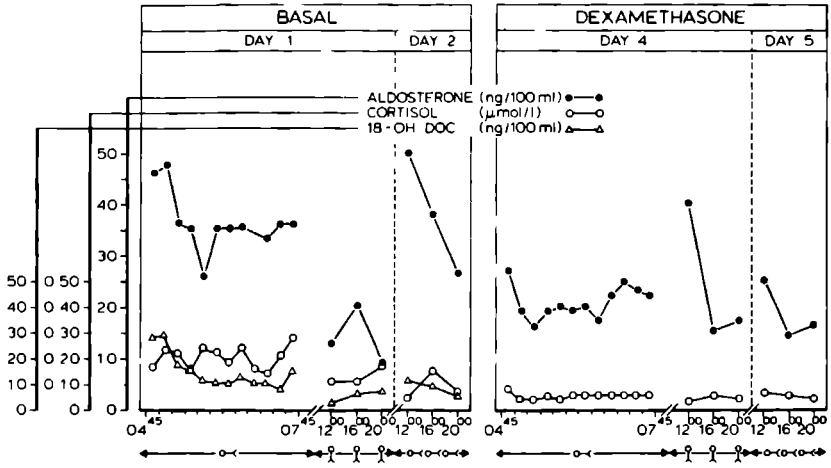


Figure A-17 Diurnal variations of plasma aldosterone, cortisol and 18-OH DOC in patient P-R with an aldosterone-producing adenoma

fasciculata The zona glomerulosa was slightly increased and showed locally a wedge-shaped extension between the cells of the zona fasciculata Conclusion adrenocortical adenoma with micronodular hyperplasia of the adjacent cortex

8 Postoperatively, the aldosterone secretion rate decreased to 8 µg/24 hr as measured on the 10th day after operation during a daily sodium intake of 115 mmol Plasma sodium and potassium were restored to normal Blood pressure was still elevated to 164/118 mmHg on discharge from hospital, but was normal (126/88 mmHg) at the first visit one month after operation and at the regular control visits thereafter During the first two months after operation the patient had complaints of orthostatic hypotension, which resolved spontaneously Attacks of headache disappeared

Patient 18 (♀, S-KI, 27 11 33)

1 The patient is a 45 years old woman, who was referred in 1979 by her family doctor to the department of internal medicine, because of hypertension She had taken oral contraceptives from 1961 to 1973 During this period blood pressure was normal In 1973 treatment with oral contraceptives was discontinued and a laparascopic tubal coagulation was performed A few months later hypertension was detected on the occasion of a neurologic examination on account of persistent headache for many years From 1974 to 1979 she had been treated by an internist elsewhere with medical antihypertensive treatment (propranolol, methyldopa and chlorothiazide) without a satisfactory decrease of blood pressure being achieved The patient discontent with the results of antihypertensive treatment, asked her family doctor for a reference to a university centre At her first visit she complained of chronic fatigue, muscle weakness and palpitations Attacks of headache had disappeared 4 years previously She had no paresthesia, tetany, polydipsia or polyuria Occasionally she had edema of the ankles Her previous history was uneventful Blood pressures had been normal during each of two pregnancies (1958 and 1959) At her first visit blood pressure, measured during antihypertensive treatment with methyldopa and chlorothiazide 500 mg/day, was 210/110 mmHg Fundoscopy revealed a mild hypertensive retinopathy with increased light reflexes and arteriovenous crossing defects No ankle edema Normal central venous pressure The heart was not enlarged Abdominal vascular bruits were absent Laboratory urinary protein and glucose were negative Plasma electrolytes sodium 141 mmol/l, potassium 2 5 mmol/l, chloride 96 mmol/l and bicarbonate 37 6 mmol/l Renal function was unimpaired Radiologic examination of the chest heart-to-lung quotient 13 29 5 Intravenous pyelography revealed no abnormalities Electrocardiography sinus rhythm and marked U-waves The finding of a marked hypokalemia was erroneously attributed to the use of the weak diuretic

chlorothiazide The patient was treated with metoprolol 300 mg/day hydralazine 150 mg/day and chlorothiazide 500 mg/day The blood pressure did not respond to this therapeutic regimen Hypernatremia and hypokalemia with values as low as 2 2 mmol/l were repeatedly found After 10 months treatment antihypertensive medication was discontinued because the patient was still discontent about the results of treatment and asked for a thorough analysis of her hypertension Persistent hypernatremia and hypokalemia after withdrawal of medication led to the tentative diagnosis of primary aldosteronism

2 Clinical evaluation with measurements of aldosterone secretion rates and other clinical and biochemical data (table A 22) confirmed this diagnosis

Table A-22

Aldosterone secretion rates and additional clinical and biochemical findings in patient S Kl

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol 24 hr
Blood pressure (mmHg)		205/117 (n=12)	
Sodium (mmol/l)	136	137	141
Potassium (mmol/l)	3 3	3 4	3 0
Creatinine (µmol/l)	68	67	63
UV sodium (mmol/24 hr)	34	130	389
UV potassium (mmol/24 hr)	86	84	116
UV creatinine (mmol/24 hr)	8 8	9 1	8 4
PRA (ng/10 ml/3 hr)	43	34	–
ASR (µg/24 hr)	240	259	244

4 Adrenal scintigraphy using ^{131}I 6β Iodomethyl 19 Nor-Cholesterol was performed during dexamethasone suppression Dexamethasone was given at a dose of 2 mg/day starting 14 days before injection of the radiopharmaceutical which was given at a dose of 2 1 mCi On the 5th 7th and 9th days p i the right adrenal gland was clearly visualized No adrenal uptake was found on the left side These findings were highly suggestive of an aldosterone producing adenoma in the right adrenal gland

5 Treatment with spironolactone 400 mg/day resulted in a decrease of blood pressure from 205/117 to 150/112 mmHg Side effects of the treatment included fatigue and Ravnoud s phenomenon After lowering the dose to 150 mg and 100 mg day blood pressures remained within the normal range (125/90 mmHg) Side effects however did not subside Medical treatment with amiloride 20 mg day and chlorthalidone 50 mg every 2 days resulted in a fall of blood pressure to 135/95 mmHg after 2 weeks treatment This medication was given concurrently with dexamethasone

6 On October 3rd 1980 the right adrenal gland was surgically removed via a right lumbotomy between the 10th and 11th ribs The right pleural cavity was accidently opened After operation the patient was treated for a pneumothorax by suction drainage through an intrapleural catheter

7 The right gland weighed 8 2 g and contained a yellow adenoma measuring 1 9 cm The adjacent adrenal cortex was flat Light microscopy the adenoma was sharply separated from the adjacent adrenal cortex by a broad connective tissue capsule The tumor was composed of relatively large cells with a small round nucleus and abundant foamy and eosinophilic cytoplasm The cells were arranged in solid fields divided by thin connective tissue septa The tumor did not show any evidence of malignancy The adrenal cortex outside the tumor was normal Conclusion adrenocortical adenoma composed of zona fasciculata type cells

8 Postoperatively plasma electrolytes were restored within a few days to normal values Urinary aldosterone excretion measured on the first day after operation was 0 1 µg/24 hr Aldosterone secretion rate measured on the 10th day after operation during a 115 mmol sodium diet was 23 µg/24 hr Blood pressure decreased to 160 100 mmHg on discharge from hospital and to 140/90 mmHg 2 weeks after operation

Patient 19 (♂, v N, 25 05 16)

1 The patient is a 52 years old man, who was referred to the department of internal medicine on March 8th 1968 Hypertension was detected in July 1966 at a routine medical examination He was treated medically (methyldopa, chlorothiazide, guanethidine) without a satisfactory decrease of blood pressure In January 1968 he was admitted to a hospital elsewhere for hypertension analysis Blood pressure values averaged 263/131 mmHg Plasma potassium values varied from 3 3 to 3 8 mmol/l Primary aldosteronism was suspected, for the analysis of which the patient was referred to our hospital On admission the patient had no complaints He had no headache, muscle weakness, nycturia or paresthesia His previous history was uneventful, except for a hypersensitivity nephritis after the use of sulfonamides (1947) Physical examination Blood pressure on admission was 270/135 mmHg Central venous pressure was R-3 cm H_2O There was no edema Fundoscopy revealed no hemorrhages or exudates The heart was not enlarged A late-systolic murmur was found at the apex of the heart Abdominal bruits were absent Laboratory no proteinuria or glucosuria Plasma electrolytes sodium 144 mmol/l, potassium 3 6 mmol/l, chloride 103 mmol/l, bicarbonate 34 6 mmol/l Renal function was unimpaired Electrocardiography sinus rhythm without signs of left ventricular hypertrophy X-ray of the chest heart-to-lung quotient was 15 32 Intravenous pyelography was normal Seldinger arteriography revealed a slight stenosis at the origin of the right renal artery with a post-stenotic dilatation Retroperitoneal gas insufflation did not reveal a tumor in the adrenal regions

2 Aldosterone secretion rates were clinically measured before and after moderate sodium loading (table A-23) High aldosterone secretion, unresponsive to sodium loading, dexamethasone and DOC treatment, together with mild hypokalemia and hyporeninemia established the diagnosis of primary aldosteronism The slight stenosis of the right renal artery was considered to be hemodynamically unimportant

Table A-23

Aldosterone secretion rates and additional clinical and biochemical findings in patient v N

	SODIUM INTAKE	
	15 mmol 24 hr	115 mmol/24 hr
Blood pressure (mmHg)	243/124 (n=14)	
Sodium (mmol/l)	144	149
Potassium (mmol/l)	3 6	3 5
Creatinine (µmol/l)	85	87
PRA (ng/10 ml/3 hr)	85	–
ASR (µg/24 hr)	481	476

6 On September 5th 1968 the left adrenal gland was surgically explored via a left lumbotomy with resection of the 12th and part of the 11th ribs The left adrenal gland was enlarged (7x2x1 cm) but did not contain a palpable tumor A part of the left gland was resected and about 2x½x½ cm was left in situ Subsequently the right adrenal gland was explored after a right lumbotomy and resection of the 12th rib No tumor was found in the right adrenal, which was enlarged to the same extent as the left adrenal The right adrenal gland was resected in toto

7 The macroscopic aspect of the removed adrenal tissue did not show a macronodular architecture of the cortex Light microscopy the adrenal cortex was of normal width, without adrenocortical nodules The outer adrenocortical layer was composed of alveolarly arranged cells of the zona glomerulosa – or zona fasciculata – type The presence of numerous spironolactone bodies in the outer cortex suggested a well-developed and broad zona glomerulosa Conclusion hyperplasia of the zona glomerulosa with numerous spironolactone bodies

8 Postoperatively, the patient was followed up at the out-patient clinic at irregular intervals for 12 years Blood pressure did not normalize after operation (180/110 – 230/130 mmHg) However, blood pressures responded well to treatment with rauwolfia alkaloids and chlorothiazide (140/85-180/105 mmHg) Aldosterone secretion rate measured in 1969, one year after operation, was normal (70 µg/24 hr) In 1980 blood pressure was 160/85 mmHg during treatment with chlorothiazide 50 mg/day and triamterene 25 mg/day

Patient 20 (♂, S. 30 03 10)

1 The patient is a man who was 56 years old when he was referred to the department of internal medicine in 1966 Hypertension (180/110 mmHg) was detected in 1965 His previous history was uneventful Blood presure did not respond to medical treatment with rauwolfia alkaloids for 2 years Mild spontaneous hypokalemia was repeatedly found He had no complaints of nycturia, muscle weakness paresthesia or tetany On physical examination at admittance to the hospital for clinical evaluation in 1968, his heart was found to be enlarged Fundoscopy revealed no signs of hypertensive retinopathy No vascular abdominal bruits were heard The electrocardiogram did show a sinus rhythm with a sign of a left ventricular strain On X-ray of the chest the heart appeared to be enlarged with a heart-to-lung quotient of 19 32 5 Intravenous pyelography and arteriography were not performed

2 Aldosterone secretion rates were measured at two different levels of sodium intake An elevated aldosterone secretion at a sodium intake of 115 mmol Na^+/24 hr mild hypokalemia and a suppressed renin activity confirmed the diagnosis of primary aldosteronism (table A-24)

Table A-24

Aldosterone secretion rates and additional clinical and biochemical findings in patient S

	SODIUM INTAKE	
	15 mmol/24 hr	115 mmol/24 hr
Blood pressure (mmHg)	184/96	
Sodium (mmol/l)	143	147
Potassium (mmol/l)	3 8	3 6
Creatinine (μmol/l)	88	92
UV sodium (mmol/24 hr)	–	147
UV potassium (mmol/24 hr)	–	48
UV creatinine (mmol/24 hr)	–	15 3
PRA (ng/10 ml/3 hr)	42	–
ASR (μg/24 hr)	281	401

7 On postmortum examination both adrenal glands appeared enlarged and weighed 50 g (L+R) No adrenocortical adenoma was found Light microscopic examination revealed a marked broadening of the adrenal cortex with focally a nodular architecture The cortex was mainly composed of clear vacuolated cells as found in the zona fasciculata Subcapsularly, the cells could be identified as zona glomerulosa-type cells More inwards, however no histologic distinction could be made between zona glomerulosa-type cells and zona fasciculata-type cells devoid of lipoid

8 On January 31th 1971 the patient died from an acute pancreatitis Postmortum examination revealed an acute hemorrhagic pancreatitis, peritoneal fat necrosis and a hypertrophy of the left myocardium

Patient 21 (♀, L. 03 10 14)

1 The patient is a 54 years old woman, who was referred to the department of internal medicine on June 25th 1969 for analysis and treatment of hypertension High blood pressure was detected in January 1968, when she visited her family doctor with complaints of a pulsatile swelling above the right clavicle Angiography of the aortic arch had revealed an elongation of the aorta with a hitch of the right carotid and left subclavian arteries Surgical correction was not performed Antihypertensive treatment had been unsuccessful At the first visit she complained of fatigue, headache and nycturia There was a long history of backache She had undergone four operations for prolapses of both thoracic and lumbar discs Physical examination blood pressure was 230/130 mmHg Central venous pressure was R-6 cm H_2O No edema Fundoscopy revealed no hemorrhages or exudates A pulsatile swelling with a diameter of 6 cm was found above the right clavicle The heart was enlarged and an exaggerated apical impulse was found Abdominal vascular bruits were absent The spleen was enlarged to 5 cm under the left costal margin The liver was not palpable Laboratory the urine was

normal Plasma electrolytes sodium 146 mmol/l potassium 3 1 mmol/l, chloride 106 mmol/l bicarbonate 29 8 mmol/l Renal function was moderately impaired with a creatinine clearance of 55 ml/min Intravenous pyelography showed a delayed appearance time of the contrast material The renal pelvis and calyces in the upper pole of the right kidney and in the left kidney were dilated The renal cortex was relatively small on both sides The radiologic features were characteristic of chronic pyelonephritis Seldinger arteriography of the renal arteries did not disclose renal artery stenosis Electrocardiography sinus rhythm, signs of left ventricular hypertrophy, and sporadically ventricular premature beats, T-inversion in leads III, AVF and V4-V6, U-waves

2 Aldosterone secretion rates were measured both during sodium restriction and after moderate sodium loading (table A 25) Aldosterone secretion rate after moderate sodium loading was slightly elevated This finding, together with hypertension hypokalemia and hyporeninemia confirmed the diagnosis of primary aldosteronism It was decided not to explore the adrenal glands because 1 Signs and symptoms of primary aldosteronism were relatively mild and 2 The impairment of renal function diminished the prospects of successful adrenal surgery

Table A 25

Aldosterone secretion rates and additional clinical and biochemical findings in patient L

	SODIUM INTAKE	
	15 mmol/24 hr	115 mmol/24 hr
Blood pressure (mmHg)	215/131 (n=22)	
Sodium (mmol/l)	141	143
Potassium (mmol/l)	3 4	3 3
Creatinine (μmol/l)	163	117
UV sodium (mmol/24 hr)	9	101
UV potassium (mmol/24 hr)	18	29
UV creatinine (mmol/24 hr)	7 3	9 1
PRA (ng/10 ml/3 hr)	32	-
ASR (μg/24 hr)	418	222

7 Postmortum examination of the adrenal glands revealed no adrenocortical adenoma Macroscopically the adrenal cortex did not show macronodular hyperplasia Total adrenal weight, however was increased to 20 g Light microscopic examination showed a zona glomerulosa, which was present over the full length of the preparation The cells of the zona glomerulosa were arranged in solid fields One solitary adrenocortical nodule that was found was composed of cells with a fine vacuolated cytoplasm and a round nucleus The nodule was clearly separated from the adjacent tissue, although it was not surrounded by a capsule The zona fasciculata showed only focally a slight increase of the number of cells The zona reticularis was normal Conclusion micronodular adrenocortical hyperplasia

8 During regular control visits to the out-patient clinic from October 1969 to February 1971 the blood pressure remained elevated and did not respond to medical treatment with rauwolfia alkaloids and hydralazine On February 25th 1971 the patient was admitted to the hospital because of fever severe abdominal pain radiating to the right shoulder jaundice and vomiting A tentative diagnosis of acute cholecystitis was made, and she was referred to the department of surgery On March 5th she died suddenly Postmortum examination disclosed a dissecting aneurysm of the aorta extending from the aortic valves to the coeliac trunk chronic pyelonephritis hypertrophy of the heart and splenomegaly

Patient 22 (♀, S-B, 13 08 28)

1 The patient is a 42 years old woman who was referred to the department of internal medicine in October 1970 for analysis and treatment of high blood pressure Hypertension was detected in June 1970, when she visited the department of surgery because of rectal hemorrhages Extensive examination, including rectoscopy and radiography of the gastro-intestinal tract had revealed no abnormalities Blood pressure was still normal in February 1969, when an abdominal hysterectomy was performed At the first visit, she complained of hot flushes and attacks of dizziness and generalized sweating In addition she complained of fatigue, ankle edema in the evening and nycturia She had no

muscle weakness or headache She had a long history of heavy cigarette smoking and chronic bronchitis She had never been pregnant and had never taken oral contraceptives Physical examination at the first visit revealed a blood pressure of 230/120 mmHg Central venous pressure was R-6 cm H_2O Edema was absent Fundoscopy revealed a mild hypertensive retinopathy with arteriovenous crossings and copper-wire arteries No hemorrhages or exudates were found The heart was not enlarged No abdominal vascular bruits were heard Laboratory no proteinuria or glucosuria Plasma electrolytes sodium 145 mmol/l potassium 3 3 mmol/l chloride 101 mmol/l bicarbonate 26 6 mmol/l Renal function was unimpaired X ray of the chest showed that the heart was not enlarged Intravenous pyelography was normal Seldinger arteriography did not disclose narrowing of the renal arteries The adrenal glands were not visualized Imaging of the adrenal glands by adrenal venography was unsuccessful Electrocardiography sinus rhythm and marked U-waves No signs of left ventricular hypertrophy

2 Adosterone secretion rates before and after sodium loading are presented in table A-26 The clinical and biochemical findings are in accordance with a relatively mild primary aldosteronism

Table A-26

Aldosterone secretion rates and additional clinical and biochemical findings in patient S B

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol 24 hr
Blood pressure (mmHg)		173/105 (n=12)	
Sodium (mmol/l)	143	147	143
Potassium (mmol/l)	3 8	3 4	3 1
Creatinine (µmol/l)	82	92	62
UV sodium (mmol/24 hr)	2	176	460
UV potassium (mmol/24 hr)	27	85	92
UV creatinine (mmol/24 hr)	12 6	14 9	13 9
PRA (ng/10 ml/3 hr)	21	-	-
ASR (µg/24 hr)	-	242	219

5 Antihypertensive treatment with spironolactone 400 mg/day resulted in a decrease of blood pressure from 173/105 (mean value during clinical admission) to 125/85 mmHg after 4 weeks treatment and 140/80 mmHg after 8 weeks treatment (values measured at the out-patient clinic) During treatment the patient developed Ravnaud s phenomenon which is a known side effect of spironolactone treatment

6 On July 7th 1971 the left adrenal gland was explored via a left lumbotomy and resection of the 12th rib The left adrenal gland was firmly attached to the diaphragm No palpable adrenal tumor was found Subsequently the right adrenal gland was explored via a right lumbotomy This gland appeared to have grown together with the upper pole of the right kidney The right adrenal also did not contain a palpable tumor The right gland was resected in toto Subsequently two-thirds of the left adrenal were resected

7 The right adrenal gland weighed 4 g An adrenocortical adenoma was not found on dissection of the gland The adrenal cortex had width of 1 mm The tissue resected from the left adrenal gland weighed 3 g and showed on its outer surface a pattern comparable with that found in the right gland An adrenocortical adenoma was not found Light microscopy the zonae glomerulosae of both adrenal glands were widened and contained large cells with a clear cytoplasm and a centrally located nucleus Many of these cells contained spironolactone bodies It was found difficult to differentiate these cells from those normally found in the zona fasciculata Conclusion hyperplasia of the zona glomerulosa of both adrenal glands Spironolactone bodies

8 One month after operation the patient was admitted to the hospital for evaluation of the results of the operative procedure Mean blood pressure on admission was 115/81 mmHg (n=10) Aldosterone secretion rate measured during a 115 mmol sodium diet was in the low to normal range (79 µg/24 hr)

Plasma renin activity, however, showed a high value of 1475 ng/10 ml/3 hr on a sodium-restricted diet, while plasma sodium decreased to 130 mmol/l, plasma potassium increased to 5 2 mmol/l and plasma creatinine increased to 100 µmol/l In addition, a 30-40 mmol sodium loss per day was noted on the sodium-restricted diet These findings were suggestive of a relative mineralocorticoid deficiency Substitution therapy with 9-α-fluoro-hydrocortisone 0 1 to 0 2 mg/day was started and continued until 1975 At that time aldosterone secretion rate measured during a sodium-restricted diet after discontinuation of mineralocorticoid substitution, was normal (252 µg/24 hr), together with normal values for PRA (453 ng/10 ml/3 hr), plasma sodium (139 mmol/l), plasma potassium (3 9 mmol/l) and plasma creatinine (77 µmol/l), while urinary sodium excretion decreased to values lower than 15 mmol/24 hr The mean blood pressure value during clinical admission was 127/85 mmHg (n=17) In 1974 and 1975 a rapid deterioration of pulmonary function was noted On January 5th 1976 she died as a consequence of an exacerbation of her chronic bronchitis with respiratory insufficiency

Patient 23 (♂, J, 09 07 27)

1 The patient is a 46 years old man, who was referred to the department of internal medicine on April 25th 1973 Hypertension (210/130 mmHg) was detected in January 1973 by his family doctor At a routine medical examination in 1969 blood pressure was found to be normal Antihypertensive treatment with chlorothiazide 500 mg per day and a salt-restricted diet had resulted in an insufficient decrease of blood pressure to 170 to 180/104 to 120 mmHg The patient had no complaints, except that for a few months he felt overworked He had no headache, muscle weakness, nycturia or paresthesia In January 1973 he had developed ankle edema, which had subsequently disappeared spontaneously His previous history revealed a lung tuberculosis in 1944 and 1950 In 1964, 1966 and 1970 he had recurrent nephrolithiasis Physical examination blood pressure values at his first visit varied from 180/105 to 210/110 mmHg Central venous pressure was normal, R-5 cm H_2O No edema Fundoscopy revealed no signs of hypertensive retinopathy The heart was not enlarged Vascular abdominal bruits were absent Laboratory no proteinuria or glucosuria Urine culture sterile Plasma electrolytes sodium 143 mmol/l, potassium 2 9 mmol/l, chloride 99 mmol/l, bicarbonate 34 0 mmol/l Renal function was unimpaired Electrocardiography sinus rhythm Signs of left ventricular hypertrophy Sporadically, ventricular premature beats and U-waves Radiography of the chest showed a heart-to-lung quotient of 13 30 Intravenous pyelography did not reveal any abnormality Seldinger arteriography disclosed no renal artery stenosis The right adrenal gland was visualized, but looked normal The left adrenal was not visualized An attempt to visualize the adrenal glands by percutaneous venography was unsuccessful, due to a failure to cannulate the central adrenal vein on each side

2 Clinical measurements of aldosterone secretion rate before and after sodium loading and other relevant clinical and biochemical data are presented in table A-27 These findings established the diagnosis of primary aldosteronism

Table A-27

Aldosterone secretion rates and additional clinical and biochemical findings in patient J

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		169/118 (n=16)	
Sodium (mmol/l)	141	139	147
Potassium (mmol/l)	2 7	3 3	2 6
Creatinine (µmol/l)	94	80	78
UV sodium (mmol/24 hr)	63	271	386
UV potassium (mmol/24 hr)	62	81	100
UV creatinine (mmol/24 hr)	10 0	17 0	17 5
PRA (ng/10 ml/3 hr)	62	–	–
ASR (µg/24 hr)	426	340	388

5 Medical treatment with spironolactone 400 mg/day resulted in a decrease of blood pressure from 169/118 mmHg (mean blood pressure value during clinical admission) to 135/95 mmHg (measured at the

out-patient clinic after 4 weeks treatment) During treatment the patient experienced upper abdominal discomfort and diarrhoea

6 On November 8th 1973 the right adrenal gland was surgically explored via a right lumbotomy The adrenal gland was not enlarged and did not contain a palpable tumor Half of the gland was resected The left adrenal gland, explored via a left lumbotomy, also did not harbor a palpable tumor The left adrenal gland was resected in toto

7 The macroscopic material consisted of a large number of tissue fragments The tissue removed was not weighed Light microscopy the adrenal cortex of all tissue fragments was relatively thin The cortical zonation showed an irregular architecture Focally the clear cells of the zona fasciculata reached up to the capsule The zona glomerulosa did not show a diffuse or nodular widening Several fresh and old hemorrhages were found between the zona reticularis and the adrenal medulla Conclusion focal increase of zona glomerulosa cells No adenoma or nodular hyperplasia were found

8 Postoperatively the plasma electrolytes normalized Aldosterone secretion rates were not measured Blood pressures, measured during stay in the clinic one month after operation varied from 120 to 150/95 to 110 mmHg At the subsequent control visit during a follow-up period of 7 years, blood pressures remained slightly elevated (140 to 150/95 to 105 mmHg) The patient was not treated with antihypertensive medicaments

Patient 24 (♂, T, 19 02 24)

1 The patient is a 48 years old man, who was referred to our institute on May 25th 1972, because of hypertension High blood pressure was detected in 1968 in the course of a medical sports examination No medical treatment was prescribed His body weight increased from 90 to 110 kg From 1970 on he developed complaints of fatigue, shortness of breath, nycturia 3 to 4 times and ankle edema Hypertension analysis in a hospital elsewhere, revealed high blood pressure (185 to 200/115 to 120 mmHg), absence of heart failure, electrocardiogram without signs of left ventricular hypertrophy, a slight radiographic increase of heart size and a normal intravenous pyelogram Medical treatment with catapressan and chlorthalidone had to be withdrawn because of hypokalemia When the patient was subsequently referred to our institute, he complained of fatigue, polyuria and nycturia He had no muscle weakness, edema or tetany He had not had any antihypertensive medication for at least one month The previous medical history was uneventful Physical examination Blood pressure 230/130 mmHg No edema Slight increase of heart size No abdominal bruits Laboratory no proteinuria Plasma electrolytes sodium 142 mmol/l, potassium 3 1 mmol/l, chloride 104 mmol/l, bicarbonate 32 4 mmol/l Creatinine 107 µmol/l Fasting cholesterol 6 1 mmol/l triglyceride 5 48 mmol/l Glucose 5 0 mmol/l Impaired carbohydrate tolerance after oral glucose loading Heart-to-lung quotient on radiogram of the chest was 17 36 Intravenous pyelogram was normal Antihypertensive treatment with chlorthalidone 50 mg/day and methyldopa for 3 months did not result in a satisfactory decrease of blood pressure Plasma electrolytes repeatedly showed hypernatremia (144-144-144 mmol/l) and hypokalemia (3 1-2 8-2 7 mmol/l), despite addition of potassium supplements Unfortunately, these findings did not lead to further investigations into the presence of primary aldosteronism All hypertensive medications were withdrawn after the finding of a normal blood pressure value (125/75 mmHg) by direct intra-arterial measurement The patient was discharged from the out-patient clinic One year later, in April 1975, he was again referred to our hospital after the finding of severe hypertension (240/150 mmHg) at a routine medical examination The patient complained of headache Polyuria and nycturia were still present Physical examination weight 114,2 kg, blood pressure 250/160 mmHg Fundoscopy showed no hemorrhages or exudates Laboratory plasma sodium 148 mmol/l, potassium 2 8 mmol/l, chloride 98 mmol/l, bicarbonate 29 1 mmol/l Creatinine 119 µmol/l Electrocardiography flattening of the ST-T segments in leads I, AVL, V1-V6 Prominent U-waves The radiographic heart-to-lung quotient was 18 36 5 Intravenous pyelogram was normal Seldinger arteriography no vascular abnormalities of the renal arteries

2 The patient was admitted to the hospital for clinical examination and determinations of plasma renin activity and aldosterone secretion rate The results are presented in the table A-28 The clinical data are in accordance with the diagnosis of primary aldosteronism

3 Surprisingly, in view of the marked elevation of aldosterone secretion rates, plasma aldosterone values, both by night and by day, were within the normal range (figure A-18) Plasma aldosterone

Table A-28

Aldosterone secretion rates and additional clinical and biochemical findings in patient T

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		199/127 (n=27)	
Sodium (mmol/l)	144	147	144
Potassium (mmol/l)	3 3	2 8	2 5
Creatinine (μmol/l)	152	150	105
UV sodium (mmol/24 hr)	14	146	353
UV potassium (mmol/24 hr)	44	80	106
UV creatinine (mmol/24 hr)	20 5	21 9	18 6
PRA (ng/10 ml/3 hr)	34	–	–
ASR (μg/24 hr)	–	474	432

values during the day were somewhat higher than during the night A slight postural increase of aldosterone was found after 4 hours of ambulation in the morning Aldosterone correlated significantly with cortisol and 18-OH-DOC during the night During the night and the days, aldosterone was also significantly correlated to cortisol, not however to 18-OH-DOC

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	0 74	(p<0 01)	0 55	(p<0 05)
Aldosterone	vs 18-OH-DOC	0 72	(p<0 01)	−0 06	(n s)
Cortisol	vs 18-OH-DOC	0 91	(p<0 001)	0 56	(p<0 05)

Thus, the influence of ACTH on the regulation of aldosterone was apparent, especially during the night Dexamethasone treatment did not influence the level of plasma aldosterone concentrations during the night and the day

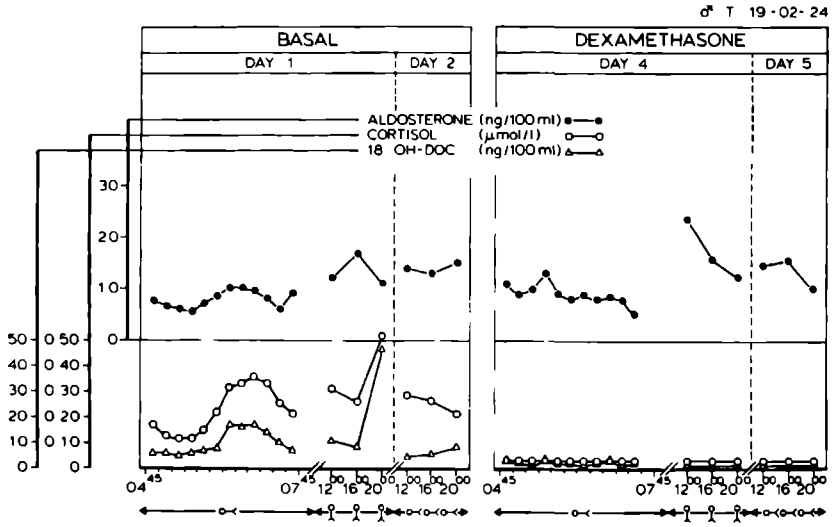


Figure A-18 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient T with idiopathic aldosteronism

4 Dexamethasone suppression scans of the adrenal glands were performed, using ^{131}I-19-Iodocholesterol Dexamethasone was given at a dose of 2 mg/day, starting 3 days before injection of 1 mCi of ^{131}I-19-Iodocholesterol Adrenal scintigrams on the 3rd, 5th, 6th and 7th days did not show any discernable accumulation of radioactivity in either of the adrenal regions On the 8th day a slight accumulation was detected over both adrenal areas The absence of unilateral accumulation of radioactivity excluded the presence of an aldosterone-producing adenoma Therefore, primary aldosteronism in this patient was considered to be caused by bilateral adrenal hyperplasia

5 The effects of medical treatment with high doses of spironolactone (400 mg/day) for 6 weeks were compared with the effects of 6 weeks treatment with high doses of amiloride (40 mg/day) (table A-29) Amiloride was not as effective as spironolactone in lowering the blood pressure Renin and aldosterone were stimulated by either drug to the same extent The patient experienced considerable side effects during spironolactone treatment gynecomastia, impotency and abdominal discomfort Amiloride caused a mild diarrhea After the spironolactone vs amiloride trial, medical treatment was continued with spironolactone at doses of 100 to 200 mg/day Despite these low doses the patient developed abdominal complaints, which appeared to be based on a duodenal ulcer Therefore, spironolactone was withdrawn for half a year

Table A-29

Comparison of the effects of treatment with spironolactone versus amiloride on some clinical and biochemical findings in patient T

	SODIUM INTAKE		
	spironolactone 400 mg/day (6 wks)	placebo (6 wks)	amiloride 40 mg/day (6 wks)
Body weight (kg)	107	110 8	110 6
Blood pressure (mmHg)*	112/92	154/104	129/90
Sodium (mmol/l)	139	141	139
Potassium (mmol/l)	5 0	3 8	4 6
Creatinine (μmol/l)	148	119	120
PRA (ng/10 ml/3 hr)	297	47	253
Aldosterone excretion (μg/24 hr)	51	20	46

* Measured by arteriosonde

Patient 25 (♀, v E-v U, 11 03 37)

1 This patient, a 35 years old woman, was referred to the out-patient clinic of our institute by her family doctor on August 23th 1971, because of a mild hypertension and a non-toxic struma Hypertension was detected during her third pregnancy in 1972, while during her first two pregnancies blood pressures had been normal Blood pressure remained elevated after the delivery and during the subsequent use of oral contraceptives The second reason for her referral was an enlarged thyroid for the previous 2 years She had no complaints of hyperthyroidism nor complaints due to enlargement of the thyroid Her previous history had been uneventful, except for an appendectomy in 1956 At the control visits to the out-patient clinic, after withdrawal of the oral contraceptives, blood pressures remained elevated 150 to 160/110 to 115 mmHg Treatment with chlorthalidone 50 to 100 mg/day for almost 2 years resulted in a decrease of blood pressure to levels of 120 to 150/85 to 90 mmHg During diuretic treatment plasma sodium levels were repeatedly above normal (141 to 147 mmol/l) concomitantly with mild hypokalemia (3 4 to 3 6 mmol/l) After discontinuation of medical treatment the patient was admitted to the hospital in 1974 for evaluation of her blood pressure On admittance she was free of complaints she had no headache, no polyuria, no nycturia, no paresthesia and no tetany Physical examination Blood pressure 160/120 mmHg Fundoscopy no signs of hypertensive retinopathy The thyroid was asymmetrically enlarged, and had a smooth surface No pathologic lymph nodes were found Central venous pressure was normal The heart was not enlarged No abdominal bruits were noted Radiologic examination of the chest revealed a normal heart size with a heart-to-lung

quotient of 13 28 Intravenous pyelography was normal Seldinger arteriography showed a normal renal artery on both sides No abnormalities were found in the adrenal regions The electrocardiogram demonstrated a sinus rhythm and absence of left ventricular hypertrophy

2 Aldosterone secretion rates, plasma renin activity and other relevant data are presented in table A-30 The findings of a hypertension, normal plasma sodium levels, normal to mildly decreased plasma potassium levels, slightly decreased plasma renin activity and insufficient suppressibility of aldosterone secretion after sodium loading, were all in agreement with the diagnosis of mild primary aldosteronism

Table A-30

Aldosterone secretion rates and additional clinical and biochemical findings in patient v E-v U

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		150/100 (n=9)	
Sodium (mmol/l)	140	141	140
Potassium (mmol/l)	3 9	3 4	3 9
Creatinine (μmol/l)	64	50	58
UV sodium (mmol/24 hr)	28	250	331
UV potassium (mmol/24 hr)	72	110	86
UV creatinine (mmol/24 hr)	10 8	15 4	12 4
PRA (ng/10 ml/3 hr)	112	–	–
ASR (μg/24 hr)	426	250	199

3 The nocturnal plasma aldosterone concentrations (figure A 19) ranged from 4 2 to 14 8 ng/100 ml Aldosterone increased markedly during subsequent ambulation (day 1) to 28 1 ng/100 ml at 12 00 hours a m and to 30 7 ng/100 ml at 16 00 hours Recumbent aldosterone concentrations (day 2)

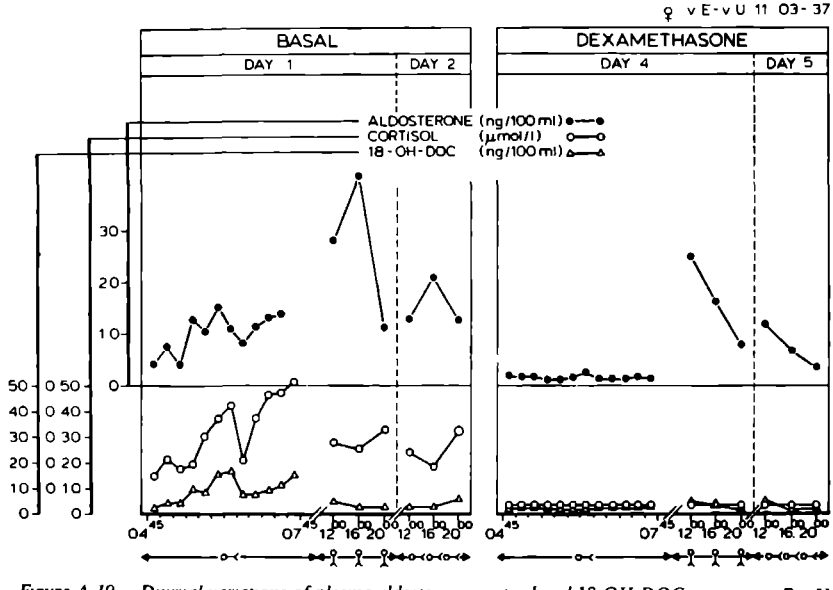


Figure A-19 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient v E-v U with idiopathic aldosteronism

remained lower than the value during ambulation (day 1) The correlation coefficients between the three adrenocortical hormones demonstrated a role for ACTH in the regulation of aldosterone during the night, not however for the regulation of the nocturnal and daytime values together

		night (n=11)		night days 1 and 2 (n=17)	
Aldosterone	vs cortisol	0 75	(p<0 01)	0 34	(n s)
Aldosterone	vs 18-OH-DOC	0 79	(p<0 01)	0 03	(n s)
Cortisol	vs 18 OH-DOC	0 71	(p<0 01)	0 62	(p<0 01)

Dexamethasone treatment reduced mean nocturnal aldosterone from 10 0 ± 3 6 to 1 4 ± 0 4 ng/100 ml The daytime aldosterone values during dexamethasone were only slightly lower than the values obtained under basal circumstances

4 Adrenal scintigraphy was performed with ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol after long term pretreatment with dexamethasone (2 mg/day) which was started 2 weeks before administration of 1 8 mCi of the radiopharmaceutical Adrenal scintigrams on the 2nd, 5th and 6th days after injection, showed no accumulation of radioactivity in the adrenal glands

5 The effects of 6 weeks treatment with spironolactone 400 mg/day on blood pressure and other clinical and biochemical parameters were compared to the effects of 6 weeks treatment with amiloride 40 mg/day (table A-31) Amiloride did not decrease blood pressure to a level as low as that found after spironolactone treatment Stimulation of PRA after spironolactone occurred concomitantly with a marked decrease of body weight After amiloride treatment body weight and PRA remained essentially unchanged Aldosterone excretions increased after either treatment The patient experienced no side effects from either of the drugs, or urinary aldosterone excretions Since this patient was considered to have primary aldosteronism without adrenocortical adenoma (idiopathic aldosteronism") it was decided not to explore the adrenal glands Medical treatment with low doses of spironolactone (50 mg/day) together with low doses of amiloride (15 mg/day) maintained diastolic blood pressures lower than 100 mmHg

Table A 31

Comparison of the effects of treatment with spironolactone versus amiloride on some clinical and biochemical findings in patient v F- v U

	spironolactone 400 mg/dav (6 wks)	placebo (6 wks)	amiloride 40 mg/day (6 wks)
Body weight (kg)	71 8	75 1	75 5
Blood pressure (mm1lg)*	102/61	130/92	115/81
Sodium (mmol/l)	137	142	137
Potassium (mmol/l)	4 4	3 4	3 5
Creatinine (μmol/l)	68	60	56
PRA (ng/10 ml/3 hr)	322	103	56
Aldosterone excretion (μg/24 hr)	53	14	34

* Measured by arteriosonde

Patient 26 (♀, C-J, 05 04 23)

1 The patient is a woman of 36 years old, who was admitted to our hospital in 1959 because of hypertension High blood pressure was detected by her family doctor in 1953 when she complained of ankle edema Earlier she was found to be hypertensive during each of her three pregnancies (1946 1948 and 1951) Antihypertensive treatment with rauwolfia alkaloids had to be withdrawn because of side effects On admission the patient complained of fatigue She had no nycturia muscle weakness, tetany or paresthesia Blood pressure was 235/145 mmHg Fundoscopy revealed only crossing phenomena No vascular abdominal bruits were heard Laboratory plasma electrolytes were normal

After three days therapy with chlorothiazide, plasma potassium decreased from 4 0 to 2 4 mmol/l Electrocardiogram was normal Heart-to-lung quotient was 13 27 5 Intravenous pyelogram was normal During medical treatment with rauwolfia alkaloids, chlorothiazide and a sodium-restricted diet blood pressure decreased to 160/95 mmHg At the second admission to our hospital in 1965, the aldosterone secretion rate, measured during a sodium-restricted diet and 5 days of sodium loading with 9 g NaCl/day, revealed a high rate of 347 μg/24 hr Blood pressures at that time were still markedly elevated (230/140 mmHg), concurrent with intermittent hypokalemia (3 2 to 4 1 mmol/l) Seldinger arteriography showed normal renal arteries Hyperaldosteronism was also found during the third admission in 1967 when she complained of ankle edema, paresthesia and fatigue Aldosterone secretion rates during a daily sodium intake of 6 g per day were elevated to 285, 286 and 364 μg/24 hr during a sodium restricted diet

2 *Aldosterone secretion rates were repeatedly measured during a clinical admission in 1979 The results* together with other relevant parameters are presented in table A-32 The data presented are in agreement with the diagnosis of mild primary aldosteronism

Table A-32

Aldosterone secretion rates and additional clinical and biochemical findings in patient C-J

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		186/106 (n=10)	
Sodium (mmol/l)	140	142	138
Potassium (mmol/l)	3 4	3 2	3 4
Creatinine (μmol/l)	84	–	71
UV sodium (mmol/24 hr)	30	79	290
UV potassium (mmol/24 hr)	79	48	86
UV creatinine (mmol/24 hr)	10 6	9 2	13 1
PRA (ng/10 ml/3 hr)	147	–	–
ASR (μg/24 hr)	468	143	163

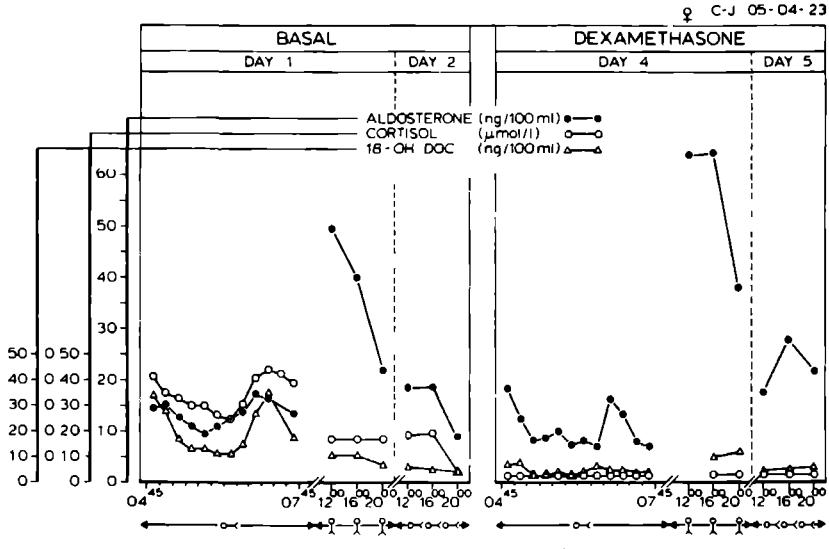


Figure A-20 Diurnal variations of plasma aldosterone, cortisol and 18-OH-DOC in patient C-J with idiopathic aldosteronism

3. Nocturnal plasma aldosterone concentrations were within the range of values found in patients with normal aldosterone secretion (figure A-20). Upright posture in the morning caused a marked increase of aldosterone from 13.3 to 49.6 ng/100 ml, with a subsequent decline, despite a persistent upright posture. The daytime recumbent aldosterone values were considerably lower than the comparative upright values. The correlation coefficients for the basal values of the three adrenocortical hormones showed a role for ACTH during the nocturnal control of aldosterone, not however, for the regulation of aldosterone during the night and days 1 and 2:

		night (n=11)		night, days 1 and 2 (n=17)	
Aldosterone	vs cortisol	0.79	(p<0.001)	−0.14	(n.s.)
Aldosterone	vs 18-OH-DOC	0.78	(p<0.001)	−0.12	(n.s.)
Cortisol	vs 18-OH-DOC	0.96	(p<0.001)	0.98	(p<0.001)

Dexamethasone slightly reduced the mean nocturnal aldosterone concentration from 13.4 ± 2.5 to 10.2 ± 3.9 ng/100 ml. Daytime aldosterone values were slightly higher during dexamethasone, especially during the upright posture.

4. Adrenal scintigrams were performed using ^{131}I-6β-Iodomethyl-19-Nor-Cholesterol, during long-term suppression of the adrenal function with dexamethasone. Dexamethasone treatment was given at a dose of 2 mg/day, starting 15 days before injection of 1.8 mCi of the isotope. Adrenal scintigrams on the 5th and 7th days after injection showed an equal accumulation of radioactivity in both adrenal glands. The findings were considered to be in accordance with the diagnosis of primary aldosteronism due to bilateral adrenal hyperplasia.

5. From 1971 to 1979 the patient was treated medically with spironolactone at doses varying from 100 to 300 mg/day. With this therapeutic regimen diastolic blood pressure levels remained between 90 and 100 mmHg. Spironolactone did not cause any side effects.

Patient 27 (♂, K, 21.04.13)

1. In 1977, when he was 66 years old, the patient was referred by an internist elsewhere to our institute. Hypertension had been detected in 1960 at a routine medical examination. Blood pressure was treated with several medicaments (rauwolfia alkaloids, hydrochlorothiazide, methyldopa). The effects of this treatment could not be evaluated, as the patient regularly withdrew from control visits. In 1975 he was referred to an internist elsewhere, who found a severe hypertension (190 to 210/110 to 120 mmHg) and spontaneous hypokalemia. The patient withdrew from control visits until 1977, when he was referred to our institute because of the repeated finding of severe hypertension with concurrent hypokalemia (2.7 to 3.4 mmol/l). Seldinger arteriography had excluded secondary hyperaldosteronism due to renal artery stenosis. He complained of polydipsia, polyuria, nycturia (3 times) and muscle weakness. In the last 2 years he had not taken antihypertensive or other medicaments. Blood pressure on admission was 234/138 mmHg. Fundoscopy revealed no hemorrhages or exudates. The heart was slightly enlarged. Central venous pressure was normal and no edema was found. No vascular abdominal bruits were heard. Electrocardiography: sinus rhythm with signs of left ventricular hypertrophy. X-ray of the chest: heart-to-lung quotient 14.5:29.

2. Aldosterone secretion rates at three different levels of sodium intake and other clinical and biochemical data are presented in table A-33. The findings of hypertension, hypokalemia, increase of kaliuresis in response to sodium loading and a low PRA unresponsive to sodium- restriction and upright posture, suggest the presence of primary aldosteronism. However, ASR is normal at a sodium restricted diet and after moderate sodium loading. The elevated ASR after a 315 mmol sodium diet illustrates that aldosterone production lacks the normal suppressibility by sodium loading. Therefore, the diagnosis of primary aldosteronism seems inevitable, despite the relatively low rates of aldosterone secretion.

3. Plasma aldosterone concentrations were within the normal range, both during the night and the days (figure A-21). Aldosterone did respond to the stimulus of upright posture in the morning. The daytime recumbent aldosterone values were lower than the comparable upright values. The correlation coefficients between the basal values of the three adrenocortical hormones excluded a significant influence of ACTH on the regulation of aldosterone.

Table A-33

Aldosterone secretion rates and additional clinical and biochemical findings in patient K

	SODIUM INTAKE		
	15 mmol/24 hr	115 mmol/24 hr	315 mmol/24 hr
Blood pressure (mmHg)		223/139 (n=14)	
Sodium (mmol/l)	140	145	141
Potassium (mmol/l)	2 7	2 6	2 8
Creatinine (μmol/l)	115	108	100
UV sodium (mmol/24 hr)	16	185	445
UV potassium (mmol/24 hr)	38	59	90
UV creatinine (mmol/24 hr)	13 1	12 2	15 5
PRA (ng/10 ml/3 hr)	69	–	–
ASR (μg/24 hr)	160	108	108

		night (n=12)		night, days 1 and 2 (n=18)	
Aldosterone	vs cortisol	−0 20	(n s)	0 11	(n s)
Aldosterone	vs 18-OH-DOC	0 44	(n s)	0 46	(p<0 05)
Cortisol	vs 18-OH-DOC	0 47	(n s)	0 77	(p<0 001)

Treatment with dexamethasone, however, reduced the mean nocturnal aldosterone concentration from 14 4 ± 5 2 to 2 4 ± 0 7 ng/100 ml The daytime aldosterone values remained essentially unchanged during dexamethasone treatment

4 Adrenal scintigrams were made on the 2nd, 5th 7th and 9th days after injection of 1 6 mCi of ^{131}I-6β-Iodomethyl 19 Nor-Cholesterol during suppression with dexamethasone 2 mg/day Dexamethasone was started 14 days before administration of the radiopharmaceutical Accumulation in the adrenals was found only on the 9th day The left adrenal gland was clearly visualized and the right gland showed only a minimal accumulation of activity The results were therefore considered to point to adenoma in the left adrenal gland

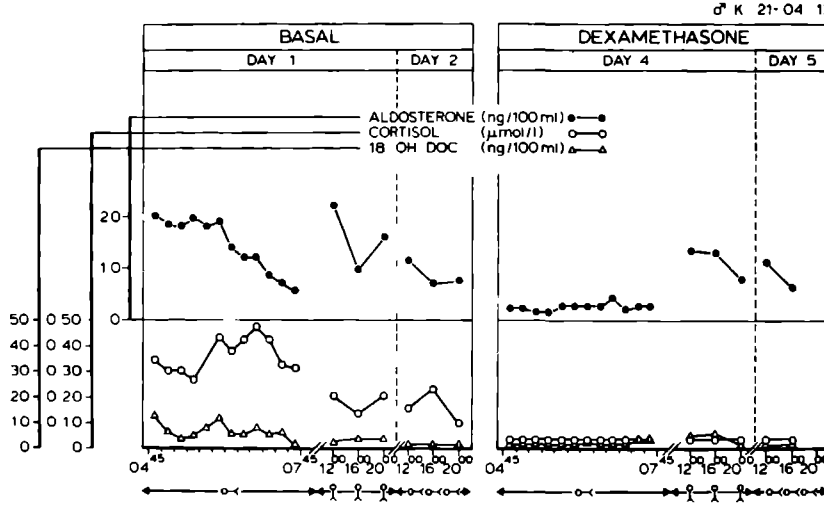


Figure A-21 Diurnal variations of plasma aldosterone, cortisol and 18-OH DOC in patient K with idiopathic aldosteronism

7 At postmortum examination of the adrenal glands both adrenals appeared enlarged, with broadening of the cortex, especially that of the left gland The adrenals weighed 30 and 40 g Light microscopy Both adrenal glands were surrounded by a broad capsule of connective tissue The adrenals showed a marked nodular broadening of the cortex The predominating cells were arranged in an alveolar pattern and characterized by a partly vacuolated, partly eosinophilic cytoplasm The cells could be identified as of the zona glomerulosa-type Locally, small areas were found, composed of large clear cells of the zona fasciculata-type Conclusion macro- and micro-adrenocortical hyperplasia of both adrenals glands No adrenal adenoma

8 On January 15th 1978 the patient suddenly developed nausea, vomiting, speech disturbances and a transient motor dysfunction of the lower limbs He did not have headache or loss of consciousness Visual acuity was unimpaired The patient was off antihypertensive treatment and took dexamethasone 2 mg/day for 18 days (see also 3) On admission, the blood pressure was 240/150 mmHg Fundoscopy revealed no papilledema, hemorrhages or exudates No manifest paralysis or paresis was found The diagnosis of hypertensive encephalopathy was made, and blood pressure was treated by intravenous infusion of diazoxide and metoprolol Despite the maintenance of blood pressure at a level of 160 to 180/90 to 110 mmHg by subsequent oral diazoxide 200 mg/day and propranolol 240 mg/day, the patient developed a complete expressive aphasia and paresis of the right arm and leg In addition, a myocardial infarction of the anterior wall occurred on the 8th day of admission After a long-lasting clinical recovery of 3 months duration with only a partial remission of the neurologic symptoms, the patient could be discharged from hospital He died one year later from bronchopneumonia with cardiac and respiratory insufficiency

WOORDEN VAN WAARDERING

Aan de totstandkoming van dit proefschrift hebben velen een belangrijke bijdrage geleverd. De dank die ik hiervoor verschuldigd ben gaat in de eerste plaats uit naar de patiënten, die bereid waren mee te werken aan de vaak belastende protocollen.
De bereidwillige houding van de verpleegkundige afdeling Endocrinologie (Hoofd: Mw. C.J. Willemsen), heeft mede garant gestaan voor de kwaliteit van het klinisch onderzoek. Mw. B. van Koolwijk-Renet heeft met grote nauwkeurigheid zorg gedragen voor het verzamelen van bloed en urine bij de opgenomen patiënten. De verpleegkundigen van de polikliniek (destijds Hoofd: Mw. T.M.M. Hoogenbosch) ben ik dankbaar voor de medewerking aan de poliklinische studies.
Dhr. J.A. Hofman van het endocrinologisch laboratorium (Hoofd: Prof. Dr. Th.J. Benraad) heeft met grote inzet en enthousiasme een nauwkeurige bepaling van aldosteron in plasma ontwikkeld. Zijn kritische interpretatie van de meetresultaten was voor mij onontbeerlijk.
Voor de vele hormoonbepalingen verdienen met name genoemd te worden: Mw. C.G.M. Camp-van Berkel, Mw. A.A.C. van Geel, Dhr. D.C. Lozekoot, Dhr. F.M.A. van Rosmalen, Mw. A.M. Thissen-Jansen, Mw. W.H.M. van de Velde-van Leeuwen, Mw. O.M.M. Voesten en Dhr. J.J. Willemsen.
Het scintigrafisch onderzoek van de bijnieren kon plaats vinden dankzij de medewerkers van de afdeling Radiotherapie (Hoofd: Prof. Dr. I. Kazem).
Dhr. J. Konings van de afdeling Medische Illustratie heeft het tekenwerk met grote zorg uitgevoerd. De afdeling Medische Fotografie (Hoofd: Dhr. A.Th.A. Reynen) heeft de fotografie verzorgd.
Dhr. E. de Graaff en medewerkers maakten dat het vergaren van literatuur op een verantwoorde en plezierige wijze kon plaats vinden.
De vertaling van een deel van dit proefschrift werd verzorgd door Dr. H.L. Beale te Amsterdam.
De pentekening op het omslag, waarmee de gelijkenis tussen een adenomateuze bijnier en een eikeblad met galappel wordt uitgedrukt, is van de hand van Ineke Kruuk, kunstenares te Valkenswaard.
Mw. L.W.M. Tempelman heeft met grote accuratesse alle versies van het manuscript getypt en meegewerkt aan de correctie van de drukproeven.
Mw. W.M. Straten en Mw. S.J.M. v.d. Werf-Morssinkhof hebben het typewerk van de publikaties verzorgd.
De collegae Frank Gribnau, Ad Kerremans en Theo Thien waren zo

vriendelijk om bij de afronding van dit proefschrift ,,bij te springen", wanneer de klinische werkzaamheden in het gedrang dreigden te komen.

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 10 augustus 1943 te Arnhem. Hij behaalde in 1962 het diploma gymnasium β aan het Katholiek Gelders Lyceum te Arnhem. Hij studeerde vervolgens geneeskunde aan de Katholieke Universiteit te Nijmegen, waar hij in 1968 het doctoraal examen en in 1970 het arts-examen aflegde. In 1970 trouwde hij met Els Kersten. Na een korte periode als waarnemer te hebben gewerkt in de huisartsenpraktijk van J.F.A. van Rijn te Arnhem, begon hij in 1970 aan zijn opleiding tot internist aan de universiteitskliniek voor Inwendige Ziekten (destijds Hoofd: Prof. Dr. C.L.H. Majoor) te Nijmegen. De registratie tot internist vond plaats in oktober 1975. Van 1974 tot 1978 was hij werkzaam op de afdeling Endocrinologie (Hoofd: Prof. Dr. P.W.C. Kloppenborg), alwaar de basis voor zijn promotie werd gelegd. Hij is sinds 1978 werkzaam als internist op de afdeling Algemene Interne Geneeskunde (Hoofd: Prof. Dr. C.L.H. Majoor).

STELLINGEN

BEHORENDE BIJ HET PROEFSCHRIFT

CLINICAL AND PATHOLOGICAL ASPECTS OF PRIMARY ALDOSTERONISM

IN HET OPENBAAR TE VERDEDIGEN
OP DONDERDAG 26 NOVEMBER 1981
DES NAMIDDAGS TE 2 UUR

DOOR

W.H.L. HOEFNAGELS

I

Het diurnale rithme van aldosteron bij patiënten met adenomateus aldosteronisme onderscheidt zich van dat bij patiënten met idiopathisch aldosteronisme in het voorkomen van hoge concentraties van dit hormoon gedurende de nacht en vroege ochtend.

dit proefschrift

II

Langdurige toediening van dexamethason, voorafgaand aan scintigrafisch onderzoek van de bijnieren, verhoogt de sensiviteit van dit onderzoek met betrekking tot het opsporen van aldosteron-producerende adenomen.

dit proefschrift

III

Behandeling met spironolacton leidt tot een relatieve inhibitie van de synthese van aldosteron, met name bij patiënten met primair aldosteronisme.

dit proefschrift

IV

Het frequent ontbreken van een atrofie van de zona glomerulosa in bijnieren van patiënten met een aldosteron-producerend adenoom, doet de vraag rijzen of deze vorm van aldosteronisme wel "primair" is.

dit proefschrift

V

Behandeling van de ziekte van Addison met uitsluitend glucocorticoïden kan een gevaarlijke stijging van de concentratie van kalium in plasma tot gevolg hebben.

Hoefnagels WHL, Drayer JIM, Kloppenborg PWC, Smals AGH, Pieters GFF, Benraad ThJ. Hydrocortisone-induced hyperkalemia in a case of Addison's disease. Neth J Med 21, 120-123, 1978

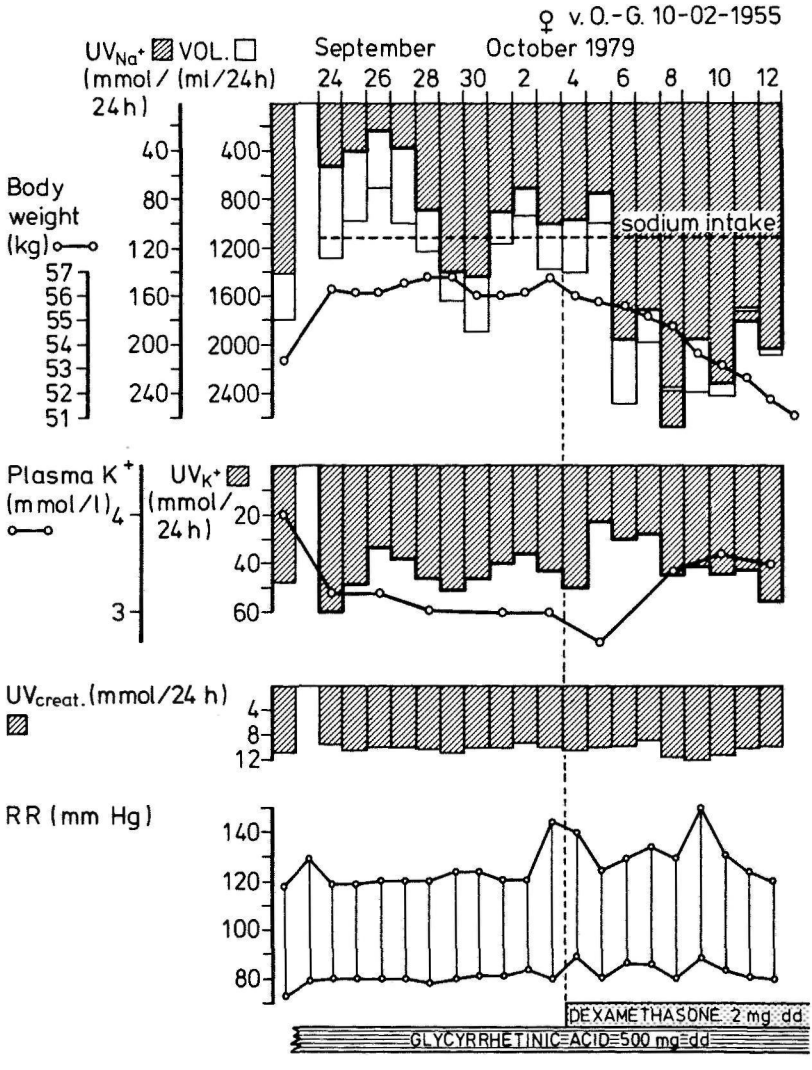
VI

Idiopathisch aldosteronisme is een variant van essentiële hypertensie en niet van het syndroom van Conn.

Padfield PL, Davies D, Lever AF, Brown JJ, Fraser R, Morton JJ, Robertson JIS. The myth of idiopathic aldosteronism. Lancet II, 83-84, 1981

De mineralocorticoïde effecten van glycyrrhetinezuur worden geantagoneerd door gelijktijdige toediening van dexamethason.

Eigen waarneming



VIII

Carriers van het hepatitis-B virus bij wie een integratie van het virus-DNA in het genoom van de levercel heeft plaats gevonden, hebben een verhoogde kans op de ontwikkeling van een hepatocellulair carcinoom.

Shafritz DA, Kew MC Identification of integrated hepatitis B virus DNA sequences in human hepatocellular carcinomas Hepatology I, 1-8, 1981

IX

Bij postmenopauzale patiënten met een oestradiol-receptor-positief mammacarcinoom en tumor-positieve okselklieren is adjuvante chemotherapie niet geïndiceerd.

Raemaekers JMM, Beex LVAM, Koenders AJM, Smals AGH, Pieters GFFM, Benraad ThJ, Kloppenborg PWC De prognostische betekenis van onderzoek naar receptor activiteit voor oestradiol in het tumorweefsel van patienten met een primair mammacarcinoom Ned T Geneesk, In press

NIH consensus - development statement Adjuvant chemotherapy of breast cancer New Engl J Med 303, 831-832, 1980

X

Melkzuuracidose bij cardiale beriberi heeft een aanmerkelijk gunstiger prognose dan melkzuuracidose tengevolge van andere oorzaken.

Majoor CI H, Hillen HFP Cardiale beriberi met melkzuuracidose en cardiovasculaire collaps (Shoshin), een bij alcoholici niet zeldzaam ziektebeeld, dat gemakkelijk wordt miskend Ned T Geneesk, in press

XI

Het plotseling en onverwacht overlijden van een baby ("wiegedood") dient direkt te leiden tot een tevoren zorgvuldig voorbereid diagnostisch, pediatrisch en patholoog-anatomisch onderzoek.

XII

Artsen in de individuele gezondheidszorg, die dokteren aan welzijnsproblemen doen een kwakzalverij en dragen bij tot een nog verdergaande medicalisering van het bestaan.

Mertens AThLM De medicus in de individuele gezondheidszorg, de sociale gezondheidszorg, de welzijnszorg Afscheidscollege, 1981, Nijmegen

XIII

Het verdient onderzoek of de toename van alcoholisme onder de jeugd verband houdt met het feit dat het geven van borstvoeding op de fles is gegaan.